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MAJOR ARTICLE

HIV-related Differences in Placental Immunology: Data From the PRACHITi Cohort in Pune, India

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Background. Maternal HIV infection can affect placental immunology and expression of the neonatal crystallizable fragment receptor (FcRn), which allows transplacental antibody transfer. This study delineated differences in placental FcRn and T-cell expression by HIV status, with or without viral suppression.

Methods. This observational cohort study in Pune, India, followed pregnant women with and without HIV through 1 year postpartum; 42 had placenta collected, stratified by HIV status. FcRn expression was analyzed by Western blot (normalized by GADPH) and compared using ImageJ. Placental CD4/CD8 abundance was assessed by immunofluorescent counting per high powered field.

Results. The median gestational age at delivery was 38.3 weeks (interquartile range [IQR] 37.5–39.1). Of 18 women living with HIV, all were on combined antiretroviral therapy with a median CD4 of 455 cells/mm^3 (IQR 281–640) at entry and 429 cells/mm^3 (IQR 317–686) at delivery. Ten had undetectable virus (≤40 copies/mL); of those with detectable virus, the median viral load was 151 copies/mL (IQR 118.15–539 334). Relative placental FcRn expression was lower in women living with HIV compared to without (median 0.54 vs 0.84, $P = .01$) and not associated with CD4 or viral load. Women with HIV had significantly higher abundance of placental CD8+ T cells, regardless of viral suppression, compared to women without.

Conclusions. Maternal HIV, even with viral suppression, is associated with lower placental FcRn expression and increased placental CD8+ T cells. These results suggest that dysregulation may not be completely reversed by antiretroviral therapy and could contribute to poorer infant outcomes, even in the absence of mother-to-child HIV transmission.

Keywords. maternal HIV; neonatal crystallizable fragment receptor; placental immunology.

Of the estimated 1.4 million pregnant women living with HIV (WLHIV) in the world, 80% receive combined antiretroviral therapy (ART) during pregnancy [1]. Though the majority of their infants remain HIV-uninfected [2]; infants exposed to HIV and uninfected (iHEU) have a higher risk of respiratory infections and infection-related hospitalizations compared to infants unexposed to HIV and uninfected (iHUU) [3–5]. Studies of iHEU also demonstrate multiple immunologic differences compared to unexposed peers, including decreased CD4 counts, decreased humoral immunity, increased systemic inflammatory markers, and even altered cord blood antibody profiles [6–8]. Therefore, maternal HIV infection, even when systemically suppressed, likely causes immune dysregulation in pregnant women and their infants.

The placenta exists at the maternal–fetal interface and serves as a buffer from maternal infections and immune-mediated insults. Untreated HIV is associated with placental inflammation, which can compromise placental function including transplacental antibody transfer [9]. Studies from the pre-ART era found lower transplacental antibody transfer among iHEU compared to iHUU, including antibodies from maternal vaccination or maternal infection. Lower antibody transfer was associated with lower maternal CD4 and higher maternal viral load [10–15]. It is unclear, however, if viral suppression resulting from ART improves placental inflammation and antibody transfer, thereby improving infant outcomes [8, 16]. People with virally suppressed HIV have persistently elevated levels of pro-inflammatory cytokines, such as interferon gamma (IFN-γ) and tumor necrosis factor. Importantly, systemic inflammation is associated with T-cell infiltration of the placenta, which can affect fetal immune development and function [17].

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Placental inflammation has also been associated with decreased expression of the neonatal Fc receptor (FcRn) [13, 18–20], which transfers maternal immunoglobulin G (IgG) to the fetus [10].

Whether there is an association between HIV infection—in the presence or absence of viral suppression—placental inflammation and FcRn expression remain unknown [16, 21]. The goal of our study was to delineate differences in FcRn expression and placental inflammation by HIV status with the hypothesis that maternal HIV infection, even when virally suppressed, results in decreased FcRn expression and increased inflammation in the placenta [8, 22].

METHODOLOGY

Study Population

We enrolled 234 pregnant women in a longitudinal observational study designed to characterize the effects of pregnancy on the immune response to *Mycobacterium tuberculosis* (PRACHITi) at BJ Government Medical College/Sassoon Government Hospital in Pune, India [23, 24]. The PRACHITi study enrolled women >18 years of age and between 13–34 weeks' gestation. It excluded women who were on antibiotics or immunosuppressive medications, diagnosed with an autoimmune disorder (excluding HIV), active tuberculosis (TB) within the past 2 years, or anemia. Placental biopsies were collected in a subset by convenience sampling balanced by HIV status.

Study Procedures

Sociodemographic and medical data were collected at baseline and follow-up visits and entered into an electronic database (Persistent Systems Limited, Salesforce platform). All women were screened for TB infection (TBI) with the IFN-γ release assay. Enrolled women followed up during third trimester, delivery, and postpartum for 1 year. For WLHIV, CD4+ count was checked at entry, delivery, and 6 weeks postpartum; viral load was checked at entry and, if detectable, again at delivery. Infants of WLHIV were tested for HIV at birth, 6 weeks, 6 months, and 18 months of age.

We obtained 42 placental biopsies for this secondary analysis. Four full-thickness placental biopsies were taken within 30 minutes of delivery and stored in RNA later. Four additional full-thickness biopsies were collected, flash frozen in dry ice, and stored at −80 °C within 30 minutes of collection. Two separate full-thickness slices were collected in 10% normal buffered formalin and used to make paraffin wax blocks after 72 hours and stored at room temperature. We collected 10 mL of cord blood before delivery of the placenta. Cord plasma was separated within 1 hour of collection and stored in liquid nitrogen.

Informed consent was obtained from women at PRACHITi enrollment. This study was approved by the institutional review boards and/or ethics committees at Weill Cornell Medicine, BJ Government Medical College, and Johns Hopkins University.

Laboratory Analysis

Immunohistochemical Staining of Placenta for FcRn and T-cell Populations. Paraffin-embedded human placentae were sectioned into 5-μm slices and mounted on Superfrost Plus Microscope Slides. The samples underwent deparaffinization using xylene and alcohol. Antigen retrieval was performed by heat-treating the samples with a pH 6.0 antigen-retrieval solution (Vector Laboratories, CA, USA). The primary antibodies used were rabbit anti-CD4 (ab133616, Abcam, Fremont, CA, USA), rabbit anti-CD8 (ab101500, Abcam), and mouse anti-FcRn (sc-271745, Santa Cruz Biotechnology, Dallas, TX, USA). The slides were incubated overnight at 4 °C, followed by conjugation with donkey anti-rabbit or mouse Alexa Fluor 568 secondary antibodies (1:500, Thermo Fisher, Halethorpe, MD, USA) at room temperature for 3 hours. To visualize the nuclei, 4′,6-diamidino-2-phenylindole (DAPI, 1:5000, Millipore, Rockville, MD, USA) was used as a counterstain. The images were captured using a Zeiss AxioCam MRM with a 20× objective.

The images for expression were captured from the same batch of experiments using identical imaging parameters, including exposure time for quantification. After setting the scale and threshold for positive expression, the percentage of positive expression relative to the entire area was calculated. The software ImageJ was employed for expression analysis. In each placenta, 6 random images in the villi were taken, and the average fluorescent area calculated for that placenta of FcRn or CD4+ and CD8+ cells were calculated.

Enzyme-linked Immunosorbent Assay of Maternal Plasma Samples. Multiplex immunoassays (Luminex assays; R&D Systems) were used to measure IFN-g, IL-1β, IL-6, IL-13, IL-17A, and tumor necrosis factor. Single-plex immunoassays were performed on plasma samples (R&D Systems) for soluble CD163, soluble CD14 (sCD14), C-reactive protein, and interferon β. These biomarkers were chosen based on their relevance to birth outcomes and HIV.

Antigen-specific IgG levels in maternal and cord blood plasma were measured using enzyme-linked immunosorbent assay kits for tetanus toxoid (Genway Bio, FCBEAB), diphtheria toxoid (Alpha Diagnostic International, #940-100-DHG), hepatitis B surface antigen (Alpha Diagnostic International #4200), *Haemophilus influenzae* type b polysaccharide (VaccZyme, MK016), *Bordetella pertussis* (Alpha Diagnostic International, #960-110-PHG), human papillomavirus 06L1 (HPV06L1), and *Streptococcus pneumoniae* (serotypes 1–5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F,

33F; VaccZyme MK012). Manufacturer instructions were followed, including positive and negative controls provided in the enzyme-linked immunosorbent assay kits.

Polymerase Chain Reaction Multiplex Array. After thawing, each placental punch biopsy sample had 2 µg RNA used for complementary cDNA synthesis in a 40-µL reaction, using Bio-Rad iScript cDNA Synthesis Kit (no. 170-8891, Bio-Rad). A TaqMan Human Immune Array v2.1 (no. 4370499, Thermo Fisher Scientific) was used to evaluate 96 immune markers. Array analyses were performed with the Quant Studio 12K Flex Real-Time PCR System (Thermo Fisher Scientific) for 40 cycles. The Thermo Fisher Connect cloud system was used for data storage.

Quantitative Real-time Polymerase Chain Reaction. Quantitative polymerase chain reactions were completed based on published protocols [25]. Total RNA was extracted with RNeasy Plus Mini Kit (No. 74136, Qiagen, Valencia, CA, USA); quantitative polymerase chain reaction was completed by using the CFX384 Touch Real-Time PCR Detection System (Bio-Rad, Hercules, CA, USA) per manufacturer's protocol. The primers were obtained from Integrated DNA Technologies (Coralville, IA, USA). All reactions were run on the StepOnePlus Applied Biosystems Real-time PCR machine under the following conditions: 50 °C for 2 minutes, 95 °C for 10 minutes, 95 °C for 15 seconds, and 60 °C for 1 minutes for 50 cycles. Transcript levels were determined by normalizing the target gene threshold cycle value to the threshold cycle value of the endogenous housekeeping gene *Gapdh* (ΔCT).

Additional details for laboratory analysis can be found in Supplemental Methods.

Statistical Analysis

Sample size for PRACHITi was calculated to delineate immune responses to *M tuberculosis* during pregnancy [23]. Placental immune changes were a secondary outcome to be defined using the 42 placental samples without power calculation. FcRn expression was compared using ImageJ software (National Institutes of Health, Bethesda, MD, USA). Continuous data were tested for normality with outliers identified using the Grubb test. The 1-way analysis of variance with Tukey post hoc test and chi-squared analysis was used for comparison of categorical variables. Statistical analysis of CD4+ and CD8+ immunofluorescence staining was done using GraphPad Prism. Mean differences were considered statistically significant if $P < .05$. A multivariable linear regression was done to explore associations between systemic and placental inflammatory markers with placental FcRn expression and CD4+/CD8+ T-cell abundance. Bonferroni-adjusted P values were generated using R statistical software to account for multiple comparisons.

Maternal and infant antibody levels were log-transformed and compared by maternal HIV status using the Welch t-test; 1-way analysis of variance was used to evaluate differences in antibody levels among women without HIV, WLHIV with viremia ≥40 copies/mL, and WLHIV with undetectable viral load (<40 copies/mL). Differences in transplacental transfer efficiency were evaluated using multivariable linear regression with infant cord blood antibody levels as the outcome variable and maternal antibody level and HIV infection status as predictors, adjusting for infant sex and birth weight-for-age z-score. Statistical analyses were performed using GraphPad Prism version 8 (GraphPad Software, La Jolla, CA, USA, www.graphpad.com) and R Statistical Software (v4.3.1; R Core Team 2023).

RESULTS

Baseline Characteristics

Of the 42 placentae, 38 were of sufficient quality to include in final analysis: 18 from WLHIV and 20 from women without HIV (Figure 1). The median age of the analyzed cohort was 25 years (interquartile range [IQR] 21–28.7). The median gestational age at delivery was 38.3 weeks (IQR 37.5–39.1). In the 18 WLHIV, their median CD4 count was 455 cells/mm^3 (IQR 281–640) at entry and 429 cells/mm^3 (IQR 317–686) at delivery; 7 (38%) had a detectable viral load (≥40 copies/mL) at delivery (median: 151 copies/mL; IQR 118–539 334). Otherwise, there were no significant clinical differences between women living with and without HIV (Table 1). The only significant difference in baseline plasma cytokines between women living with and without HIV was sCD14 (1321 pg/mL vs 1062 pg/mL, $P = .04$) (Supplementary Table 1).

Of 13 infants born to WLHIV, 2 had a positive HIV RNA polymerase chain reaction at delivery, but only 1 had a subsequent positive confirmatory HIV test. There were no significant differences in obstetric or infant outcomes between women living with and without HIV, including birthweight and placental weight (Table 1).

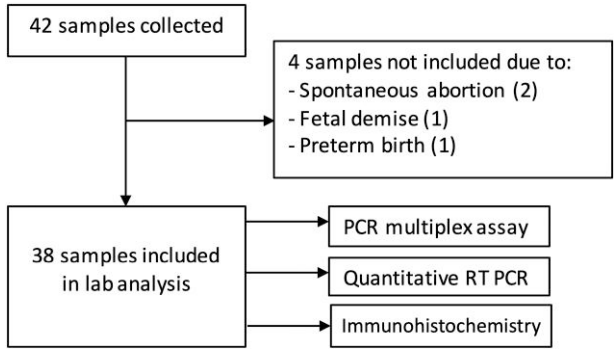


Figure 1. CONSORT diagram.

Table 1. Baseline Demographics and Clinical Features, by HIV Status

	Total Number (%)	HIV (%)	No HIV (%)	*P* Value	Total Analyzed (%)	HIV (%)	No HIV (%)	*P* Value
Total participants in group	42	20 (48%)	22 (52%)		38 (90%)	18 (47%)	20 (53%)	
Maternal characteristics								
Median age (IQR)	25 (21–29)	26.5 (22–30.3)	22.5 (21–26)		25.0 (21–28.8)	25.5 (22–30)	23 (21–26.5)	
Median gestational age (IQR)	38.5 (37.5–39.2)	39 (37.4–39.4)	38.4 (38.0–39.2)		38.5 (38.0–39.2)	39.0 (38.2–39.5)	38.2 (37.6–39.1)	
Sociodemographic characteristics								
Lower socioeconomic class	24 (57%)	11 (46%)	13 (54%)	.80	22 (58%)	11 (50%)	11 (50%)	.71
Education								
<4th grade education	5 (12%)	5 (25%)	0 (0%)	.02[a]	5 (13%)	5 (28%)	0 (0%)	.02[a]
Medical/obstetric history								
Preterm delivery (≤37 wk gestational age)	8 (19%)	2 (10%)	6 (27%)	.30	7 (18%)	2 (11%)	5 (25%)	.31
Delivery type								
Vaginal	25 (60%)	13 (65%)	12 (55%)	.62	23 (61%)	12 (67%)	11 (55%)	.47
Cesarian section	16 (38%)	7 (35%)	9 (41%)		15 (39%)	6 (33%)	19 (95%)	
Tetanus toxoid								
Given once	9 (21%)	8 (40%)	1 (5%)	.006[a]	7 (18%)	6 (33%)	1 (5%)	.03[a]
Given twice	32 (76%)	11 (55%)	21 (95%)	.006[a]	31 (82%)	12 (67%)	19 (95%)	.03[a]
Prenatal steroids given	13 (31%)	7 (35%)	6 (27%)	.60	13 (34%)	7 (39%)	6 (30%)	.58
Preeclampsia	8 (19%)	3 (15%)	5 (23%)	.53	8 (21%)	3 (17%)	5 (25%)	.54
Primigravida	11 (26%)	5 (25%)	6 (27%)	.87	10 (36%)	4 (22%)	6 (30%)	.60
Gestational diabetes	4 (10%)	2 (10%)	2 (9%)	.92	4 (11%)	2 (11%)	2 (10%)	.91
Mean placenta weight of full-term pregnancies (SD)	513.5 (138.6)	516 132.1)	510.5 (147.8)	.72	535.5 (114.8)	528.4 (123.1)	542.6 (108.7)	.89
Laboratory values								
Median CD4 count[a] (IQR)								
At entry	…	455 (291.3–640.5)	NA		…	455 (251.8–622.3)	NA	
At delivery	…	451.5 (317–686.5)	NA		…	429 (293.0–658.5)	NA	
Undetectable viral load (<40)[a]	…	7 (35%)	NA		…	7 (39%)	NA	
Median detectable viral load[a] (IQR)	…	151 (118–1 077 866)	NA		…	151 (118–1 077 866)	NA	
Positive IFN-γ release assay	32 (76%)	12 (60%)	10 (45%)		28 (74%)	10 (56%)	18 (90%)	
Antiretroviral therapy[a]								
NRTI and NNRTI	…	17 (85%)	NA		…	15 (83%)	NA	
NRTI and PI	…	3 (15%)	NA		…	3 (16%)	NA	
Infant outcomes								
Mean birthweight of full-term infants (SD)	2.5 (0.6)	2.5 (0.6)	2.6 (0.6)	0.73	2.6 (0.5)	2.6 (0.6)	2.7 (0.4)	0.89

Abbreviations: IFN, interferon; IQR, interquartile range; NA, not available; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SD, standard deviation.

[a]Only included people with HIV.

Impact of HIV on FcRn Expression

FcRn expression was lower in placental tissue from WLHIV compared to those without (Figure 2). Total FcRn expression was not significantly associated with systemic or placental cytokine expression, CD4 count and viral load at study entry, or adverse neonatal outcomes (eg, low birthweight, hospitalization). Class of ART also did not significantly correlate with FcRn expression, although the majority of women were on nonnucleoside reverse transcriptase inhibitor-based regimens (Table 1).

Impact of HIV on CD4+ and CD8+ T-cell Expression

There was a significantly higher expression of CD8+ T cells in placenta of WLHIV compared to women without HIV (Figure 3). Expression of CD8+ T cells in placenta of WLHIV was not associated with viral load (Supplementary Figure 1). Placenta with higher CD8+ T-cell expression had lower relative FcRn expression, although this association was not statistically significant (Supplementary Figure 2). Exploratory analysis demonstrated that CD8+ T-cell expression was associated with increased placental expression of HMOX1 ($P = .01$) and LRP2 ($P = .04$), which was not significant after adjustment for multiple comparisons (Supplementary Table 2). There were no significant differences in placental CD4+ T-cell expression between women living with and without HIV (Supplementary Figure 3).

Maternal Transfer of Antibodies

Despite differences in FcRn expression and maternal and infant cord antibody levels were similar among mother–infant pairs with and without HIV infection for tetanus toxoid, diphtheria, hepatitis B, *H influenzae* type b, *B pertussis*, and *S pneumoniae* (Supplementary Figure 4). Among WLHIV, there were no significant differences in antibody levels by viral suppression. Infants born to WLHIV, however, had lower anti-HPV IgG antibody levels compared to infants born to mothers without HIV (median 1.47 vs 2.34 U/mL, $P = .008$) (Figure 4), which did not differ by maternal viral suppression. Maternal HIV status was not associated with reduced transplacental transfer efficiency when adjusting for infant sex and birthweight.

DISCUSSION

Our study demonstrated that FcRn expression was significantly lower in placental tissue from WLHIV, including those who were virally suppressed with CD4+ counts >350 cells/mm^3, compared to women without HIV. Despite lower FcRn expression levels, antigen-specific maternofetal IgG antibody transfer was generally preserved, with the exception of HPV. WLHIV also had a higher placental expression of CD8+ T cells compared to women without HIV. Taken together, our data provide insight into placental differences that may contribute to immunologic and clinical differences observed between iHEU and iHUU.

Maternal infectious diseases, including HIV, can impair FcRn-mediated placental transfer of IgG [11, 19, 26–30]. Most of these data, however, come from pregnant women with malaria or untreated HIV. To our knowledge, this is the first description of lower FcRn expression associated with HIV in the presence of effective ART. FcRn expression was not associated with maternal CD4 count, HIV viral load, or cytokine protein expression in the placenta. This could be due to our small sample size. Alternatively, these findings could indicate that lower FcRn expression in WLHIV is due to a mechanism other than severity of HIV infection, such as latent HIV in the placenta, ART-specific exposures, or differences in micro-RNA related to FcRn expression [31].

We also found that placental CD8+ expression was increased in WLHIV, regardless of viral load. In contrast to our findings, a study from Uganda reported no difference in placental inflammation among WLHIV (74% undetectable virus) versus women without HIV. However, women in this cohort all took trimethoprim/sulfamethoxazole for malaria prophylaxis, which likely decreased inflammatory markers. Systemic CD8+ T cells increase with acute HIV infection and improve with decreases in viral load [32, 33]. Systemic CD8+ T cells also increase later in pregnancy, contributing to the pro-inflammatory state that precedes labor and delivery [34, 35]. Studies have shown that pregnant WLHIV have more circulating CD8+ T cells than pregnant women without HIV [34, 36]. Interestingly, these greater numbers of CD8+ T cells exhibit features of T-cell exhaustion and immunosenescence, which reduce their proliferative capacity and cytokine production [37–40]. Furthermore, CD8+ T-cell function is only partially restored by ART [41]. Taken together, our data could explain why we observed an increase in placental CD8+ T cells without a significant increase in inflammatory placental cytokines.

Like peripheral CD8+ T cells, placental CD8+ T cells are responsible for recognizing and responding to viral antigens to protect the fetus from infections [42]. But sometimes viruses evade placental CD8+ T cells. For example, in a murine model of lymphocytic choriomeningitis virus infection during gestation, lymphocytic choriomeningitis virus was cleared by the immune system from all tissues except the placenta [43]. Therefore, it is possible that HIV persists in placental tissue despite ART, resulting in the persistently elevated CD8+ T cells in the placenta that we observed [44]. Animal models have shown that increased placental CD8+ T cells are associated with poor neonatal immunologic responses, including impaired T-cell immunity and regulatory immune responses [45]. This suggests that in utero exposure to HIV-related inflammation, even in the absence of HIV transmission, could affect fetal immune development, contributing to the poorer outcomes of iHEU versus iHUU. Some studies also suggest that ART

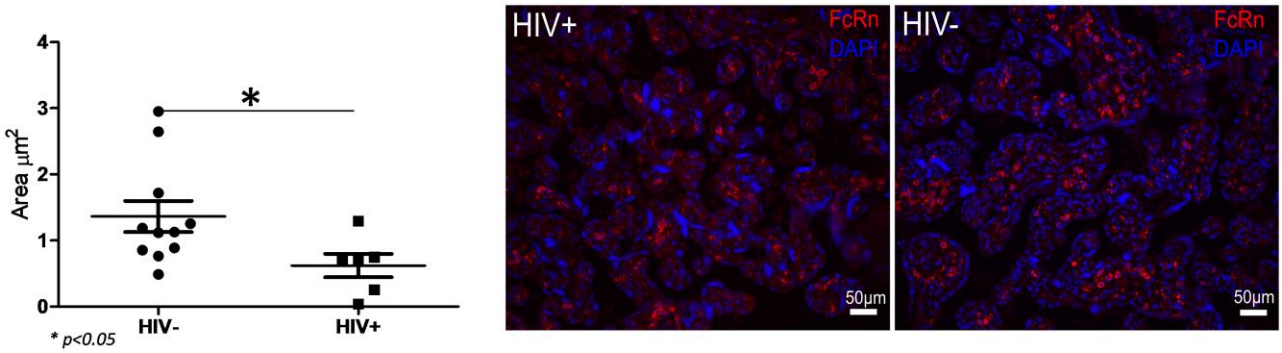


Figure 2. FcRn expression in placenta from women living with and without HIV. Left: Relative expression of FcRn was significantly lower in placenta from women living with HIV (0.54, gray bar) compared to placenta from women living without HIV (0.84, white bar) Right: Representative images of ex vivo fluorescent imaging and immunohistochemistry of FcRn expression and DAPI in placenta from a woman with HIV (left) and a woman without HIV (right). DAPI, 4′,6-diamidino-2-phenylindole; FcRn, neonatal crystallizable fragment receptor.

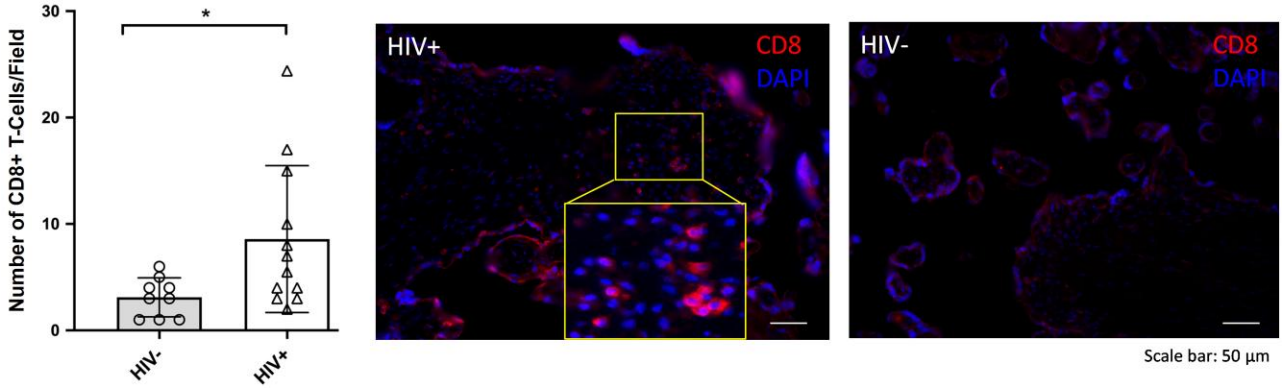
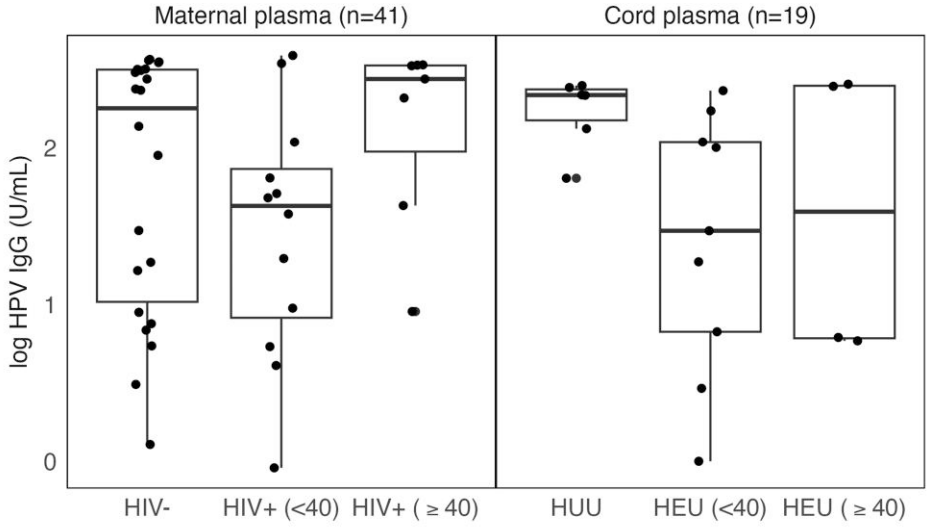


Figure 3. CD8+ T-cell expression in placenta from women living with and without HIV. Left: Immunofluorescent staining was conducted to examine the expression of CD8+ T cells in the placental villi. There was a significant increase in the number of CD8+ T cells in placentas exposed to maternal HIV infection compared to placentas from women without HIV. There were no notable differences in CD8+ T-cell levels between placentas from mothers with detectable (DVL) versus undetectable viral loads (UVL). Right: Representative images of ex vivo fluorescent imaging and immunohistochemistry of CD8+ T-cell expression and DAPI in placenta from a woman without HIV (left panel) and a woman with HIV (right panel). DAPI, 4′,6-diamidino-2-phenylindole.

regimens affect placental immunology differently [46, 47]. Protease inhibitors, for example, are associated with increased placental inflammation and increased risk of preterm birth [46–48]. If confirmed, identifying ART regimens that decrease placental inflammation and improve CD8+ T-cell function will be important in improving iHEU outcomes.

We did not find differential antigen-specific IgG antibody transfer for most pathogens by maternal HIV status, despite observing lower abundance of placental FcRn among WLHIV. Lozano et al demonstrated a direct correlation between FcRn expression levels measured by microscopy and total IgG in preterm newborns [49]. Although a quantitative threshold of FcRn expression impacting transplacental IgG transfer has not been defined, the modest differences in FcRn abundance we observed by HIV status (~1% lower FcRn area by microscopy) were similar to those associated with lower total IgG in Lozano et al's study. One explanation for the difference is that our sample size limited our ability to detect a significant difference in antibody transfer. We also did not assess FcRn expression in the neonatal gut nor antibodies to gastrointestinal-specific antigens. Finally, it is also possible that antigen-specific IgG transfer may be preserved because of antibody binding to noncanonical placental Fc receptors or selective FcRn-mediated transfer by antibody glycan profiles [13, 30]. In a Ugandan cohort of women with HIV on ART, most of whom were virally suppressed, Dolatshahi et al found preserved global transplacental antibody transfer, similar to our results [8]. Interestingly, compared to iHUU, iHEU in the Ugandan cohort had lower cord blood levels of vaccine-related antibodies, including tetanus, polio, and Hib IgG, which was related to lower vaccine-related antibody responses in their mothers. In our study, iHEU had lower HPV IgG levels



Abbreviations: HPV06L1- Human papilloma virus 6; HUU= HIV unexposed uninfected; HEU= HIV exposed uninfected

Figure 4. Maternal and cord blood anti-HPV antibodies in women without HIV, with detectable HIV, and undetectable HIV. A logarithmic scale was used to present antibody levels to HPV-6 in maternal and cord blood plasma samples from women living with and without HIV, by viral suppression (<40 copies/mL or > = 40 copies/mL), and their infants. HPV, human papillomavirus.

compared to iHUU, which may be related to lower HPV IgG levels among mothers with HIV who were virally suppressed. Interestingly, mothers without viral suppression had a lower ratio of cord: maternal HPV IgG levels compared to mothers with viral suppression.

Our study had some limitations. Many participants had TBI, which could impact placental inflammation. Because there was equal distribution of women with TBI in the cohorts with and without HIV, this was unlikely to have significantly impacted our findings. Furthermore, TBI status was not associated with FcRn expression or CD8+ abundance (Supplementary Figure 5). We were not able to assess for other infections, such as Epstein Barr and cytomegalovirus, which could affect placental CD8+ T cells. Prevalence of cytomegalovirus and Epstein Barr virus is generally high in Indian populations and likely did not significantly vary by HIV status [50, 51]. Finally, our study was not powered to link placental pathology with infant outcomes. However, our findings show that HIV infection, even when virally suppressed, is associated with distinct differences in placental immune profiles, which are known to affect fetal immune development. Ongoing studies will examine cell populations in maternal and cord blood samples.

CONCLUSIONS

iHEU comprise a growing population of children in HIV-endemic countries. Immune and inflammatory dysregulation in iHEU has been linked to adverse birth and neonatal outcomes, including pneumonia, diarrheal disease, and bacterial sepsis at increased rates and severity [52, 53]. Our study shows that WLHIV had lower total FcRn expression, despite ART, and higher placental CD8+ T-cell expression. Further research is needed to understand the relationship between virally suppressed HIV infection and FcRn expression, IgG galactosylation, placental inflammation and infant outcomes.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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