Risk of skin and subcutaneous diseases in paediatric HIV-exposed uninfected individuals in the USA

Ghida EL Banna[1,2,3] Sydney Wishner,[4] Natalie Baker[1,2] Bryan L Peacker[1,2] Natalie Braun[1,2] Kevin Sheng-Kai Ma,[1,2] Steven T Chen[1,2] and Lisa M Bebell[2,3,4]

[1]Department of Dermatology, Massachusetts General Hospital, Boston, MA, USA
[2]Harvard Medical School, Boston, MA, USA
[3]Department of Medicine, Division of Infectious Diseases, and Centre for Global Health, Massachusetts General Hospital, Boston, MA, USA
[4]Medical Practice Evaluation Centre, Massachusetts General Hospital, Boston, MA, USA
Correspondence: Lisa M. Bebell. Email: lbebell@mgh.harvard.edu
S.T.C. and L.M.B. are co-senior authors.

https://doi.org/10.1093/bjd/ljag144

Dear Editor, HIV-exposed uninfected (HEU) individuals represent a growing population globally. Despite remaining HIV-uninfected, HEU children experience disproportionately poorer health outcomes in infancy and childhood, including increased morbidity and mortality from severe infections,[1,2] although knowledge of the underlying mechanisms is limited. Little is also known about their dermatological health.

To address this knowledge gap, we conducted a retrospective cross-sectional study within the Mass General Brigham healthcare system (Boston, MA, USA) from 1995 to 2024. Using the Research Patient Data Repository, we identified 262 HEU individuals, confirmed by maternal HIV diagnosis and manual chart review, and matched them 1 : 2 to 499 HIV-unexposed uninfected (HUU) controls by age, sex, race/ethnicity and zip code (a sociodemographic measure). Dermatological diagnoses were extracted using International Classification of Diseases (ICD) 9th and 10th edition codes and validated by manual chart review. We analysed skin conditions individually and calculated relative risks (RRs) comparing HEU with HUU individuals using χ^2 and two-tailed independent sample *t*-tests. We controlled the false discovery rate using the Benjamini–Hochberg procedure. In exploratory logistic regression analyses, we examined relationships between maternal HIV parameters – including $CD4^+$ T-cell count, viral load, infection duration and antiretroviral therapy (ART) – and skin disease,

adjusting for maternal age at delivery, gestational age and delivery mode.

The median [interquartile range (IQR)] age was 9 (4–18) years for HEU and 10 (4.5–19) years for HUU individuals; sex and racial/ethnic distribution were similar. HEU children were more frequently delivered preterm (30.7% vs. 15.3%) and by Caesarean (51.5% vs. 21.4%). The median (IQR) follow-up time was comparable [2.15 (0.02–9.8) for HEU vs. 1.69 (0.01–8.6) years for HUU; $P = 0.11$].

At delivery, the mean (SD) HEU maternal age was 31.6 (6.1) years, with a median (IQR) HIV infection duration of 8.9 (2.2–8.7) years. In the first pregnancy trimester, 186 (71.0%) had HIV viral load $\leq$ 400 copies mL^{-1}, and 19 (7.3%) had no viral load documented. Of 228 (87.0%) mothers with documented $CD4^+$ T-cell counts, 19 (7.3%) had < 200, 42 (16.0%) had 200–349, 37 (14.1%) had 350–500 and 130 (49.6%) had > 500 cells mm^{-3}.

HEU individuals had significantly higher risks of mucocutaneous candidiasis [RR 2.65; 95% confidence interval (CI) 1.67–4.21], seborrhoeic dermatitis (RR 2.85; 95% CI 1.30–6.27), skin and soft tissue infection (RR 1.76; 95% CI 1.15–2.70), contact dermatitis and other eczema (RR 1.59; 95% CI 1.11–2.29) and atopic dermatitis (RR 1.57; 95% CI 1.09–2.24) than HUU individuals. There were no significant differences in risk of acne, urticaria, viral exanthems, molluscum contagiosum, herpes simplex virus, warts, scabies or nonspecific rashes between the groups (Table 1). In a logistic regression model restricted to HEU individuals, maternal viral suppression during pregnancy was associated with lower odds of any offspring skin disease (odds ratio 0.85; 95% CI 0.73–0.99). Maternal $CD4^+$ T-cell count, ART regimen and HIV infection duration were not associated with dermatological outcomes.

Our findings extend the evidence of adverse health outcomes in HEU children to dermatological disease. The observed pattern of

Table 1 Demographic characteristics and birth history; and prevalence and relative risk (RR) of dermatological conditions in HIV-exposed uninfected (HEU) individuals compared with HIV-unexposed uninfected (HUU) individuals, based on International Classification of Disease 9th and 10th edition codes

	HEU ***n*** **= 262**	**HUU** ***n*** **= 499**	***P*-value**
Demographic characteristics			
Age (years), median (IQR)	9 (4–18)	10 (4.5–19)	0.40
Male	143 (54.6)	273 (54.7)	0.97
Self-reported race/ethnicity			
White	53 (20.2)	98 (19.6)	0.93
Black	69 (26.3)	130 (26.1)	
Asian	5 (1.9)	8 (1.6)	
American Indian or Alaska Native	0 (0)	1 (0.2)	
Other	32 (12.2)	74 (14.8)	
Two or more races	6 (2.3)	14 (2.8)	
Not recorded or declined to answer	97 (37.0)	174 (34.9)	
Deceased child	2 (0.8)	5 (1.0)	0.74
Follow-up time (years), median (IQR)	2.2 (0.02–9.8)	1.7 (0.01–8.6)	0.11

Skin disease diagnosis	**HEU** ***n*** **= 262**	**HUU** ***n*** **= 499**	**RR (95% CI)**	P_{corr}**-value**[a]
Acne	12 (4.6)	24 (4.8)	0.95 (0.48–1.87)	0.9
Atopic dermatitis	47 (17.9)	57 (11.4)	1.57 (1.09–2.24)	0.01*
Mucocutaneous candidiasis	39 (14.9)	28 (5.6)	2.65 (1.67–4.21)	0.0001*
Contact dermatitis and other eczema[b]	46 (17.6)	55 (11.0)	1.59 (1.11–2.29)	0.01*
Herpes	9 (3.4)	13 (2.6)	1.32 (0.57–3.04)	0.5
Molluscum contagiosum	8 (3.1)	12 (2.4)	1.27 (0.53–3.07)	0.6
Rash, unspecified	25 (9.5)	37 (7.4)	1.29 (0.79–2.09)	0.3
Scabies	6 (2.3)	7 (1.4)	1.63 (0.55–4.81)	0.4
Seborrhoeic dermatitis	15 (5.7)	10 (2.0)	2.85 (1.30–6.27)	0.009*
Skin and soft tissue infection	36 (13.7)	39 (7.8)	1.76 (1.15–2.70)	0.01*
Tinea	19 (7.3)	18 (3.6)	2.01 (1.07–3.76)	0.03*
Urticaria	16 (6.1)	24 (4.8)	1.27 (0.68–2.35)	0.5
Viral exanthem	23 (8.8)	32 (6.4)	1.37 (0.82–2.29)	0.2
Warts	8 (3.1)	14 (2.8)	1.09 (0.46–2.56)	0.9

Values are *n* (%), unless otherwise noted. CI, confidence interval; IQR, interquartile range. [a]*P*-values were corrected using the Benjamini–Hochberg procedure. [b]When irritant contact dermatitis was excluded in a sensitivity analysis, results were similar: RR 1.5 (95% CI 1.1–2.3). *****Statistically significant at *P*-value < 0.05.

dermatological disease suggests phenotype-specific immune alterations. Our results align with a Zimbabwean HEU cohort that observed more skin infections and oral thrush,[3] although another US cohort study found no increased risk of skin and soft tissue infections.[1] Increased susceptibility to candidal and bacterial infections may reflect altered innate immunity and T-cell responses.[4–6] The increased prevalence of eczematous conditions may reflect T-helper 2-skewed immunity, which has been reported in HEU individuals and linked to increased atopy. This shift could also explain the increased atopic dermatitis risk in our cohort.[4] Increased risk of candidiasis and seborrhoeic dermatitis in HEU individuals suggest that early detection and treatment may be beneficial for candida and yeast-related skin conditions.

Our study has several limitations. Firstly, follow-up time was relatively short, potentially underestimating the risk of conditions developing later in adolescence. Secondly, reliance on ICD coding may bias diagnosis ascertainment. Thirdly, as 97% of HEU individuals were exposed to both maternal HIV and ART peripartum, we cannot disentangle their independent effects. Fourthly, our study population was drawn from a US tertiary healthcare system, limiting generalizability. Fifthly, although we used zip code and self-reported race/ethnicity to adjust for socioeconomic factors, residual confounding could remain. Lastly, while our results are statistically significant, effect sizes were moderate. However, even modest RR increases for these common childhood conditions may translate into clinically meaningful absolute differences in this growing population.

Despite these limitations, we highlight dermatological manifestations as an under-recognized morbidity in HEU individuals. Dermatologists and paediatricians should be aware of this potential risk, particularly for HEU children with recurrent dermatitis or infections. Longitudinal studies are needed to clarify persistence of these skin conditions, and mechanistic research is needed to define the immunological pathways by which perinatal HIV exposure shapes cutaneous health.

Acknowledgements: We would like to thank Emily Santos for her technical assistance with the Institutional Review Board submission; Virginia Triant and Lindsay Fourman for their guidance on International Classification of Diseases code acquisition and data collection through the Research Patient Data Repository; Kaitlyn James for providing access to the mother–baby delivery repository at Massachusetts General Hospital; and James Meigs for his valuable feedback on the study design.

Author contributions: Ghida EL Banna (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Writing—original draft, Writing—review & editing [equal]), Sydney Wishner (Data curation, Writing—review & editing [equal]), Natalie Baker (Writing—review & editing [equal]), Bryan L. Peacker (Writing—review & editing [equal]), Natalie Braun (Writing—review & editing [equal]), Kevin Sheng-Kai Ma (Conceptualization, Writing—review & editing [equal], Supervision [supporting]), Steven T. Chen (Conceptualization, Supervision, Writing—review & editing [equal]), and Lisa M. Bebell (Conceptualization, Data curation, Writing—review & editing [equal], Supervision [lead]).

Funding sources: This work was supported by the National Institutes of Health (NIH) grant R25AI147393 to G.E.B.

Conflicts of interest: The authors declare no conflicts of interest.

Data availability: The dataset used in this manuscript is available on reasonable request to the corresponding author and execution of a data use and sharing agreement.

Ethics statement: This study was approved by the Mass General Brigham Institutional Review Board (no. 2024P002511).

Patient consent: Written patient consent for publication was obtained.

References

1 Labuda SM, Huo Y, Kacanek D *et al.* Rates of hospitalization and infection-related hospitalization among human immunodeficiency virus (HIV)-exposed uninfected children compared to HIV-unexposed uninfected children in the United States, 2007–2016. *Clin Infect Dis* 2020; **71**:332–9.
2 Afran L, Garcia Knight M, Nduati E *et al.* HIV-exposed uninfected children: a growing population with a vulnerable immune system? *Clin Exp Immunol* 2014; **176**:11–22.
3 Evans C, Humphrey JH, Ntozini R, Prendergast AJ. HIV-exposed uninfected infants in Zimbabwe: insights into health outcomes in the pre-antiretroviral therapy era. *Front Immunol* 2016; **7**:190.
4 Bunders MJ, Van Hamme JL, Jansen MH *et al.* Fetal exposure to HIV-1 alters chemokine receptor expression by $CD4^+$ T cells and increases susceptibility to HIV-1. *Sci Rep* 2014; **4**:6690.
5 Velilla PA, Montoya CJ, Hoyos A *et al.* Effect of intrauterine HIV-1 exposure on the frequency and function of uninfected newborns' dendritic cells. *Clin Immunol* 2008; **126**:243–50.
6 Chougnet C, Kovacs A, Baker R *et al.* Influence of human immunodeficiency virus-infected maternal environment on development of infant interleukin-12 production. *J Infect Dis* 2000; **181**:1590–7.