Advances in HIV immunology

OAA2705

Maternal Human Milk Immune Profiles Associated with Postnatal HIV Transmission to Infants During Breastfeeding in the PROMISE Study

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AIDS 2026

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Summary

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What is the main question?

Do specific human milk oligosaccharide (HMO) fractions and immunoglobulin (Ig) subclasses differ between infants acquiring vs. not acquiring HIV through breastmilk?

What did we find?

- **HMOs:** Total HMO concentration in maternal human milk was not associated with transmission of HIV; high levels of lacto-N-neotetraose and sialyllacto-N-tetraose b trended toward lower odds of transmission
- **Igs:** High levels of IgG3, IgM, and HIV gp120-specific IgG were significantly associated with higher odds of transmission of HIV through maternal human milk

Why is it important?

Postnatal HIV transmission persists despite maternal ART. Understanding breastmilk immune composition may identify modifiable factors and guide strategies to protect infants from HIV acquisition during breastfeeding

Background

- In the absence of maternal ART, breastfeeding accounts for a substantial share of vertical transmission in resource-limited settings, up to 44% of transmission occurred postnatally in a randomized trial of breastfeeding vs. formula feeding[1,2]

- Maternal ART with sustained viral suppression markedly reduces breastfeeding HIV transmission to below 1%, but does not appear to eliminate it[3]

- Prior data suggest a protective role of human milk oligosaccharides (HMOs), but HMO fractions are understudied in the ART era

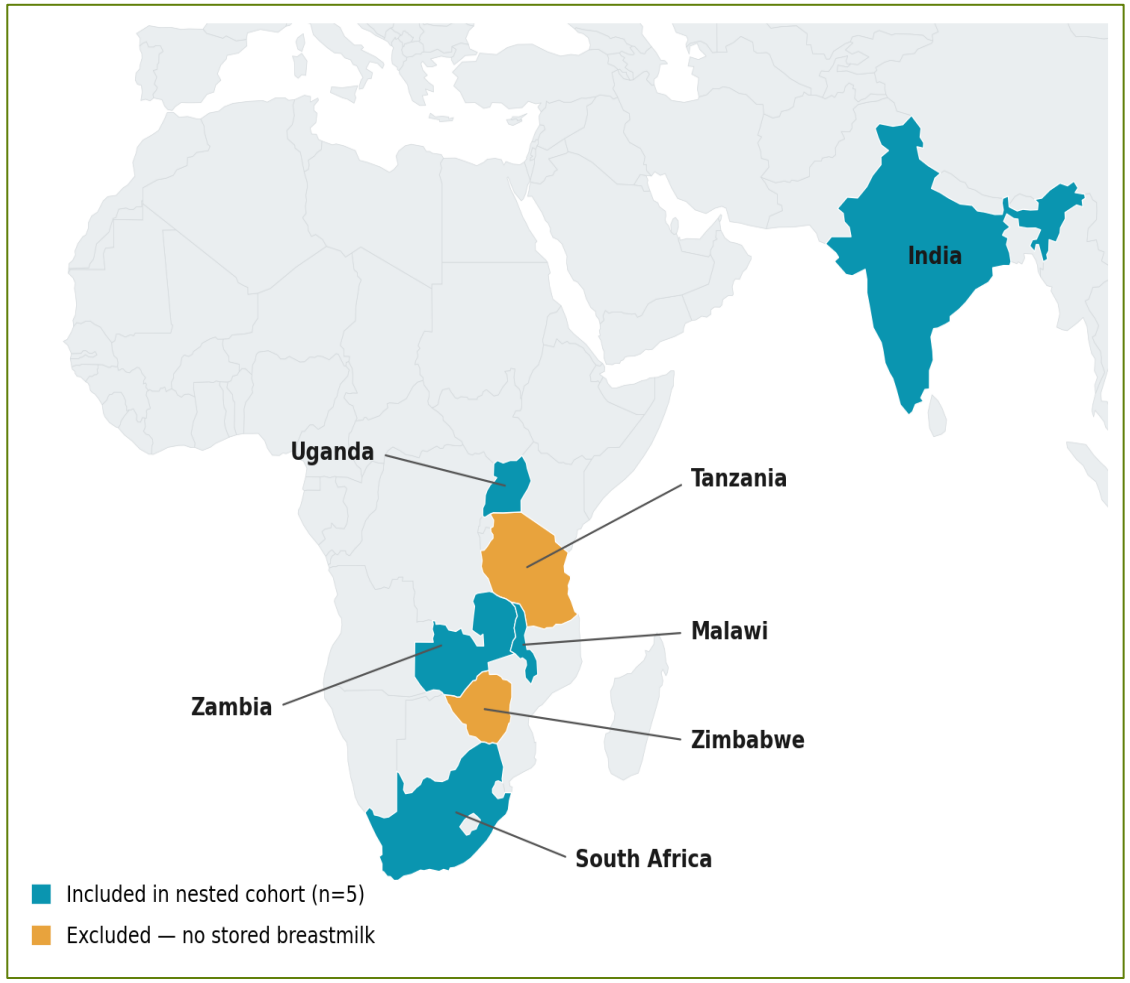
- Data are sparse on HIV-specific immunoglobulin responses in breastmilk and their role in breastmilk-associated transmission

[1] *Nduati R, John G, Mbori-Ngacha D, Richardson B, Overbaugh J, Mwatha A;Effect of breastfeeding and formula feeding on transmission of HIV-1: a randomized clinical trial published JAMA 2000 Mar;283(9):1167–74; PMID 10703779.*

[2] *De Cock KM, Fowler MG, Mercier E, de Vincenzi I, Saba J, Hoff E; Prevention of mother-to-child HIV transmission in resource-poor countries: translating research into policy and practice published JAMA 2000 Mar;283(9):1175–82; PMID 10703780*

[3] *Flynn PM, Taha TE, Cababasay M, Fowler MG, Mofenson LM, Owor M; Prevention of HIV-1 transmission through breastfeeding: efficacy and safety of maternal antiretroviral therapy versus infant nevirapine prophylaxis for duration of breastfeeding in HIV-1-infected women with high CD4 cell count (IMPAACT PROMISE) published JAIDS 2018 Apr;77(4):383–92; PMID 29239901*

Methods



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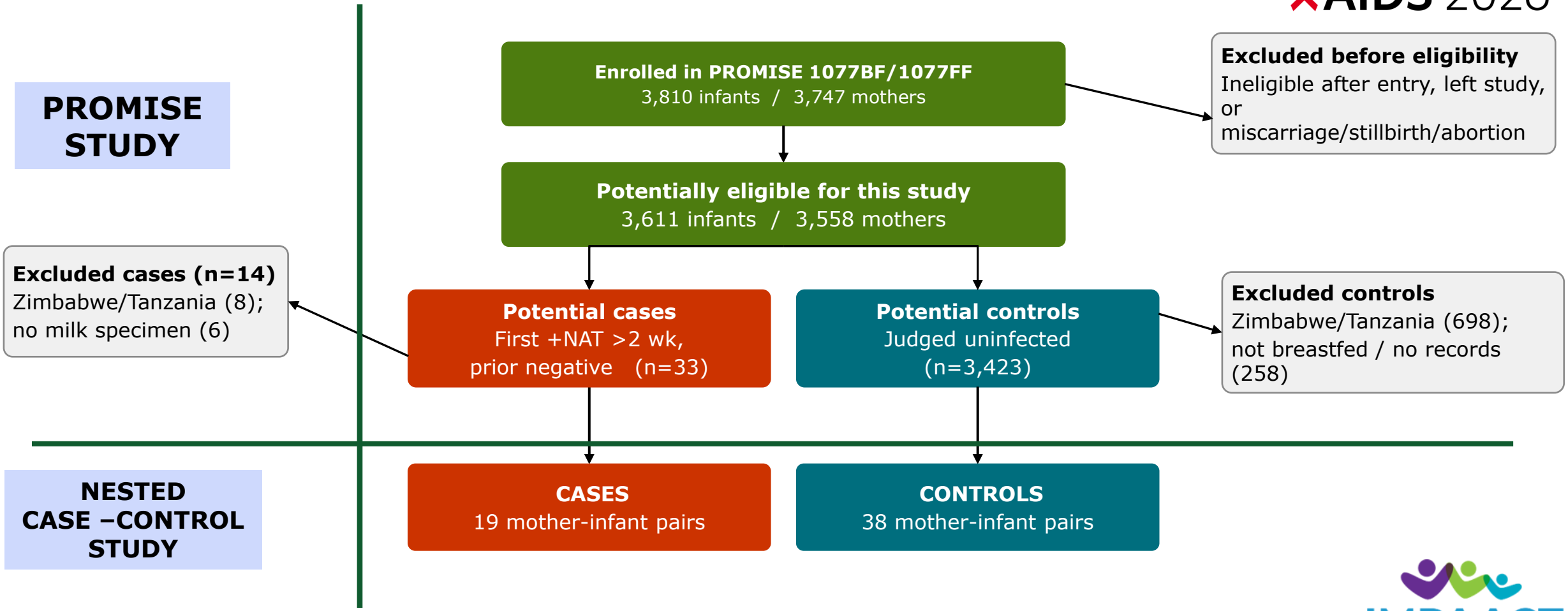
- Previously completed randomized multi-country trial (14 sites, 7 countries in SSA and India) of antiretroviral interventions to prevent vertical transmission; 3,611 live-born infants of women with HIV

Nested case-control design among breastfeeding participants

- **Cases (n=19):** Women with HIV (WHV)whose infants acquired HIV postnatally
- **Controls (n=38):** WHV whose infants did not acquire HIV postnatally
- Cases: controls matched 1:2 by site, specimen availability, & follow-up type:

  Follow-up type: postpartum randomization to maternal ART;OR postpartum randomization to infant prophylaxis (i.e., no maternal ART); or observational follow-up

Methods: Participant Flow



Controls matched 1:2 on enrollment site, follow-up type, and availability of a milk specimen at an age near the case specimen. Counts shown for infants.

Methods

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Maternal Human milk specimens:

- Collected at delivery (0–2 weeks) and closest to but before infant HIV diagnosis (cases) or matched infant age, site, and available breast milk specimen (controls)

Laboratory assays:

- 19 HMOs by HPLC (Bode Lab, UC San Diego)
- Ig isotypes/subclasses (IgM, IgA, IgG1/2/3/4) and HIV-1 gp120-specific IgG by ELISA (Luzuriaga Lab, UMass Chan)
- Data from the parent study on Breast milk RNA assays (only on transmission cases)

Statistical analysis:

- Conditional logistic regression of standardized $\log_{10}$-transformed HMO and Ig levels (reported aOR per 1-standard-deviation increase, adjusted for maternal age, plasma HIV RNA, and CD4 count at delivery, and infant gestational age at birth)
- Exploratory: among cases, HMO and Ig levels correlated with breastmilk HIV RNA viral load (Spearman's ρ)

Results: Participant Characteristics

Characteristic	Cases (n=19)	Controls (n=38)	Total (n=57)
Maternal age, median (IQR), years	26 (23, 29)	28 (22, 31)	27 (22, 30)
Country: Malawi / Uganda / S. Africa / India	58% / 21% / 16% / 5%	58% / 21% / 16% / 5%	58% / 21% / 16% / 5%
CD4, median (IQR), cells/mm³	496 (431, 548)	515 (446, 578)	508 (443, 553)
WHO Clinical Stage I	84%	100%	95%
Plasma HIV RNA >1,000 copies/mL at delivery	**79%**	53%	61%
Infant sex: female	53%	61%	58%
Gestational age at birth, median (IQR), weeks	38 (37, 40)	38 (38, 40)	38 (38, 40)
Breastfeeding duration, median (IQR), months	19 (12, 22)	17 (13, 20)	17 (12, 20)
Age at infant HIV diagnosis, median (IQR), months	8 (3, 14)	—	—

Results: Association of Human Milk Oligosaccharide Levels with Postnatal HIV Transmission

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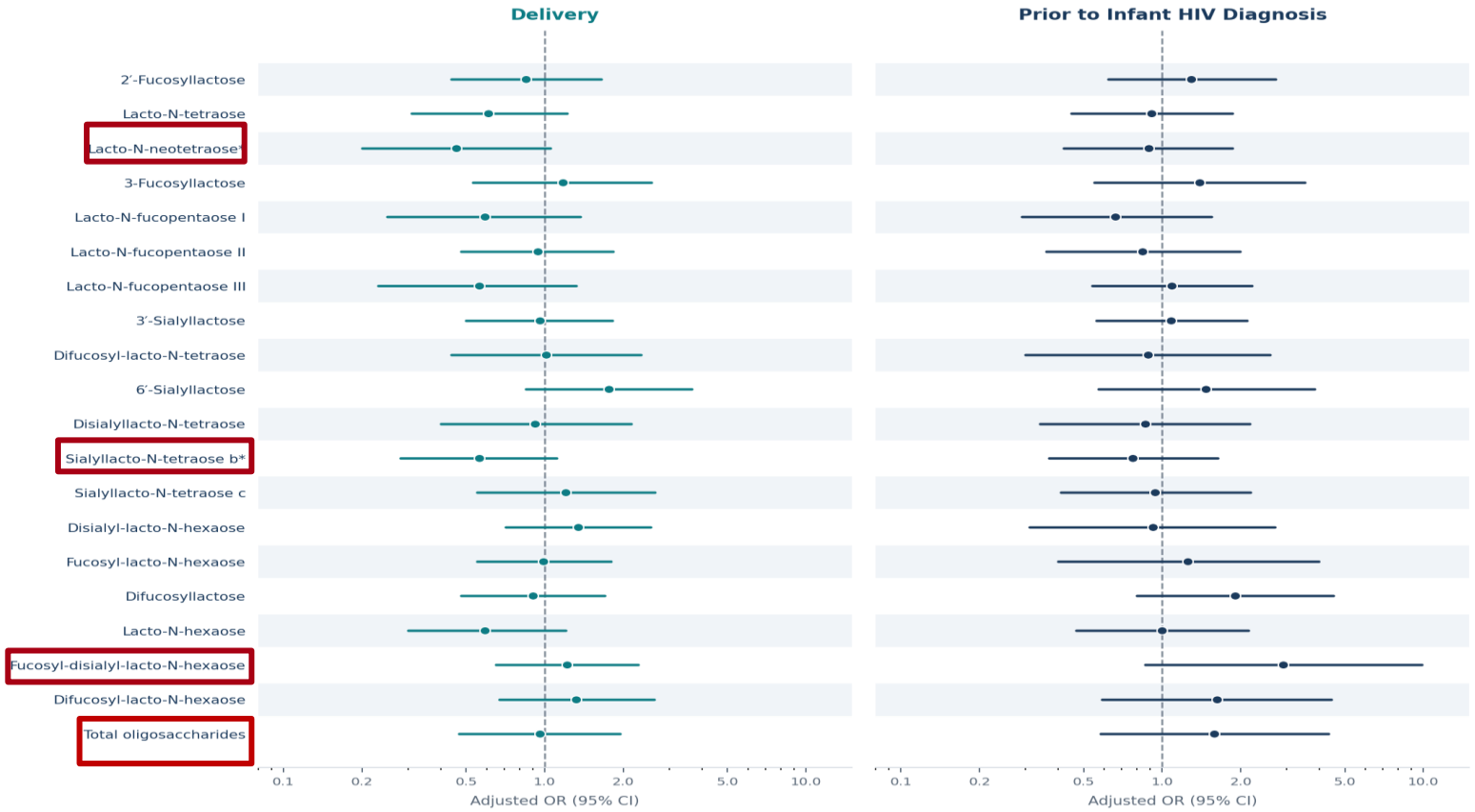
Lacto-N-neotetraose
Delivery: aOR 0.46 (0.20–1.05); p=0.065
trending ↓ Odds (NS)

Sialyllacto-N-tetraose b
Delivery: aOR 0.56 (0.28–1.11); p=0.096
trending ↓ Odds (NS)

Fucosyl-disialyl-lacto-N-hexaose
Prior to dx: aOR 2.91 (0.86–9.88); p=0.086
trending ↑ Odds (NS)

Total HMOs
Not associated with transmission at any timepoint



Delivery Prior to infant HIV diagnosis * p<0.10 (trending)

*aOR represents the change in odds of transmission per 1-SD increase in log_{10}-transformed HMO. * p<0.10 (trending); NS = not statistically significant (p>0.05).*

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Results: Association of Immunoglobulin Levels with Postnatal HIV Transmission

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HIV gp120-specific IgG

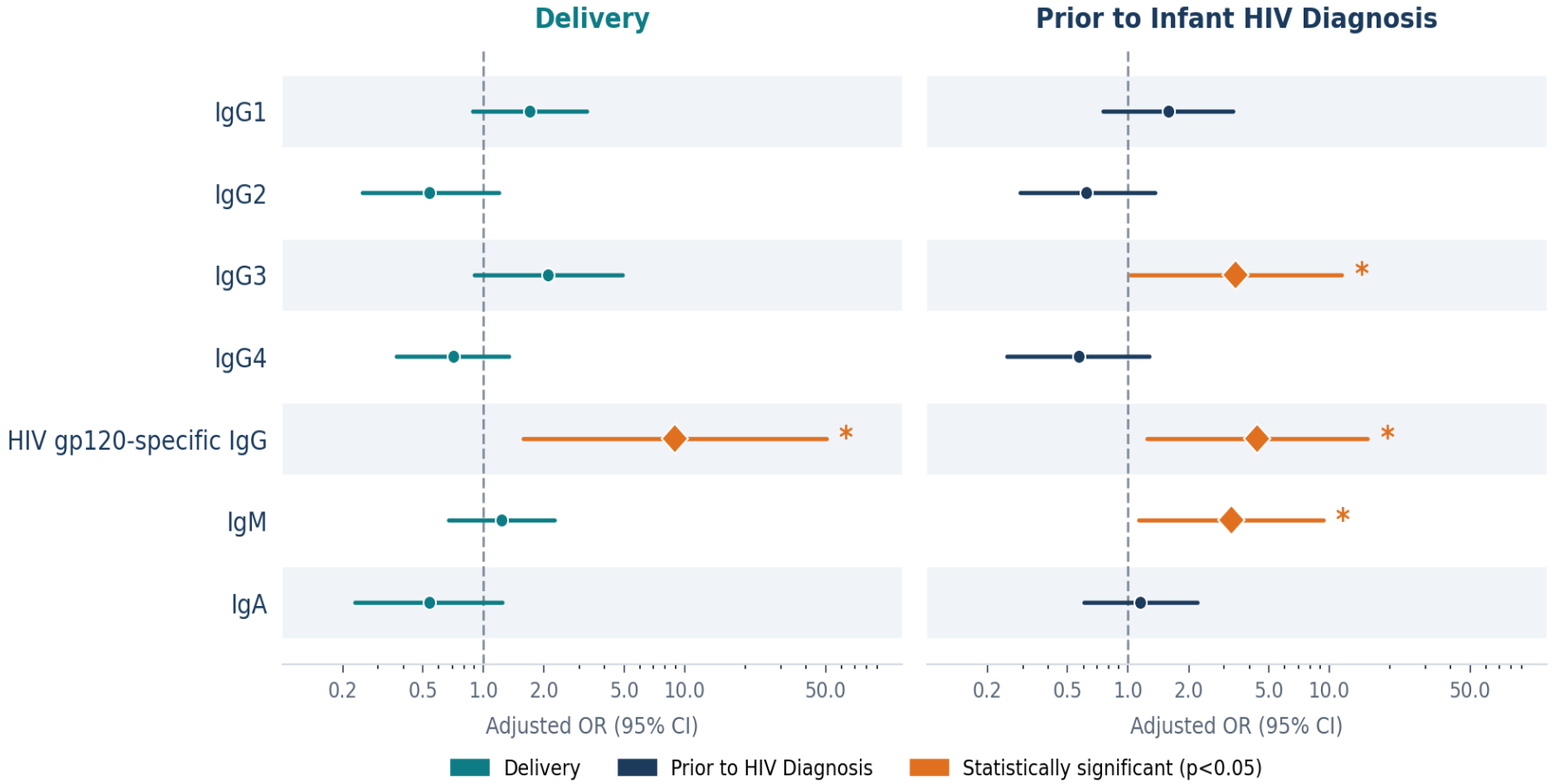
Associated with odds of transmission at delivery (aOR 8.9[1.6–50.7]) and prior to dx (aOR 4.4 [1.2–15.5]), p<0.05

IgG3

Associated with odds of transmission prior to dx: aOR 3.4 (1.02–11.5), p<0.05

IgM

Associated with odds of transmission prior to dx: aOR 3.3 (1.1–9.3), p<0.05



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Breastmilk Viral Load Correlations

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Among cases, breastmilk analyte levels were correlated with breastmilk HIV RNA viral load near the time of infant diagnosis (Spearman ρ):

Immunoglobulins

- IgG3 (ρ = 0.63), IgM (ρ = 0.51),HIV gp120-specific IgG (ρ = 0.45) **positively correlated**
- IgG4 (ρ = −0.40) **negatively correlated**

Human Milk Oligosaccharides

- 6’-Sialyllactose (ρ = 0.46) and sialyllacto-N-tetraose c (ρ = 0.40) **positively correlated**
- Lacto-N-neotetraose (ρ = −0.19) and sialyllacto-N-tetraose b (ρ = 0.03; our analysis fractions) **not correlated**

Ig associations tracked with viral load (may reflect local replication); the HMO fractions from our analysis did not, consistent with an effect independent of viral load

Exploratory Spearman rank correlations among cases; coefficients reported without significance testing (|ρ| ≥ 0.4 highlighted).

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Limitations

- Small sample size (n=19 transmitters) limited statistical power; several trends were observed but did not reach significance.
- Breastmilk HIV RNA PCR testing was only done for the WHV whose infants acquired HIV
- Findings from southern and eastern African settings, as well as India, may not be generalizable to other settings among breastfed infants born to mothers living with HIV

Conclusions

- Maternal human milk immune profiles may influence postnatal HIV transmission independent of ART regimen and maternal plasma viremia.
    - Specific HMO fractions, rather than total HMO levels, may have protective effects.
    - Higher levels of breastmilk immunoglobulins were associated with increased human milk viral load, suggesting local viral replication.
- Human milk viral dynamics may be a key determinant of postnatal HIV transmission and warrant further investigation.

Acknowledgements

Mentors & Co-authors **Jennifer Jao**; **Shahin Lockman**; Kristin Baltrusaitis; Patricia DeMarrais; **Adeodata R Kekitiinwa**; Lars Bode; Katherine Luzuriaga; Louise Kuhn; L. Chinula; S. Dadabhai; M. Owor; M.G. Fowler; P. Flynn; K. Spann; R. Brody; For the PROMISE Study Team

Data Team: Barbara Heckman; Kevin Knowles | Frontier Science

Laboratories: Bode Lab, UC San Diego (HMO assays by HPLC); Luzuriaga Lab, UMass Chan Medical School (Ig assays by ELISA)

Baylor Foundation Uganda leadership and CRS leadership: Dithan Kiragga; Patricia Nahirya Ntege; Grace Paul Kisitu; Adeodata R Kekitiinwa; Rogers Sekabira

JHU CTU team: Aaron Tobian; Philipa Musoke; Mary Glenn Fowler; Mahnaz Motevalli; Victoria Chou
The IMPAACT ECI team at FHI and the IMPAACT grants team at Johns Hopkins: Lisa Levy; Marisa Guptarak; Rachel Scheckter; Rachel Schmidt; Kim Enders; Dionne McGree

IMPAACT Early Career Investigator Award – Funded the project

AIDS 2026 – Travel Scholarship

Acknowledgements

- The PROMISE Protocol Team gratefully acknowledges the dedication and commitment of the more than 3,500 mother-infant pairs, their communities, and CAB representatives, without whom this study would not have been possible. The authors also wish to acknowledge the PROMISE 1077BF Protocol team, NIAID, NICHD, and NIMH, and the fourteen IMPAACT sites and staff. The study products were provided free of charge by Abbott, Gilead Sciences, Boehringer Ingelheim, and GlaxoSmithKline

- Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases (NIAID) with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH), all components of the National Institutes of Health (NIH), under Award Numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC) and UM1AI106716 (IMPAACT LC), and by NICHD contract number HHSN275201800001I. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH