Title: Breastfeeding with HIV: An Evidence-based Case for New Policy

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Précis

To help eliminate perinatal HIV transmission, the US Department of Health and Human Services recommends against breastfeeding for women living with HIV, regardless of viral load or combined antiretroviral therapy (cART) status. However, cART radically improves HIV prognosis and virtually eliminates perinatal transmission, and breastfeeding’s health benefits are well-established. In this setting, pregnancy is increasing among American women with HIV, and a harm reduction approach to those who breastfeed despite extensive counseling is suggested. We assess the evidence and ethical justification for current policy, with attention to pertinent racial and health disparities. We first review perinatal transmission and breastfeeding data relevant to US infants. We compare hypothetical risk of HIV transmission from breastmilk to increased mortality from sudden infant death syndrome, necrotizing enterocolitis and sepsis from avoiding breastfeeding, finding that benefits may outweigh risks if mothers maintain undetectable viral load on cART. We then review maternal health considerations. We conclude that avoidance of breastfeeding by women living with HIV may not maximize health outcomes and discuss our recommendation for revising national guidelines in light of autonomy, harm reduction and health inequities.
**Introduction**

To help eliminate perinatal HIV transmission, the United States Department of Health and Human Services (DHHS) strongly recommends avoidance of breastfeeding for women living with HIV (WLHIV), regardless of maternal viral load or combined antiretroviral therapy (cART) status.[1,2] However, cART radically improves HIV prognosis and virtually eliminates perinatal transmission, and breastfeeding’s benefits are well-established.[3,4] As more US WLHIV are pursuing pregnancy, some breastfeed despite recommendations, for which a harm reduction approach is proposed.[1,5-9] Conversely, breastfeeding is recommended for WLHIV in low-income countries given high-quality randomized controlled trials demonstrating 1-2% total perinatal transmission and decreased child mortality with cART starting in the third trimester and continued during breastfeeding.[10] However, these data come from settings where child mortality is high, largely from gastrointestinal and respiratory infections, and replacement feeding is often not “affordable, feasible, acceptable, sustainable or safe,” limiting generalizability to US populations.

To assess US policy, we conducted a critical review of primary, secondary and gray literature relevant to perinatal transmission, risks and potential health benefits of breastfeeding for infants and women in high-income settings. US health surveillance data, government and professional society guidelines were reviewed.[11] Pubmed, EMBASE, Cochrane, Web of Science and Google searches were performed in 10/2016 and periodically updated through 9/2018. Scoping review of literature cited in official documents and review articles was performed. MG

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conducted the review; findings were vetted by HT, CT, and JC in their respective areas of expertise. Supporting data and nonessential references are included in online supplement due to space constraints.

First, we delineate the risk of HIV transmission from breastfeeding for HIV-exposed US infants. Next, we delineate the risks to this same population of children if they are not breastfed, including excess mortality from sudden infant death syndrome (SIDS), necrotizing enterocolitis (NEC) and sepsis. We then discuss maternal health considerations. We conclude that strict avoidance of breastfeeding by WLHIV may not maximize health outcomes, particularly given existing infant and maternal health disparities (see Figure 1). Supported by ethical considerations of autonomy, harm reduction and social justice, we suggest eliminating the categorical recommendation against breastfeeding for cART-adherent WLHIV.

**Clinical Considerations**

**Risk of Perinatal HIV from Breastfeeding**

Perinatal transmission in high-income-countries continues to decrease with more effective, tolerable cART and treatment upon HIV diagnosis, including in pregnancy.[12] Approximately 8700 (95% CI: 8400-8800) US WLHIV deliver annually.[5] In 2014 an estimated 63 infants

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1 See data tables 1-3 in online supplement. Insert Figure 1 at beginning of Clinical Considerations section
(0.8%) contracted perinatal HIV.[13] However, viral load (VL) is the greatest predictor of perinatal transmission, and infants whose mothers have detectable VL (>50 copies/ml) are disproportionately affected.[14] Factors that increase the risk of perinatal transmission include high VL, as in acute HIV during pregnancy or breastfeeding, non-adherence with cART, inadequate prenatal care, injection drug use, substance use, CD4 T cell count <200, age ≤24, genital infections, and not receiving DHHS recommended antepartum cART, intrapartum care or postpartum infant prophylaxis.[14-17]

Conversely, cART-adherent women with undetectable VL near delivery have very low perinatal transmission rates, e.g. 0.05% from 2000-2011 per United Kingdom/Ireland national surveillance data.[12] Those who transmit HIV despite attaining undetectable VL before delivery have significant obstetrical risks, such as premature rupture of membranes of unknown duration in the setting of placenta previa, placental abruption, or preterm delivery shortly after achieving virologic control.[14] Initiation of cART early in pregnancy further reduces transmission, irrespective of VL. A French national cohort had 0.2% transmission with preconception cART vs. 0.4%, 0.9%, and 2.2% with first, second, or third trimester initiation.[15] The DHHS states that VL should be undetectable on cART before attempting conception.[1] In France (n=2615) and United Kingdom/Ireland (n=1894), transmission was 0.0% with preconception cART and undetectable VL near delivery.[12,15]

However, evidence above does not account for risk of breastmilk transmission, since high-income governments recommend WLHIV avoid breastfeeding. These policies have discouraged

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the study of breastfeeding outcomes in high-income settings, and current US perinatal HIV exposure data are insufficient for guiding practice.[17] For example, a chart review of HIV-exposed infants found that perinatal HIV was more common among the 1% (80/8054) who breastfed (aOR 4.6, 95% CI 2.2-9.8), however key details like maternal VL were omitted.[16] Meanwhile, in our 2016 survey, 33% of providers reported having patients who breastfeed despite recommendations, and latest US guidelines have introduced a harm reduction approach, suggesting possible ascertainment bias in the review above in which perinatal HIV cases may have been more likely to have their breastfeeding status exposed.[18] Surreptitious breastfeeding and coincident nonadherence with other perinatal HIV recommendations may further confound the picture, though a harm reduction approach may attenuate these concerns moving forwards.

In contrast, a 2011 systematic review found 8 studies from low-income settings in which breastfeeding for 6 months was associated with 0–1% perinatal transmission (n=3202).[9] In Mma Bana, the largest cohort in the review, 709 women initiated cART between 26-34 weeks of pregnancy, and at 6 months postpartum there were two breastmilk transmissions (0.3%): one mother was non-adherent with medications, and the other had VL >170,000, delivered prematurely, and breastfed before achieving viral suppression.[17] One meta-analysis was identified which included 6 studies (n=2109) with pooled transmission of 1.08% (95% CI 0.32-1.85) over 6 months of breastfeeding, though this was deemed ‘very low’ quality evidence, and applicability to US population is limited by absent VL or adherence data, late initiation of cART, and lack of standard postnatal infant prophylaxis.[20] The more recent PROMISE study (n=2431) also found 0.3% transmission through 6 months of breastfeeding.[21] Breastmilk

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transmission in high-income settings may be similar, and cART-adherence with undetectable VL may virtually eliminate transmission risk, much as it has from pregnancy and delivery.

**Health Benefits of Breastfeeding for Infants**

Breastfeeding decreases major causes of US infant mortality, including SIDS and complications of prematurity.[3,4,22] In a meta-analysis of 23 studies, SIDS was half as likely among breastfed vs. formula-fed infants.[4] NEC and sepsis have highest incidence among non-breastfed premature and low birthweight infants, and mortality is inversely related to weight and gestational age.[4,22-24] Prematurity and low birthweight affects 11.4% and 8.2% of US infants, respectively, and breastfeeding decreased NEC 58% in four randomized-controlled trials and urosepsis 69% in a large preterm cohort.[4,23] A UK study modeling preterm infant feeding estimated 190 excess deaths from NEC or sepsis annually if no premature infants breastfeed (n=51,703).[24]

Notably, black infants suffer 2.2-fold mortality (3.5-fold preterm-related death) and black women have twentyfold higher incidence of HIV when compared to white counterparts.[22,25] Thus, accounting for existing health disparities is critical for appreciating potential benefits of breastfeeding in this population. For example, SIDS causes 38.7 deaths/100,000 US livebirths, but 74.0/100,000 for black infants.[26] HIV-exposed US infants are also more likely to have low birthweight (22.9%, n=980) or be preterm (18.6% overall, and 21% among women receiving cART in the first trimester; n=1869).[27] If US WLHIV breastfed, there may be significantly fewer SIDS and prematurity-associated deaths among their infants.

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Breastfeeding also prevents potentially fatal gastroenteritis (OR 0.36, 95% CI 0.18–0.74) and hospitalization for respiratory infections (RR 0.28, 95% CI 0.14–0.54) for US infants.[4,26] Acute otitis media, which affects >80% under 3 years, is decreased 50% with breastfeeding.[4] Victora et al presented confounder-adjusted meta-analyses showing: 35% reduction in type 2 diabetes; 13% lower rate of overweight/obesity; 9% reduction in asthma; 19% reduction of childhood leukemia; and, an increase in child intelligence quotient (IQ) of 3.4 points.[3] Exclusive breastfeeding during the first 6 months of life with continued breastfeeding for at least the first year is the most effective strategy for conferring these benefits, and is the normative standard for infant feeding in high income settings.

Weighing Risks and Benefits for Infants

To determine the best feeding method for HIV-exposed US infants, we must reconcile the hypothetical increased duration of perinatal transmission risk with current excess health risks from lack of breastfeeding, as outlined above.[28] First, while breastmilk transmission in low-income-countries is <1% with cART, many of the data come from clinical trials, which may affect cART-adherence by providing medications and other support. For example, in Mma Bana >90% achieved and maintained viral suppression during pregnancy and 6 months of breastfeeding.[19] Although cART uptake among US WLHIV is increasing over time, adherence remains suboptimal: population-based data from New York State 2008-2010 (n=980) demonstrated that only 75% were virally suppressed at delivery, and among those, just 44% remained suppressed one year postpartum.[28] Retrospective studies from Mississippi and Philadelphia found that <40% were optimally engaged in HIV care throughout the year after
Postpartum non-adherence to cART and loss to care among US WLHIV yield significant concerns about the safety of breastfeeding for their infants.

Simultaneously, data demonstrate how HIV diagnosis >2 years before pregnancy, preconception HIV care, early and adequate prenatal care, older maternal age, viral suppression at delivery and low infant birthweight, among other factors, can predict postpartum retention in care and sustained viral suppression.[29-32] Documented breastmilk transmissions appear to occur with cART nonadherence, detectable VL, or loss to follow up, and known risk factors could inform individualized infant feeding recommendations. Momplaisir et al highlight the interpersonal, community and health systems-level issues impacting postpartum retention, suggesting a five-pronged approach to improve outcomes.[30] Importantly, a substantial proportion of US WLHIV do maintain ongoing viral suppression, and breastfeeding itself may increase postpartum cART-adherence by prolonging unified maternal and child interests. Development of clinical algorithms to identify candidates for breastfeeding, and support for postpartum retention in HIV care would be crucial for introducing personalized feeding recommendations for HIV-exposed US infants.

Notably, in the US, perinatal HIV is a serious, but chronic disease with very low mortality (0.05/100 child-years) and morbidity dominated by treatment side-effects.[33,34] Thus, breastmilk transmission of HIV may not substantially impact infant mortality, and any increased HIV-morbidity might be compensated for by breastfeeding’s health benefits. One concern regarding potential HIV-related morbidity is risk of genotypic resistance for perinatally infected infants whose mothers breastfeed without viral suppression. However, this is less likely to...
impact US infants, as it has occurred among low-income-countries among infants, including those infected antepartum/intrapartum, who received prolonged antiretroviral prophylaxis for breastfeeding in lieu of maternal cART or whose mothers first initiated cART postpartum.[35]

Finally, regarding theoretical increased drug toxicity for infants via breastmilk or prolonged prophylaxis, studies have shown that severe adverse events (SAEs) are equally rare for 1 vs. 28 weeks of breastmilk exposure, and found no differences between breastfeeding infants receiving 6 weeks vs. 6 months of prophylaxis.[10,36] While infant antiretroviral prophylaxis and breastmilk exposure appear safe and well tolerated, recommendations for optimal maternal treatment and infant prophylaxis during breastfeeding and weaning in US populations continue to evolve.[1,37]

Overall, the significant benefits of breastfeeding may outweigh risks for infants of cART-adherent US WLHIV. Likewise, while 6 months of breastfeeding may confer the majority of benefits with acceptably low risk, the duration of breastfeeding that would optimize risks/benefits for infants is beyond the scope of this discussion, but important to address. A statistical model would be helpful for extrapolating how alternative feeding recommendations would impact morbidity and mortality for HIV-exposed US infants.

**Health Benefits of Breastfeeding for Women**

Breastfeeding also affects leading causes of US women’s mortality, including heart disease (#1), cancer (#2), diabetes (#7), and hypertension (#13).[26] In the Nurses’ Health Study (n= 89,326),

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2 years of cumulative breastfeeding reduced myocardial infarction by 23%, and any breastfeeding decreased hypertension, diabetes and hyperlipidemia, with direct dose-response.[38] Breastfeeding also decreases stroke by 23%.[39] Meta-analysis showed that breastfeeding decreased type 2 diabetes by 32% (RR 0·68, 95% CI 0·57–0·82).[3] Breastfeeding consumes ~480 kcal/day, increasing postpartum weight loss, and body mass index was 1% lower per 6 months of breastfeeding among 740,000 British women.[3,40]

Breast cancer is US women’s most common cancer and second leading cause of cancer death.[26] Victora et al report adjusted metaanalyses demonstrating 7% reduction of invasive breast cancer with breastfeeding in high-income-countries, and worldwide premenopausal breast cancer decreased 4.3% per year of breastfeeding.[3] Ovarian cancer is the fifth leading cause of US women’s cancer death, and breastfeeding reduces risk by 30%.[3,26] In a 2017 meta-analysis, risk of endometrial cancer, the most common gynecologic malignancy among US women, was decreased 11% with breastfeeding.[41]

Per the American College of Obstetricians and Gynecologists, "underserved women are disproportionately likely to experience adverse health outcomes that may improve with breastfeeding."[40] WLHIV are predominantly socioeconomically disadvantaged women of color, and avoiding breastfeeding compounds their already increased obesity, hypertension, diabetes, heart disease, stroke and cancer risks.[25,33] For example, black women are especially susceptible to hormone-and-triple-negative breast cancers, whereas breastfeeding could decrease that risk by 19%.[42] While causality remains unclear, postpartum depression has a strong

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inverse relationship to breastfeeding, and current guidelines may worsen WLHIV’s undue psychiatric morbidity.[3,43]

Lastly, exclusive breastfeeding induces lactational amenorrhea, preventing 98% of pregnancies for six months.[44] This significantly reduces risks of subsequent short interval pregnancies: maternal and infant death, uterine rupture, placental abruption, placenta previa, preterm rupture of membranes, fetal growth restriction and premature delivery.[45] WLHIV, like many minority and low-income women, disproportionately experience unintended pregnancies and their sequelae.[40] Ultimately, breastfeeding protects US women’s health, and recommending against breastfeeding especially harms minority and low-income women.

Ethical Considerations

Autonomy

Our review illustrates the clinical equipoise regarding optimal feeding practices for US WLHIV.[37,46] Critically, the prevailing argument that curtailing women’s autonomy is justified given the value of protecting infants’ best interests is undermined by the potential benefits of breastfeeding for infants whose mothers maintain undetectable VL. The addition of “patient-centered, evidence-based counseling” for women who question the recommendation against breastfeeding and harm reduction strategies for “when women with HIV choose to breastfeed despite intensive counseling” make major strides towards respecting women’s autonomy.[1] However, discussing breastfeeding as a matter of maternal “choice” may trivialize

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the health benefits that infants and women stand to gain. Yet, current guidelines state that “breastfeeding is not recommended [sic]” and prompt providers to address “potential barriers to formula feeding,” falling short of the genuine shared-decision making clinical equipoise enjoin.[1]

While DHHS recommendations do not have the force of law, legal authority has loomed large for WLHIV who attempt to breastfeed.[47] The American Academy of Pediatrics has suggested the “rare circumstance” in which women with undetectable VL on cART may breastfeed “despite intensive counseling” without constituting “grounds for automatic referral to Child Protective Services.”[2] Women cannot make free, informed choices if they fear breastfeeding may jeopardize parental rights, particularly when “intensive counseling” continues immediately-postpartum period, when lactation support is critical for successful breastfeeding. Telling women not to breastfeed may also subject them to social pressure, grief, shame, and guilt, further curtailing maternal autonomy.[48]

The availability of safe formula in the US is cited as justification for the recommendation against breastfeeding for WLHIV.[1] Instead, donor human milk and formula could be a part of a shared decision-making framework that could facilitate informed collaboration between WLHIV and their physicians.[49] Frequent healthcare visits during pregnancy and infancy allows for ongoing risk-benefit assessments and close monitoring. Anticipatory guidance and heightened surveillance paired with skilled breastfeeding support help minimize transmission risk, for example, by promoting early detection of mastitis and prompting unilateral pumping and

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discarding of breastmilk during acute infection.[1] Recent updates to DHHS guidelines offer support for WLHIV who breastfeed “despite intensive counseling” and provide valuable practical guidance for providers regarding postpartum management. However, clinical equipoise regarding infants’ interests suggests that the recommendation against breastfeeding may be replaced with individualized, evidence-based recommendations and strategies to promote cART-adherence.

**Harm Reduction**

Acknowledging that a wide range of factors, from familial pressures and stigma to awareness of health benefits and desire for bonding, may lead WLHIV to breastfeed contrary to US recommendations, Levison and others have promoted a harm reduction approach.[7,8] They argue that a hardline stance against breastfeeding may increase perinatal transmission by prompting some to conceal their choice from providers and others to avoid treatment altogether.[7] They emphasize replacement feeding as optimal, but suggest exclusive breastfeeding with cART for “those who decide to breastfeed despite being fully informed of the risks.” Harm reduction compassionately recognizes the difficult, often complex choices individual WLHIV face. Critically, its adoption may assuage providers’ fear of legal or professional repercussions from promoting informed feeding choices.

However, harm reduction and current DHHS Recommendations treat breastfeeding with HIV as a *harm*, and thus may not be the appropriate framework for approaching this issue. First, with cART-induced viral suppression, breastfeeding’s health benefits may outweigh its risks, whereas
avoiding breastfeeding may cause net harm. Likewise, routine cesarean delivery for WLHIV was discontinued given evidence that iatrogenic harms from surgery outweighed marginal reductions in perinatal transmission when risk was already very low due to maternal virologic control.[1,9] Furthermore, retaining the expectation that WLHIV avoid breastfeeding and asserting that breastfeeding is “reasonable but inferior,” introduces judgment that may unintentionally jeopardize forthright patient-provider interactions, compromising both shared decision-making and the disclosure required for breastfeeding women to participate in observational studies.

Finally, 84% of HIV healthcare providers have stated that they would require government and/or professional society guidelines before supporting breastfeeding among WLHIV with undetectable VL, and the DHHS continues to strongly recommend against breastfeeding. It is unclear whether acceptance of harm reduction truly satisfies those criteria for individual providers or if it will lead to corresponding updates in hospital and health system policies.[18] In this regard, harm reduction may be insufficient to substantially change practice, promote informed decisions or close evidence gaps.

Health and Socioeconomic Inequities

Current recommendations against breastfeeding likely further disadvantage already disadvantaged women and infants, largely due to existing socioeconomic and racial disparities. Unfortunately, minority women suffer disproportionately from diseases breastfeeding may prevent, such as obesity, hypertension, heart disease, stroke, depression and female cancers.[39-42] Additionally, current policy imposes financial hardship via formula’s costs, including loss of

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Women Infant and Children (WIC)’s breastfeeding incentives, and lost wages due to infant or maternal illness.[50,51] Ironically, WLHIV who adhere to healthcare recommendations generally are least likely to transmit HIV and most likely to experience current recommendations as unjust. The extent to which postpartum adherence can be addressed by increasing awareness, care coordination, peer-and-technology-based interventions, and long-acting cART formulations puts the onus on the US healthcare system to close gaps that undermine WLHIV’s access to breastfeeding’s benefits.

Further, HIV-exposed US infants disproportionately experience health risks that could be mitigated by breastfeeding. In 2013, mortality for black infants was more than double that of white infants, chiefly attributed to greater burdens of prematurity and SIDS.[22] Since preconception cART is associated with prematurity and low birthweight, the HIV-exposed infants least likely to contract HIV are most likely to be harmed by not breastfeeding.[27] Socioeconomically disenfranchised infants would especially benefit from decreased diabetes, obesity, and asthma, plus a higher IQ with corresponding adult educational attainment and income. While donor breastmilk may partially alleviate consequences of current policy, most HIV-exposed infants do not have access to banked milk, and breastfeeding itself is more beneficial, feasible, and cost-effective.[28,52] Discouraging WLHIV from breastfeeding may inadvertently contribute to poor health outcomes among vulnerable infants and women, systematically reinforcing racial inequity by deepening disparities in health and wealth.[53,54]

**Conclusion and recommendations**

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Given potential benefits of breastfeeding and very low perinatal transmission risk with undetectable VL, breast may be best for infants of cART-adherent WLHIV. As with decisions about having children, WLHIV have a right to make an informed choice about breastfeeding, especially given clinical equipoise regarding infant outcomes, maternal health considerations and personal significance. Additionally, women and select HIV-exposed infants may be harmed by avoiding breastfeeding, and further policy change may be required to fully support shared-decision making, necessitating an approach beyond harm reduction. Finally, avoiding breastfeeding may inadvertently increase health inequities by further disadvantaging WLHIV and their infants.

We suggest DHHS recommendations include breastfeeding as an option for cART-adherent WLHIV who maintain undetectable VL, ideally within a prospective cohort emphasizing informed consent and close observation. Clinical tools should be developed to help providers identify dyads who may safely breastfeed and to facilitate shared-decision making, and care should be taken to ensure that patient counseling is unbiased and evidence-based. Case management should ensure ongoing cART access, and donor milk or, if unavailable, formula should be subsidized when breastfeeding is not recommended or desired.

References

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Figure 1. Health risks of not breastfeeding for United States women living with HIV and their infants

Adverse Health Outcomes
Increased Without Breastfeeding

Infants
- Short Term
  - Infection
    - NEC
    - Sepsis
    - GE
    - PNA
    - AOM
    - UTI
  - SIDS
- Long Term
  - Obesity
  - Asthma
  - DM
  - Leukemia
  - Lower IQ
  - 2nd Sibling
- Short Birth Interval
  - SGA
  - LBW
  - Perinatal Death

Women
- Cancer
  - Breast
  - Uterus
  - Ovary
  - HTN
  - Obese
  - DM
- Metabolic Syndrome
  - CAD
  - MI
  - Stroke
- Obstetric Complications
  - Unintended Pregnancy
    - Short birth interval + prior CS
      - Uterine Rupture
      - Placental Abruption
      - Placenta previa

Health problems for which WLHIV and their infants have increased baseline risk due to health disparities

NEC= necrotizing enterocolitis, GE=gastroenteritis, PNA=pneumonia, AOM=acute otitis media, UTI=urinary tract infection, DM=diabetes mellitus, LBW=low birthweight, PTB=preterm birth, HTN=hypertension, CAD=coronary artery disease, MI=myocardial infarction, CS=cesarean section
### Table 1: Risk of Vertical Transmission of HIV with cART

<table>
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<tr>
<th>Ref</th>
<th>Location</th>
<th>Study Group</th>
<th>Study design</th>
<th>Years (data collection, if available, or publication)</th>
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▪ VT declined from 2.1% in 2000-2001 (17/816, 95% CI: 1.2–3.3%) to 0.46% in 2010-2011 (9/1975, 95% CI: 0.21–0.86).  
▪ VT was 0.09% (6/6345) with undetectable VL (<50 copies/ml) near delivery, and 0.05% (2/3859) with undetectable VL on cART.  
▪ With preconception cART: 93% had undetectable VL at delivery (1894/2045), 5% were virally suppressed (50–399 copies/mL; 101/2045), and 2% had ≥400 copies/mL (50/2045).  
▪ With preconception cART: overall VT was 0.19% (4/2105), and VL was detectable (n = 3) or missing (n = 1) for transmitting mothers.  
▪ No transmissions occurred among those with preconception cART and undetectable VL at delivery (n=1894). |
▪ VT was 0.2% (6/3505) with preconception cART, vs. 0.4% (3/709), 0.9% (24/2810), and 2.2% (23/1051) for those starting during the first, second, or third trimester (P < .001). |
| 3   | United States                 | Ponce Family and Youth Clinic of the Grady Health Systems | Retrospective chart review          | 2005-2012                                             | ▪ In review of all perinatal HIV cases treated in a regional referral center Atlanta, GA during this period, 24/27 (89%) were delivered by mothers with detectable VL.  
▪ Of those perinatally infected infants who delivered in the setting of undetectable VL, each had additional risk factors: prolonged rupture of membranes of unknown duration, placental abruption, and preterm delivery after third trimester VL >100,000.  
▪ Clear risk factors for VT: insufficient cART and/or prenatal care, illicit drug use |
| 4   | United States                 | IMPAACT                                           | Prospective cohort                  | 2002-2011                                             | ▪ In this multicenter study, 671 ART-naïve women started cART during pregnancy and 13.1% had a detectable VL at delivery.  
▪ 91.4% (117/128), 87.7% (399/455) and 76.1% (67/88) starting in first, second and third trimesters, respectively, achieved undetectable VL by delivery (P = 0.003).  
▪ The only case of VT (0.2%) in this cohort had third trimester initiation, nonadherence to cART, and VL >1000 near delivery. |
| 5   | Malawi, Mozambique, Tanzania, Rawanda, Botswana, Uganda, and Kenya* | DREAM, Mitra, Mitra Plus, AMATA, Mma Bana, Kisumu | Systematic review                    | 2001-2009                                             | ▪ In 8 high quality clinical trials, up to 6 months of exclusive BF while on cART was associated with 0–1% postnatal VT. |
### Supplementary Tables

<table>
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<th>Study Description</th>
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<td>6</td>
<td>South Africa, Malawi, Tanzania, Uganda, Zambia, Zimbabwe and India*</td>
<td>PROMISE</td>
<td>Randomized controlled trial 2006-2011</td>
<td>* Postnatal VT (n=2431) after 6, 9 and 12 months of BF with maternal cART was 0.3% (95% CI 0.1-0.6), 0.5% (95% CI 0.2-0.8) and 0.6% (95% CI 0.4-1.1), respectively.</td>
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| 7 | Botswana*                                                                         | Mma Bana     | Randomized controlled trial 2006-2008 | 730 women initiated cART from 26-34 weeks:  
  * At enrollment: 13.6% had VL ≤1000, 19.6% had VL ≥100,000 and 23.3% had AIDS.  
  * At 6 months postpartum, >90% had achieved and maintained viral suppression (<400 copies/mL) during pregnancy and BF.  
  * Total VT was 1.1% (8/709), with 0.3% postnatal transmissions (2/709).  
  * Of the two postnatal transmitting mothers, one postnatal had undetectable VL at delivery but subsequent “adherence issues” (by pill count or self-report); the other had VL >170,000 at enrollment and delivered at 32 weeks with a detectable VL. |
| 8 | Malawi*                                                                           | BAN          | Randomized controlled trial 2004-2010 | 849 infants BF for 28 weeks while mothers took cART:  
  * Grade 3 or 4 adverse events included: 0.4% transaminitis (3), 19.6% anemia (166), 0.5% leukopenia (4), 1.1% thrombocytopenia (9), and 0.1% hypersensitivity rash (1).  
  * These infants did not have an increased rate of events compared to 668 controls with just 1 week of postpartum maternal prophylaxis (RR 1.1; 95% CI 0.86-8.45). |
| 9 | Tanzania*                                                                         | Kilombero and Ulanga Antiretroviral Cohort (KIULARCO) | Prospective cohort 2013-2016 | 215 women started ART before delivery, and continued it while exclusively BF for ≥ 5 months:  
  * During BF, 91% of mothers had VL <1000 copies/mL, with 75% <100 copies/mL.  
  * Two infants (1%) were infected from BF: one mother had high VL (144,111 copies/mL) one month postpartum, and the other mother stopped ART during BF.  
  * There was no VT through BF among mothers with suppressed VL in this cohort |
| 10| Mozambique, Malawi, Kenya, South Africa, Tanzania, Uganda, Zimbabwe, and India*   | HPTN046 trial, Kisumu, BAN, DREAM, Mitra Plus, Vicente Ferrer HIV Cohort Study (VFHCS) | Systematic review and meta-analysis 2003-2010 | Meta-analysis of 6 studies, including 3 cohorts embedded in RCTs and 3 observational studies, published 2009-2012, comprising 2109 BF infants with mothers on cART:  
  * In pooled analysis, postpartum VT after 6 months of BF was 1.08% (95% CI 0.32-1.85), with range 0.24% (1/413; 95% CI 0.0%-1.40%) to 3.10% (4/127; 95% CI 1.20%-7.80%).  
  * Limited or absent maternal VL or adherence data, routine initiation of cART late in pregnancy for majority of participants, many BF without viral suppression, rare preconception cART only in the setting of advanced HIV/AIDS, and infants did not receive current standard-of-care prophylaxis.  
  * Very low quality evidence (GRADE profile) with “very serious” risk of bias, “very serious” inconsistency (I²=66.4%), “serious” indirectness, “not serious” imprecision. |
Table 2: Impact of Breastfeeding on Infant Health in High Income Countries

<table>
<thead>
<tr>
<th>Ref</th>
<th>Location</th>
<th>Study design</th>
<th>Years (data collection, if available, or publication)</th>
<th>Data</th>
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| 11  | International     | National surveillance data             | 2014                                                 | ▫ Under-5 child mortality is 6.5/1000 in the US, vs. 83.1/1000 livebirths in Sub-Saharan Africa  
▫ Gastrointestinal and respiratory infections are leading causes of child mortality in low-income-countries, but not in high-income-countries.  
▫ In the US 83% of under-5 child deaths occur in the first year of life, a similar proportion to low-income-countries. |
| 12  | United States     | National surveillance data             | 2013                                                 | ▫ Infant mortality (5.96/1000 livebirths) is predominantly from complications of prematurity (36.1%) (eg. NEC, sepsis), and SIDS (6.7%).  
▫ Preterm infants disproportionately bear the morality burden, as they comprise 11.4% of livebirths, but 66.4% of deaths.  
▫ Infant mortality per 1,000 livebirths was 11.11 for non-Hispanic blacks vs. 5.06 for non-Hispanic whites, largely attributed to disparities in death from prematurity and SIDS (3 and 2 times higher mortality, respectively). |
| 13  | United States     | Prospective cohort and retrospective review | 2007-2010                                           | ▫ 18.6% of HIV-exposed infants are preterm (n=1869), with highest rates of spontaneous preterm delivery among those with preconception cART (OR 1.59, 95% CI 1.10-2.30).  
▫ Preterm birth occurred among 155 of 748 women (21%) with first-trimester exposure to cART and among 155 of 924 women (17%) with initial exposure to cART during the second or third trimester (P =.043, by the Fisher exact test).  
▫ Very preterm birth occurred among 3% of those with first-trimester exposure and among 1% of those with later exposure to combination regimens (P =.005, by the Fisher exact test), with risk up to 4 times greater with PI containing ART regimens, adjusted analysis (adjusted OR, 4.17; 95% CI, 1.70–10.26; P =.003), compared with no combination regimen in the first trimester. |
| 14  | United States     | Prospective cohort                     | 2001-2011                                            | ▫ Of 183 HIV-exposed infants, 31.2% were small for gestational age ≤10th percentile, with 12.6% weighing ≤3rd percentile. |
| 15  | France            | Prospective cohort                     | 2005-2009                                            | ▫ HIV-exposed infants (n=11,377) were twice as likely as the general population to be premature, with rates highest among those with preconception treatment. |
| 16  | High Income Countries | Confounder-adjusted meta-analyses       | 2016                                                 | ▫ 11 studies showed 35% reduction (95% CI 14–51) in type 2 diabetes;  
▫ 23 high-quality studies with ≥1500 participants showed 13% lower overweight/obesity (95% CI 6–19);  
▫ 29 studies on asthma showed 9% (95% CI 2–15) reduction;  
▫ 18 studies on childhood leukemia showed 19% (95% CI 11–27) reduction; and,  
▫ 16 studies showed child intelligence quotient (IQ) increased by 3.4 points (95% CI 2.3–4.6). |
<p>| 17  | Israel            | Case-control                           | 1995-2003                                            | ▫ Among 6198 preterm infants (&lt;37 weeks), BF significantly decreased urosepsis (OR 0.314, 95% CI 0.140–0.707, P &lt;.009). |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Geographical Location</th>
<th>Study Type</th>
<th>Year</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>High Income Countries</td>
<td>Systematic review and meta-analysis</td>
<td>2007</td>
<td>4 randomized-controlled trials demonstrate BF decreases NEC 58% (95% CI 4-82). In 23 studies, comprising 4,251 cases and 58,055 controls, “the overall risk of SIDS was twice as great for bottle-fed infants compared to [BF] infants,” (OR 2.11; 95% CI 1.66–2.68). BF prevents gastroenteritis (OR 0.36, 95% CI 0.18–0.74, P=0.005) and hospitalization for respiratory infections (RR 0.28, 95% CI 0.14–0.54). Sub-analysis of 6 high-quality studies showed BF decreased SIDS by 36% (95% CI 19–49), adjusted summary odds ratio [SOR]: 0.64 [95% confidence interval (CI): 0.51–0.81]).</td>
</tr>
<tr>
<td>19</td>
<td>United Kingdom</td>
<td>Systematic review and economic model</td>
<td>2013</td>
<td>A model of the impact of BF on preterm infants (n=51,703, the number born in the index year) demonstrated 190 fewer deaths from sepsis and NEC if the infants were BF vs. formula-fed while in the NICU.</td>
</tr>
<tr>
<td>20</td>
<td>High Income Countries</td>
<td>Meta-analysis</td>
<td>1995-2009</td>
<td>The multivariable pooled estimate revealed decreased SIDS with any BF (OR 0.55, 95% CI: 0.44–0.69). SIDS risk is lowest with exclusive BF (OR 0.27; 95% CI, 0.27–0.31).</td>
</tr>
<tr>
<td>21</td>
<td>United States</td>
<td>Monte Carlo simulation and cost-analysis</td>
<td>2016</td>
<td>An estimated 721 excess pediatric deaths/year were attributed to suboptimal BF in the US, mostly from SIDS (n = 492) and NEC (n = 190). Increased uptake of BF decreased this estimate from 911 excess deaths in 2010.</td>
</tr>
<tr>
<td>22</td>
<td>United States</td>
<td>National surveillance data</td>
<td>2014</td>
<td>Acute lower respiratory and gastrointestinal infections caused 476 US infant deaths (12/100,000 livebirths). 275 deaths of children &lt;15 years old from sepsis.</td>
</tr>
<tr>
<td>23</td>
<td>United States</td>
<td>Umbrella review</td>
<td>2016</td>
<td>Acute otitis media, which affects &gt;80% under 3 years, is decreased by 40-50% with BF (OR 0.50, 95% CI 0.36–0.70).</td>
</tr>
<tr>
<td>24</td>
<td>United States</td>
<td>National surveillance data</td>
<td>2014</td>
<td>Mortality from perinatal HIV is extremely low: there was 1 death among 1,995 children &lt;13 with perinatal HIV, 0.05/100 child-years.</td>
</tr>
<tr>
<td>25</td>
<td>United States</td>
<td>National surveillance data and population-based surveys</td>
<td>2014-2015</td>
<td>Healthy People 2020 Objectives: 81.1% of US women initiate BF; target 81.9% 51.8% are BF at 6 months; target 60.6% 50.7% are BF at 1 year; target 34.1% Exclusively BF at 3 months: 44.4%; target 46.2% Exclusively BF at 6 months:22.3%; target 25.5% Reduce proportion of BF newborns who receive formula supplementation in first two days of life: 17.1%; target 14.2% Increase proportion of livebirths occurring in facilities providing recommended lactation care: 18.3%; target 8.1%</td>
</tr>
</tbody>
</table>
### Table 3: Impact of Breastfeeding on Maternal Health in High Income Countries

<table>
<thead>
<tr>
<th>Ref</th>
<th>Location</th>
<th>Study design</th>
<th>Years (data collection, if available, or publication)</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>United States</td>
<td>Secondary analysis of prospective cohorts</td>
<td>1994-2005</td>
<td>Among 139,681 parous participants in the Women’s Health Initiative, women who had lactated were less likely to be obese, hypertensive, diabetic or hyperlipidemic than those who had not, with direct dose-response observed.</td>
</tr>
<tr>
<td>27</td>
<td>United States</td>
<td>Secondary analysis of prospective cohort</td>
<td>1986-2002</td>
<td>In the Nurses’ Health Study of 89,326 parous women over 1,350,965 years of follow-up demonstrated that 2 years of cumulative lifetime BF reduced myocardial infarction by 23% (95% CI 6–38%, p-value=0.02), with 34% reduction (HR 0.66, 95% CI, 0.49-0.89) in first 30 years after last delivery.</td>
</tr>
<tr>
<td>28</td>
<td>United States</td>
<td>Secondary analysis of prospective cohort</td>
<td>1991-2005</td>
<td>Women who never BF are more likely to develop hypertension than those who BF ≥6 months (HR 1.29, 95% CI: 1.20-1.40).</td>
</tr>
<tr>
<td>29</td>
<td>United States, Italy, Canada, Australia, Poland, China, and Sweden</td>
<td>Meta-analysis</td>
<td>1992-2013</td>
<td>Analysis of 8,981 women with endometrial cancer and 17,241 control women demonstrated that ever having BF was associated with an 11% reduction in risk of endometrial cancer (pooled OR 0.89, 95% CI 0.81-0.98).</td>
</tr>
<tr>
<td>30</td>
<td>United Kingdom</td>
<td>Cross-sectional analysis of population-based survey</td>
<td>1996-2001</td>
<td>BMI decreased 1% per 6 months of BF among 740,628 British women.</td>
</tr>
<tr>
<td>31</td>
<td>United States, Germany, Australia, and China</td>
<td>Systematic review and meta-analysis</td>
<td>1989-2008</td>
<td>Meta-analysis demonstrates 32% lower risk of type 2 diabetes (OR 0.68, 95% CI 0.57–0.82), with risk decreasing ~11% per 3 months of BF.</td>
</tr>
<tr>
<td>32</td>
<td>High Income Countries</td>
<td>Systematic review and meta-analysis</td>
<td>2015</td>
<td>Meta-analysis of 72 studies showed 19% decrease in breast carcinoma (pooled OR 0.81, 95% CI 0.77-0.85, p&lt;.001) with any BF compared to never BF, and after fine adjustment of international data for parity and other confounders risk was reduced 7% (OR 0.93, 95% CI 0.89–0.97). 35 studies on ovarian cancer demonstrated 26% reduction with any BF (OR 0.74, 95% CI 0.68–0.80, p&lt;.001), and 18% reduction in finely adjusted sub-analysis of international data (OR 0.82, 95% CI 0.75–0.89).</td>
</tr>
</tbody>
</table>
Among parous women, BF has a stronger inverse association with hormone/triple-negative breast cancer (OR 0.78; 95% CI 0.66–0.91) than BF alone.

Meta-analysis shows a protective effect of ever BF against hormone receptor-negative breast cancers, which are more common in younger women and generally have a poorer prognosis than other subtypes of breast cancer.

Because black women have elevated baseline risk of hormone-and-triple-negative breast cancers, BF decreases their risk by 19%.

Among 1466 singleton infant deaths, short interpregnancy intervals significantly increased mortality and preterm birth, even after adjusting for confounders.

Mortality risk was increased with short birth intervals (aOR 1.68, 95% CI 1.09–2.59, p <.05) vs. the optimal interval (18–23 months); infant mortality is 76% higher for interpregnancy interval <6 months and 38% higher for 12–17 months.

After adjusting for confounders, short intervals increased risk for subsequent preterm birth: aOR 4.44 (95% CI 3.35–5.89, p<.01), and small for gestational age: aOR 1.96 (95% CI 1.45–2.66, p<.01).

Among 456,889 Latin American women, maternal death was more likely with interpregnancy interval <6 months (aOR 2.5; 95% CI 1.2–5.4)

A second pregnancy within 12 months postpartum significantly increased the risk of placental abruption by 52% and 111% among women whose first births were vaginal and cesarean, respectively. Interpregnancy intervals <12 months were associated with 70% increased risk of placenta previa for women with a prior cesarean first birth (n= 156,475; RR 1.7, 95% ci 0.9-3.1).

Subsequent pregnancies are also affected, as birth intervals <18 months are independently associated with SGA (aOR 1.51), prematurity (aOR 1.58), and infant mortality (aOR 1.83).

Approximately 2,605 maternal deaths per year are attributed to suboptimal initiation and duration of BF.
Works Cited for Supplemental Tables (bold entries not referenced directly in primary manuscript)


Ethics of Breastfeeding with HIV— An Evidence-based Case for New Policy

Revised Manuscript

Supplementary Tables

Durban, South Africa.


Supplementary Tables


Supplementary Tables


Supplementary Tables


37. See reference #21 above
Supplementary Tables


Additional sources for online supplement: works consulted but not cited

Risk of vertical transmission with cART

Ethics of Breastfeeding with HIV—An Evidence-based Case for New Policy

Revised Manuscript

Supplementary Tables


Health risks for HIV-exposed US infants


Breastfeeding impact on maternal and infant health in high-income settings

Supplementary Tables


**Ethics and health disparities affecting WLHIV**


Supplementary Tables


