Does U=U for breastfeeding mothers and infants? Breastfeeding by mothers on effective treatment for HIV infection in high-income settings

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Can the campaign Undetectable=Untransmittable (U=U), established for the sexual transmission of HIV, be applied to the transmission of HIV through breastfeeding? European AIDS Clinical Society and, to some extent, American guidelines now state that mothers with HIV who wish to breastfeed should be supported, with increased clinical and virological monitoring. This Viewpoint summarises existing evidence on transmission of HIV through breastfeeding, differences in HIV dynamics and viral load between breastmilk and plasma, and the effects of antiretroviral therapy on infants. At present, insufficient evidence exists to make clear recommendations for the required frequency of clinical and virological monitoring for mother and infant in a breastfeeding relationship or for the action to be taken in the event of viral rebound. We propose a roadmap for collaborative research to provide the missing evidence required to enable mothers who wish to breastfeed to make a fully informed choice.

Lancet HIV 2018; 5: e531–36

Published Online
June 27, 2018
http://dx.doi.org/10.1016/S2352-3018(18)30098-5

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Background

In October, 2017, the European AIDS Clinical Society (EACS) stated that if "a woman insists upon breastfeeding, we recommend follow-up with increased clinical and virological monitoring of both the mother and the infant", in an updated guideline.[1] US guidelines were updated in March, 2018, to describe how to counsel and to support women who make this choice, while clearly recommending against breastfeeding in general.[2] These recommendations recognise both the increasing numbers of women with HIV who are virologically suppressed on combination antiretroviral therapy (ART) and wish to breastfeed their children, and the framework of respect for human rights.

Globally, effective cART in pregnancy and post partum has resulted in a marked reduction in rates of mother-to-child transmission (MTCT) of HIV, such that elimination of MTCT is now embraced as a realistic goal.[3] Since 2015, global guidelines have recommended that pregnant women with HIV start combination ART as soon as possible and remain on it for life.[4] MTCT rates less than 1% have consistently been reported from high-income countries where most mothers who are HIV-positive do not breastfeed.[5–7]

The updated US guideline states that women "who desire to breastfeed should receive patient-centred, evidence-based counselling on infant feeding options".[2] But do we know enough to provide this evidence-based advice? People who are HIV-positive and virologically suppressed on cART, cannot sexually transmit the virus to others. The Undetectable=Untransmittable (U=U) campaign, launched in early 2016,[8] led to changes in HIV prevention advice given to serodifferent sexual partners. The success of U=U for sexual transmission raises the question of its applicability to other contexts, such as in breastfeeding.

In this Viewpoint we address major questions that need to be answered to produce evidence-based recommendations for breastfeeding with HIV in high-income settings.

Breastfeeding guidelines differ between high-income and low-income regions

Clinical guidelines from high-income countries all recommend against breastfeeding with HIV, even though recent updates acknowledge that women who choose to breastfeed should be supported.[2,9,10] In low-income settings, WHO recommends breastfeeding for at least 6 months and continuing up to 12 months or 24 months.[11] The recommendations are based on the same sources of data, but the balance of benefit versus harm of breastfeeding differs. In low-income settings, the morbidity and mortality from infection in infants receiving formula milk outweighs the risks of HIV transmission through breastmilk, because of unclean water and lost protection from maternal antibodies in breastmilk.[11]

The risk of HIV transmission through breastfeeding

The risk of HIV transmission through breastfeeding in high-income countries remains unknown because randomised, controlled trials of prevention of MTCT (PMTCT) using combination ART are not feasible. A 2017 meta-analysis of six studies in low-income settings in which mothers started ART before or during their most recent pregnancy, estimated a postnatal HIV transmission rate of 1·08% (95% CI 0·32–1·85) at 6 months, with higher rates from mothers who commenced ART in the later stages of pregnancy.[12] The Promoting Maternal Infant Survival Everywhere (PROMISE) trial in southern Africa,[13] comparing maternal combination ART with prolonged infant nevirapine, (until 18 months post-delivery or cessation of breastfeeding) reported MTCT of 0·3% (95% CI 0·1–0·8) at 6 months and 0·7% (0·3–1·4) and 12 months in the maternal ART arm.[13]

The estimates from low-income and middle-income countries are likely to overestimate HIV transmission risk in high-income settings. First, early trials included women who started combination ART at any time up to, and including, the third trimester and discontinued at 6 months post partum.[14–18] Given the time taken to attain virological suppression, the increased risk of postnatal transmission from mothers who started therapy in the third trimester is not surprising.[14,16,17,19] Second, most studies reported transmission events after discontinuation of maternal ART and reported cessation of breastfeeding, so the findings might not be generalisable to mothers who remain on treatment for life.

Association between transmission and maternal plasma and breastmilk HIV viral load

Elevated maternal plasma and breastmilk HIV RNA are associated with increased risk of transmission to infants, but a safe threshold has not been defined. Earlier studies using assays with detectability thresholds of 1000 copies per mL[15,17] or 400[16] copies per mL might have missed clinically important viraemia.

In the Malawian Breastfeeding, Antiretrovirals and Nutrition (BAN) study, among mothers receiving 28 weeks of post-partum combination ART, detectable HIV RNA in breastmilk was associated with increased transmission (hazard ratio 3·8, 95% CI 1·2–12·1) in a secondary analysis.[20] All transmitting mothers had at least one plasma HIV RNA sample of more than 100 copies per mL, 73% had detectable HIV RNA in breastmilk at any time, and 53% had so at the nearest timepoint to the transmission.[20] Two mothers had detectable HIV RNA in breastmilk with undetectable HIV RNA in plasma. In a large case-control study nested into the Vertical Transmission Study in KwaZulu Natal, South Africa, the estimated total breastmilk exposure to HIV RNA was strongly associated with postnatal transmission.[21] Transmission of HIV during breastfeeding has occurred despite undetectable HIV RNA in breastmilk[20,22] and postnatal HIV transmission was documented from a woman who had both plasma and breastmilk HIV RNA less than 37 copies per mL at the timepoint closest to transmission.[18] Although these transmission events might represent elevations in HIV RNA between sampling intervals or assay limitations, the presence of cell-associated HIV DNA is also a possible explanation.

The question of breastmilk cells in relation to MTCT

Both cell-associated DNA and cell-free RNA in breastmilk have been associated with HIV transmission from mother to child.[23,24] A study comparing the infecting virus (in the infant) with viruses characterised by their C2 to C5 *env* fragment sequences in the cellular and acellular parts of breastmilk showed that, before 9 months post partum, HIV-1 is mainly transmitted by cells containing HIV-1 provirus, whereas cell-free virus is frequently involved later.[25] Breast tissue might be seeded with a long-lived lineage of latently infecting resting T cells.[26] Decline of HIV RNA, but not HIV DNA in breastmilk was seen with combination ART, although mothers had been on treatment for a median of 98 days;[27] this might not directly inform the situation where a woman has been on long-term suppressive treatment.

Van de Perre and colleagues suggest postnatal transmission from a mother receiving suppressive combination ART can result from cell-associated viral transmission, due to several differences between blood and breastmilk cells.[28] Breastmilk immune cells are frequently activated and express homing markers signalling their mucosal origin (maternal gut, respiratory mucosae).[29] Latently HIV-infected, resting CD4-positive T lymphocytes harbour HIV-1 proviral DNA. These cells have a half-life of about 44 months,[30] are not affected by current treatment regimens,[30] and constitute an inducible reservoir of HIV-producing cells, which can transcribe HIV DNA generating infectious viral particles.[31] Activated CD4 cells spontaneously secreting HIV-1 antigen detected by enzyme-linked immunospot assay (ELISPOT) are found in both breastmilk and blood, irrespective of treatment.[32] Even when HIV DNA levels are similar between blood and breastmilk, polyclonal activation resulted in ten-times more HIV antigen-secreting cells in breastmilk than blood, making the breastmilk CD4 cells 17-times more effective than their blood counterparts in producing HIV antigens.[33]

Furthermore, breastmilk contains other cell types susceptible to HIV infection, such as macrophages, dendritic cells, and CD4-positive progenitor T cells, which could also be involved in transmission.[28] The transfer and persistent nesting of maternal cells into infant tissues (maternal microchimerism) involving breastmilk cells is reported in many mammalian species, and has been suggested in humans.[34]

The role of mastitis is uncertain. Activation of breastmilk cells and leakage of HIV from plasma into the breast could promote HIV shedding,[35] and data from the pre-ART era indicate an increased risk of MTCT in this situation.[36] Reactivation of latent viral infections such as cytomegalovirus or Epstein-Barr virus in breastmilk could similarly and synergistically favour HIV shedding.[37] There are no data on the effects of mastitis on HIV RNA in breastmilk or cell-associated HIV DNA among women on combination ART who have suppressed plasma HIV RNA.

What about drug exposure to breastfed infants?

The two main concerns about transmammary exposure to maternal ART are the development of HIV resistance in infants should transmission occur, and toxic effects from long-term low-dose exposure to drugs. Almost all data on drug exposure to breastfed infants are derived from populations in low-income and middle-income

countries. Exclusively breastfed infants receive up to 10% of the weight-adjusted infant dose of nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors, whereas transfer of protease inhibitors to the infant is low.[38] Genetic differences, such as CYP2B6 polymorphisms in the case of efavirenz, result in higher infant drug exposure through pregnancy and breastfeeding.[39] Individual patient data indicate transfer of dolutegravir to the breastfed infant,[40] with ongoing studies exploring this question (DolPHIN-1, NCT02245022). Reduced infant clearance of dolutegravir likely relates to the immature metabolism of the neonates.[41] No breastmilk pharmacokinetic data yet exist for drugs including tenofovir alafenamide, which are increasingly used in high-income countries. Infant ingestion of low concentrations of ART through breastmilk can promote emergence of drug-resistant mutants in the infant. Two large PMTCT studies showed that infants who acquired HIV during breastfeeding despite maternal combination ART had high rates of multiclass drug resistance, with demonstration of different resistance patterns to those seen in their mothers.[42,43]

Pharmacovigilance of infant exposure to drugs through breastfeeding is poor, with under-reporting of adverse drug reactions and a probable skew towards the most serious events.[44] Although the Antiretroviral Pregnancy Registry is well established, no parallel system exists to collect data relating to clinical outcomes, growth, and development in breastfed infants. Furthermore, clinical methods needed to record subtle toxic effects alongside clinical care have not been established. Few large PMTCT trials in low-income countries reported on infant safety data. The PROMISE study described similar rates of grade 3 or more adverse events between infants given prolonged treatment with nevirapine (18 months or until cessation of breastfeeding) compared with having transmammary exposure to maternal combination ART.[13]

What is optimal infant prophylaxis?

Given the uncertainty regarding the absolute risk of HIV transmission to breastfed infants, prophylaxis might be an option, particularly as a rescue strategy in the event that the mother has viral rebound. EACS guidelines make no reference to infant prophylaxis.[1] Consistent with most European guidelines,[45] British HIV Association guidelines recommend nevirapine monotherapy for 4 weeks in infants whose mothers have plasma HIV RNA less than 50 copies per mL; maternal combination ART is seen to provide sufficient prophylaxis for breastfed infants of virologically suppressed mothers.[10] The Swiss national guidelines do not recommend infant postexposure prophylaxis in mothers with undetectable HIV RNA at delivery.[46] The US guidelines recommend at least 6 weeks of infant zidovudine or nevirapine, or both.[2] A systematic review of the evidence to support the optimal infant ART prophylactic regimen in high-risk infants included European data.[47] However, high risk included situations in which a pregnant woman has never received ART, has received insufficient ART, or had a detectable viral load around the time of delivery, but did not mention breastfeeding as a risk factor.[48] From such data, virologically suppressed mothers who choose to breastfeed would not be considered high risk.

Post-partum adherence to ART and virological suppression

Adherence to combination ART in the post-partum period can be more challenging than either the mother or health-care provider predict. In one systematic review of 51 studies involving 20 153 pregnant women with HIV from Kenya, South Africa, the USA, and Zambia, 76% had adequate adherence (defined as >80%) ante partum, but only 53% post partum.[49] Several studies in high-income countries indicate adherence among post-partum women is difficult. The UK Collaborative HIV Cohort compared data from 623 parturient women with 1225 women who did not deliver between 2006 and 2011. 10·7% of post-partum women had viral rebound (HIV RNA >200 copies per mL), compared with 7·4% of controls.[50] Among the 363 women diagnosed with HIV and started on ART during the recent pregnancy, 27% had results suggesting viral rebound within 6 months post partum.[50] The Swiss HIV Cohort Study found that 12% of 695 women were lost to follow-up in the first year post partum.[51] In the USA, a retrospective cohort found that only 39% of 695 mothers were retained in care and 31% were virologically suppressed at 1 year post partum.[52]

What virological monitoring should breastfeeding women on combination ART receive?

There are no specific data to guide the required frequency of increased virological monitoring,[1] whether viral load should be monitored in plasma alone or also in breastmilk, or the action to be taken in the event of an unexpected result. The British HIV Association recommends monthly testing of both mother and infant if breastfeeding takes place, with a grading of 1C (a strong recommendation, but where some of the supporting evidence is of low quality).[10] Swiss guidelines suggest testing the mother every month (for 6 months) and the child after 1 month and after 6 months depending on how long they were breastfed, until weaning.[46] US guidelines recommend maternal viral load 1–2 times per month, and to consult an expert in the event of detectable viraemia.[2]

Future guidelines should consider whether increased contact with health-care providers for monitoring might improve patient–clinician relationships and adherence, or might overburden the post-partum woman. Qualitative research could inform the best models of care.

	What is known	Research priorities
What is the significance of cell-associated virus?	Might be associated with transmissions in women with or without suppressed VL	Does this still hold for women on long-term ART? Do any newer drugs influence cell-associated virus?
What is the genuine rate of transmission? Is it truly zero?	Very low rates are reported in the context of suppressive ART, and most transmissions can be explained through detectable virus or poor adherence	Establishment of a registry of mother–infant pairs to capture any transmissions
What are the pharmacokinetics of newer antiretrovirals in mother–infant pairs?	Data exist surrounding NNRTI, NRTI, and older PIs, with emerging data on dolutegravir	Sparse pharmacokinetic sampling from mother–infant pairs in Europe where the mother has elected to breastfeed
How do we monitor infants for toxicities?	Little data exist for breastfeeding exposure to newer ART	Establishment of a registry linked to clinical care for longer term follow-up of exposed infants
Are any regimens better suited for use in breastfeeding?	Almost all data exist for regimens of one NNRTI + 2 NRTIs in low-resource settings	Clinical monitoring and pharmacokinetic among mother-infant pairs on individualised regimens
What is the optimal frequency of virological monitoring?	No evidence base on which to form a guideline	Establishment of a cohort to describe experience
What steps should be taken in the event of detectable viraemia?	No evidence base on which to form a guideline	Cohort data correlating viral rebounds with adverse events. Qualitative research on maternal attitudes and practice if abrupt weaning advised
What is the significance of clinical or subclinical mastitis?	In pre-ART era, mastitis was associated with increased breastmilk HIV RNA, and risk of MTCT	Evaluation of subclinical mastitis and breast milk HIV VL among breastfeeding mothers on ART
Should infant prophylaxis be given during breastfeeding? If so, which is the optimal regimen and duration?	Existing evidence largely from sub-Saharan Africa	Definition of optimal prophylaxis for the breastfed infant whose mother has a plasma HIV VL of <50 copies per mL. To define optimal infant prophylaxis to be given in the event of detectable maternal HIV RNA
What clinical or psychosocial support would benefit these mothers?	Existing qualitative work on post-natal ART intake and adherence stems from LMIC.	Do different subpopulations of women who wish to breastfeed exist who require different models of care? Qualitative research among mothers who choose to breastfeed in well resourced settings

VL=viral load. ART=antiretroviral therapy. NNRTI=non-nucleoside reverse transcriptase inhibitor. NRTI=nucleoside reverse transcriptase inhibitor. PI=protease inhibitor. MTCT=mother-to-child transmission. LMIC=low-income and middle-income countries.

***Table*: Unanswered questions and research priorities**

When and how to stop breastfeeding in the event of virological rebound?

Firm data defining a rescue strategy are absent in situations where a breastfeeding mother has detectable HIV RNA in plasma or breastmilk. Clinical judgment might suggest immediate cessation of exposure to breastmilk and infant antiretroviral prophylaxis as both pre-exposure or post-exposure prophylaxis.[53] However, stopping breastfeeding abruptly is difficult and mammary tissue remains partly functional for a long period, which could lead to intermittent breastfeeding against medical advice. Professional support from an expert in lactation is recommended when cessation of breastfeeding for other medical reasons is needed.[54] As adherence to combination ART is crucial, HIV-positive women need continued emotional and social support. Anecdotal evidence suggests that women can feel pressured to inform clinicians that they are no longer breastfeeding, when this is not the case. Most studies indicate MTCT occurred in women who stated that breastfeeding has ceased,[12] suggesting that this is a real phenomenon.

Research priorities

Our synthesis of the salient issues shows that there are important gaps in the evidence base needed to define the optimal clinical and virological monitoring of a breastfeeding woman who is HIV-positive and her infant in a well resourced setting. The principles might be of relevance to low-income settings as access to resources improves.

If women with HIV wish to breastfeed, both clinicians and patients need accurate, up-to-date information about the risks and benefits to enable an informed decision. Detailed information about the necessary additional tests and their frequency for breastfeeding mother–infant pairs is needed. Should viral rebound occur, statements on the need for cessation of breastfeeding, together with advice on how to support the mother in this process, or how to choose the optimal pre-exposure or post-exposure prophylaxis for the infant must be clear. New research studies could help to understand the motivations for breastfeeding and issues related to combination ART adherence, which could provide support for the diverse populations of women with HIV infection. This includes women who have migrated from low-income countries for whom breastfeeding is the first choice, and those born in high-income countries who wish to breastfeed and are highly motivated to adhere to treatment.

There is insufficient evidence to state with certainty that U=U in the context of breastfeeding. To address gaps in the specific evidence applicable to clinical guidance in high-income countries, we propose an Expert Networking Group to exchange knowledge based on cases in real-time. Anecdotal evidence suggests that each clinical centre is likely to have only a few patients who choose to breastfeed while on suppressive combination ART, and therefore multicentre collaboration and shared research protocols will be necessary to maximise the knowledge gained.

Existing networks, including the Paediatric European Network for Treatment of AIDS and Women Against Viruses in Europe within EACS, and the North American Perinatal HIV Clinicians Network, which is linked through the HIVE[55] ReproID HIV Listserv, could provide the logistical support for a collaboration that should involve patients' groups. At the first level, this would be simple documentation of data on mother–infant pairs, including the country of origin, timing, and type of

Search strategy and selection criteria

We searched PubMed (US National Library of Medicine) for papers published between October, 2017, and April, 2018. We used the search terms "HIV transmission OR mother to child transmission AND breastfeeding", and "antiretroviral AND breast milk". We selected publications that appeared to be relevant and supplemented these with references that were cited in identified papers. All papers identified were in English.

maternal combination ART, viral load at delivery and subsequent (possibly monthly) timepoints, and the final infant HIV status after cessation of breastfeeding.

Key unanswered questions and research priorities exist (table). Alongside these efforts, collaborators should develop protocols for pharmacokinetic, virological, and pharmacovigilance studies, and social science research that includes evaluation of maternal quality of life. Most of all, a coalition of researchers and mothers with HIV would generate the research to allow a consensus of the best available information for clinicians and mothers about the prevention of HIV transmission through breastfeeding.

Contributors

CW and KA-P were responsible for the initial concept for the paper, literature searches, data interpretation, and writing. NL, FL, and ML were responsible for critical input into the selection and interpretation of material reviewed and synthesis of conclusions presented. PVdP provided a major contribution to sections relating to cell-associated virus, and critical input throughout.

Declaration of interests

ML has received funding for research, travel, and presentations from Gilead Science, ViiV Healthcare and Merck Frosst Canada. All other authors declare no competing interests.

Acknowledgments

CW is funded by a Wellcome Postdoctoral Training Fellowship for Clinicians WT104422MA. We thank Claire Thorne for critical review of the manuscript.

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