Published in final edited form as:

Curr Opin Pediatr. 2018 February ; 30(1): 144–151. doi:10.1097/MOP.0000000000000579.

Current Opinion: What's New in Perinatal HIV Prevention?

Mary Glenn Fowler, MD MPH,

Professor, Department of Pathology, 443 Carnegie Building, Johns Hopkins U. School of Medicine, 600 N. Wolfe Street, Baltimore, MD 21287, Tel: 410 502 3011

Patricia Flynn, MD, and

Deputy Clinical Director, Member, Department of Infectious Diseases, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, Tennessee 38105, (P)901-595-4662

Jim Aizire, MBChB, MHS, PhD

Assistant Scientist, Department of Epidemiology, 615 N. Wolfe St., E713B, Johns Hopkins U. Bloomberg School of Public Health, Baltimore, MD 21205, Tel: 410 502 8988

Abstract

Purpose of this review—on Prevention of Mother to Child Transmission of HIV (PMTCT) is to describe recent clinical trial, laboratory and observational findings that highlight both the progress that can be achieved in elimination of new pediatric infections in international clinical trial settings among HIV infected breastfeeding women while also describing recent safety concerns related to currently used antiretroviral regimens. The article will also address the ongoing adherence challenges for HIV infected mothers in taking their antiretroviral drugs. This information is timely and relevant as new regimens are being considered for both PMTCT and treatment options worldwide.

Recent findings—The main themes described in this article include both efficacy of different ART regimens currently being rolled out internationally for PMTCT; as well as safety findings from recent research including a large multi-site international trial, PROMISE.

Summary—The findings from the IMPAACT PROMISE trial as well as other recent trial and observational findings, suggest that while progress has been steady in reducing PMTCT worldwide, the goal of virtual elimination of pediatric HIV worldwide will require careful attention to optimizing safety of new regimens; and that are less dependent on maternal daily ART adherence; and safer in preventing certain toxicities.

Keywords

Current PMTCT efficacy; adverse safety outcomes

Correspondence to: Mary Glenn Fowler.

Funding Support: Not grant or contractual support was used to fund this manuscript preparation.

No Conflicts of Interest. The authors, MG Fowler, P Flynn, J Aizire, report No conflicts of Interest or external sources of funding for preparation of this Current Opinion manuscript.

Introduction

This review will focus on recent research findings on Prevention of Mother to Child Transmission of HIV (PMTCT) in resource limited international settings, including the efficacy and safety findings from the recently completed multi-site PROMISE 1077 trial. This update also highlights the steady progress in prevention of perinatal HIV transmission worldwide since the dramatic results of the first successful perinatal prevention trial ACTG 076 using zidovudine (ZDV) were announced in 1994.¹ Since that time, major advances in PMTCT have continued worldwide with transmission rates dropping from one in three newborns of HIV infected women becoming infected to less than 1 in a hundred with available combination antiretroviral therapy (ART) in the recent PROMISE 1077 randomized trial. (Table 1) However ART regimens have also been documented to be associated with certain safety concerns for both mothers and their infants. Thus the quest continues for the optimal antiretroviral regimen for mothers and their infants in terms of both safety and effectiveness.

Snapshot of the Global Perinatal HIV Epidemic

In 2016, UNAIDS reported that 160,000 infants worldwide had acquired HIV infection from mother-to-child-transmission of the virus; with greater than 90% of the new pediatric HIV infections occurring in Africa.² Following WHO 2013 recommendations³ for immediate initiation of ART at time of diagnosis in pregnancy, by 2016 about 76% of pregnant HIV infected women were on ART,² (see Figure 1, African specific country PMTCT ART uptake³) and new pediatric HIV infections had declined by nearly 50% since 2010.² Since 2013 and updated in 2015–2016, WHO guidelines have focused on harmonizing ARVs used for adult, pediatric HIV treatment and PMTCT; and with most recent recommendations for a universal “test and treat” strategy offering immediate initiation of lifetime ART at time of diagnosis, irrespective of CD4 immune or clinical status.^{4–6}

Background

Since the dramatic results of the ZDV ACTG 076 trial¹ in 1994, the world has seen steady progress in reducing perinatal HIV transmission, albeit with more rapid declines in resource rich settings. By the late 1990's in the US, and Europe, with use of dual and then triple antiretrovirals during pregnancy followed by 6 weeks of zidovudine prophylaxis to newborns, along with avoidance of breastfeeding, perinatal transmission rates had declined to less than 3% among women who were tested and begun on antiretrovirals during pregnancy.^{7–8}

Internationally, in resource constrained settings such as Africa and midlevel settings in the Far East, the initial focus was on testing cost effective and deliverable shorter course prevention of transmission in the peripartum period, including the third trimester and at labor/delivery where two thirds of perinatal HIV infections were estimated to occur.⁹ These trials included short course zidovudine (ZDV) trials, single dose SD oral nevirapine (SD-NVP) given to the mother at labor onset and to her newborn. Transmission rates in Thailand with short course ZDV were reduced by 50% compared to no intervention¹⁰ and also with use of single dose peripartum NVP in Uganda compared to 1 week peripartum ZDV.¹¹

However later HIV transmission continued to occur during extended lactation;^{12–13} and accounted for up to one third of all HIV transmission to infants in breastfeeding settings.⁹ Initial approaches by WHO¹⁴ were then to recommend shortened periods of breastfeeding for HIV infected women but this then led to increased mortality due to competing causes of infant mortality such as diarrhea and malnutrition that extended breast feeding protected against. In 2010 and 2016 WHO revised its guidance on infant feeding to recommend extended breastfeeding for HIV Infected women but with use of ARVs to reduce the risk of HIV transmission.^{15–16} Given the need for extended breastfeeding for overall early child survival particularly in resource limited settings in Africa where safe water and affordable breastmilk substitutes are not widely available, more recent perinatal HIV trials then focused on protecting the infant from HIV infection throughout extended breastfeeding by use of ARVs given either to the breastfeeding mother or to her HIV exposed infant.^{17–18} (See also Figure 2, summary of key PMTCT trials)^{17–29}

PROMISE Trial and other recent research PMTCT results

In order to address remaining research gaps in PMTCT, the multi version, multi- site randomized open label PROMISE 1077 trial was conducted between 2011 to 2016 to address the optimal antiretroviral regimens for PMTCT and maternal treatment balancing the relative safety and efficacy of already proven antiretroviral regimens for PMTCT among asymptomatic HIV Infected women who did not meet country criteria for HIV treatment at the time of the trial. The 1077BF and 1077FF versions of the PROMISE protocol were designed for resource limited international settings where use of antenatal ZDV followed by SD-NVP were recommended as standard of care for PMTCT; and where either extended breastfeeding was recommended; or for those HIV infected women who could safely formula feed in settings where formula was available and water supply was safe. In the 1077BF PROMISE protocol (Figure 3 schema), HIV infected pregnant women were randomized in the antepartum period to either ZDV and SD-NVP with a “tail” of tenofovir/emcitrabine (TDF/FTC) or to maternal ART using either TDF/FTC with Lopinavir/ritonavir (Lop/r) or ZDV/3TC with Lop/r; in the postpartum breastfeeding period to either maternal ART with TDF/FTC/Lop/r or infant daily NVP; and in the maternal health component at breastfeeding cessation, to either continue or to stop maternal ART.²⁹

Antepartum PROMISE Results

The multi-site PROMISE 1077BF/1077FF antepartum results were published in November 2016 based on randomized trial data from 6 countries in Southern and East Africa, and from India, among 3490 HIV infected pregnant women with CD4 counts ≥ 350 cells/mm³ who did not meet country criteria for treatment.²⁹ Maternal median age was 26 years at entry, median gestational age was 26 weeks and median CD4 count was 530 cells/mm³. The antepartum PROMISE results were that both the ZDV antepartum regimen with single dose NVP and 2 week “tail” of TDF/FTC and the maternal ART regimens with either ZDV/3TC/Lop/r or TDF/FTC/Lop/r achieved transmission rates below <2%; the maternal ART regimens transmission rates were significantly lower compared to the ZDV regimen at (0.56% versus 1.8%, repeated Confidence Interval difference was -1.3 (-2.1 to -0.4). However the PROMISE results also found a significantly increased risk of preterm delivery (PTD), 20.5% versus 13.1%, $p < .001$ or low birth weight (LBW) 12% vs 23%, $p < .001$ or

composite adverse outcome (40% versus 27.5%, $p < .001$) for women randomized to the maternal ART regimens compared to the antenatal ZDV regimen; as well as increased rates of maternal liver function toxicity for the maternal ART arms. The overall conclusions from the PROMISE antepartum results were to support the WHO recommendations for use of maternal ART for PMTCT but also the importance of follow up of infant survival and testing of new ART regimens to see if they might ameliorate the increased risk of adverse pregnancy outcomes found with maternal ART regimens compared to ZDV.

Post Partum PROMISE Results

The postpartum results of the PROMISE 1077BF addressing the relative safety and efficacy of regimens to reduce the risk of transmission of HIV during breastfeeding were presented in July 2016.³⁰ This part of the PROMISE trial randomized postpartum women at the one week post delivery visit (6–14 days postpartum) to receive either maternal ART (TDF/FTC/Lop/r) or for their infant to receive daily infant NVP. There were 2431 postpartum women randomized including 1220 women to the maternal ART arm and 1211 women to the infant NVP arm. The mothers' median age was 26 years and median CD4 count was 686 (533–869) cells/mm³ with no significant differences by study arm; average duration of breastfeeding was 16 months. Findings were that overall transmission through the duration of breastfeeding as measured at 18 months post delivery was extremely low with either of the two regimens: 0.57% and 0.58% for the maternal ART and infant NVP arms respectively. Both maternal ART and infant NVP prophylaxis throughout breastfeeding were safe and with no significant differences in maternal progression to AIDS or death events.

Maternal Health PROMISE Results

The Maternal Health PROMISE results of 1077BF/1077FF were also presented in July 2016 and found no significant differences in disease progression to AIDS or death for mothers randomized to stop versus continue maternal ART after the period of risk of transmission of HIV to the infant was over.³¹ The median maternal age was 26 years, 97% were WHO clinical stage 1, median CD4 count 698 cells/mm³ and the majority of women were Black African (97%). After a median follow-up of 1.6 years, the primary composite endpoint rate of AIDS or death was 0.49 person years (PYs) and not significantly different between arms. However WHO Stage 2 and 3 events were reduced with continued ART (HR 0.60; 95%CI 0.39, 0.90, $p=0.01$). The PROMISE results on lack of progression to AIDS or death contrast with the START trial results³² conducted in general adult populations--which may reflect the younger age of the women in PROMISE and their generally asymptomatic status with high CD4 counts.

PROMISE Substudy Findings on Maternal Bone/ Kidney Health

Currently, TDF based ART is the preferred regimen for HIV-infected pregnant women according to both US and WHO guidelines.^{4,5} However, there are concerns that TDF exposure may be associated with maternal bone or kidney health adverse effects. In a PROMISE sub-study (P1084s), there were no concerns regarding kidney toxicity with no differences in creatinine clearance by study arm for TDF versus other regimens. However P1084s did demonstrate a significantly greater decline in bone mineral density (BMD) from weeks 1 to 74 postpartum among HIV-1 infected breastfeeding mothers randomized to

receive TDF-based ART versus mothers not randomized to ART (i.e. whose infants received nevirapine for the duration of breastfeeding); with a mean maternal hip BMD change of -2.29% (-3.20% , -1.39%), p -value <0.001 ; and mean lumbar spine BMD change of -2.86% (-4.03 , -1.70) for mothers on ART compared to mothers whose infants were on NVP, p -value <0.001 .³³ Future research is planned to explore alternatives to TDF use during pregnancy and breastfeeding periods. Tenofovir alafenamide fumarate (TAF) based ART has similar efficacy but more favorable safety profile than TDF based ART.³⁴ IMPAACT 2010 a phase III, randomized, open-label study among HIV-1 infected pregnant women will assess the relative safety and efficacy of Dolutegravir (DTG) and TADF/FTC based ART compared to EFV/TDF/FTC based ART.³⁵ In addition, an ongoing PEPFAR funded observational follow-up of PROMISE trial mothers will assess if life time ART is associated with further BMD decreases with repeat pregnancy and breastfeeding.

(See Table summary 1077BF results)

Other Recent Trial and Safety Findings

Besides the PROMISE randomized clinical trial results,²⁹ other recent trials explored different ART regimens and infant prophylaxis for prevention of perinatal HIV transmission. In a recent Thailand study, increased perinatal transmission risk associated with less than 8 weeks of maternal ART prophylaxis was reported in the Perinatal HIV Prevention Trial PHPT-5 trial.³⁶ In the ANRS 12174 trial, infants randomized to daily LPV/r versus daily 3TC had similar rates of postnatal transmission, and HIV-free survival rates, at 50 weeks of age, respectively.³⁷ And in a recent Ugandan study, there were no significant differences in HIV-free survival among children born to HIV-infected mothers randomized to AZT/3TC/LPV/r versus AZT/3TC/EFV, initiated at 12–28 weeks' gestation and continued through labor, and the duration of breastfeeding through 1 year.³⁸

Increasing rates of resistant mutations in perinatal populations

As described in a 2017 meta-analyses review,³⁹ Boerma et al documented increasingly high rates of ARV resistance over the past decade among HIV infected infants and young children (47%) in 13 countries who failed PMTCT; as well as resistant virus among HIV infected children not reported to be exposed to PMTCT antiretrovirals (26.8%). These include studies from Southern and East Africa^{40–42} as well as West Africa with the highest proportion of resistance being to nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs) followed by Nucleoside Reverse Transcriptase Inhibitors (NRTIs).^{43–44} Likewise HIV infected pregnant women in international settings have also shown increased rates of resistance to NNRTI and NRTIs' with a study from KwaZulu-Natal South Africa,⁴⁵ reporting 65% of pregnant women having an NNRTI resistance and 7% with TAMS resistance using Ultra-deep sequencing (UDS) assays; and a study from Tanzania reported similar findings with drug resistance mutants in 69% of women based on UDS assays.⁴⁶ Persistence of resistant mutations at low levels has been documented in adult European studies to be associated with increased risk of treatment failure.⁴⁷ The high rates of persistent NNRTI mutants suggests that PI or integrase inhibitor regimens may need to be continued for infected children over 3 years of age to ensure long term treatment success.

Challenges and Research Gaps

Despite these remarkable advances in prevention strategies, there are multiple remaining challenges worldwide. Clinical trials successes often have barriers to implementation when disseminated to other areas; while strategies that are simple and implementable across all populations of women with HIV have been most successful—such as WHO recommendations for immediate initiation of ART at time of diagnosis in pregnancy, regardless of CD4 count.⁴ As WHO efforts move to harmonizing the ARVs used for adult, pediatric treatment and PMTCT, we are further challenged to assure that the ART regimens recommended have adequate efficacy and safety information among pregnant women and infants.

Newborn HIV vaccines or other immunologic adjuvants, such as monoclonal antibodies, could provide additional protection beyond ARVs, particularly for women who are high risk of transmission such as those with acute HIV infection in pregnancy, those with ARV resistant virus and those with uncontrolled viral replication close to delivery. However testing these agents is challenged by demonstrating efficacy in settings with low HIV transmission (e.g. < 1–2%) because very large patient enrollment would be required to demonstrate efficacy.

The largest remaining barrier to eliminating perinatal HIV transmission is overcoming poor adherence to lifelong ART regimens. The meta-analyses by Nachega et al⁴⁸ documented poor adherence of HIV-infected mothers worldwide to taking ART, particularly after the risk of PMTCT has ceased. Several studies have demonstrated that adherence to maternal ART during the postpartum period is worse than antepartum, and decreased adherence has been associated with increases in breastmilk viremia and increased risk of postpartum transmission.^{49–51} The later postpartum period (>12 months) is often a time of transfer of women from antenatal ART services to general ART clinics, with increased risk of loss to care for up to 25% of women following transfer.^{52–53} After initial viral suppression following starting ART during pregnancy, a number of studies have shown decreased rates of viral suppression at 12 and 24 months postpartum, putting the breastfeeding infant at risk of postnatal infection as well as risk of acquisition of resistant virus.^{54–56} Among women on life-long ART, one recent study show that a significant minority of women taking ART pre-conception enter antenatal care with detectable viremia.⁵⁷ Another major challenge is how best to decrease new HIV infections among adolescent females who are continuing to fuel the global HIV epidemic.

Future Directions

The findings presented above highlight the substantial progress that has been made in PMTCT over the past two decades but also the challenges to achieve an HIV free generation. Given the safety concerns with the current ART regimens used for PMTCT noted in a number of studies^{58–59} including PROMISE²⁹ with increased risk of adverse pregnancy outcomes as well as the association of maternal ART use during pregnancy and breastfeeding with decreased maternal bone mineral density,³³ it will be important to test the safety of promising new antiretrovirals such as integrase inhibitors among pregnant and

breastfeeding women. Another promising area is adding in immune strategies such as monoclonal antibodies and HIV vaccines as part of perinatal interventions.

Other key areas for future research are 1) to test primary prevention strategies with long acting ARVs such as Cabotegravir for pre-exposure prophylaxis among high risk sexually active adolescents and 2) test novel strategies to improve maternal adherence to taking life-time antiretrovirals. The issue of how best to support mothers to adhere to life time ART is complex and multi-faceted.⁶⁰ Innovative strategies reported that look promising are use of peers as well as community interventions.^{61–62} Further implementation science research efforts will need to focus on upscaling successful maternal adherence interventions.

Conclusions

The recent trends in PMTCT are encouraging and clinical trial data suggest that transmission rates of less than 1% can be achieved with maternal ART. However, in global programmatic settings, the PMTCT cascade continues to reveal gaps at all points. In addition, current ART regimens for PMTCT are associated with increased rates of adverse pregnancy outcomes; and with rapidly emerging resistance among PMTCT-ART exposed mothers and HIV-infected infants. These findings underscore the importance of studying the safety/ pharmacokinetic profile of new ART regimens among perinatal populations as they become available in order to further optimize efficacy while minimizing toxicity of ART regimens used for PMTCT.

Acknowledgments

We acknowledge the dedicated perinatal researchers and the HIV infected women who participated in the clinical trials cited in this manuscript. Without their collaborative efforts, the remarkable progression seen in prevention of mother to child transmission of HIV would not have occurred over the past two decades.

References

1. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med.* 1994; 331:1173–80. [PubMed: 7935654]
- 2*. UNAIDS Facts Sheet. 2016. <http://www.unaids.org/en/resources/fact-sheet> (accessed October 5, 2017). This Facts sheet demonstrates the significant increases in uptake of maternal ART during pregnancy and the encouraging reductions in perinatal transmission with use of ART.
3. UNAIDS Global Plan 2016. UNAIDS; Geneva: 2016. http://www.unaids.org/sites/default/files/media_asset/GlobalPlan2016_en.pdf [accessed last Oct 17, 2017]
4. World Health Organization. Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: recommendations for a public health approach (2013 version). WHO Press; Geneva, Switzerland: 2013.
- 5*. World Health Organization. Guidelines on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva: World Health Organization; 2015. URL: <http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/> (accessed October 5, 2016). This is the first time WHO recommended initiation of antiretroviral treatment for all at the time of diagnosis without regard to immune or clinical status based in large part on the START results. This led to increasing numbers of HIV infected individuals being offered ART worldwide.
- 6**. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, second edition, June 2016. <http://www.who.int/hiv/pub/arv/arv-2016/en/> These WHO recommendations emphasizing test and treat, and initiation of pregnant

women onto life time ART at time of diagnosis, paired with international donor funding has resulted in the substantial decreases in new pediatric HIV infections being documented in the last several years.

7. Cooper ER, Charurat M, Mofenson L, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr*. 2002; 29:484–94. [PubMed: 11981365]
8. Mandelbrot L, Landreau-Mascaro, Rekacewicz E, et al. Lamivudine-zidovudine Combination for Prevention of Mother–infant Transmission of HIV-1. *JAMA*. 2001; 285:2083. [PubMed: 11311097]
9. Decock KM, Fowler MG, Mercier E, et al. Prevention of mother-to-child transmission in resource-poor countries: translating research into policy and practice. *JAMA*. 2000; 283:1175–1182. [PubMed: 10703780]
10. Shaffer N, Chuachoowong R, Mock PA, et al. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. Bangkok Collaborative Perinatal HIV Transmission Study Group. *Lancet*. 1999; 353:773. [PubMed: 10459957]
11. Guay LA, Musoke PM, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother –to-child transmission of HIV-1 in Kampala, Uganda; HIVNET012 randomised trial. *Lancet*. 1999; 354:795–802. [PubMed: 10485720]
12. Wiktor SZ, Ekpin E, Karon JM, et al. Short-course oral zidovudine for prevention of mother-to-child transmission of HIV-1 in Abidjan, Côte d'Ivoire: a randomised trial. *Lancet*. 1999; 353:781–5. [PubMed: 10459958]
13. Nduati R, John G, Mbori-Ngacha D, et al. Effect of breastfeeding and formula feeding on transmission of HIV-1: a randomized clinical trial. *JAMA*. 2000; 283:1167–1174. [PubMed: 10703779]
14. World Health Organization. Global Strategy for Infant and Young Child Feeding. Copyright WHO; Geneva Switzerland; 2003.
15. World Health Organization. Guidelines on HIV and infant feeding. 2010. Principles and recommendations for infant feeding in the context of HIV and a summary of evidence. Geneva: World Health Organization; 2010.
16. World Health Organization, United Nations Children's Fund. Guideline: updates on HIV and infant feeding: the duration of breast feeding and support from health services to improve feeding practices among mothers living with HIV. Geneva: World Health Organization; 2016.
17. Chasela CS, Hudgens MG, Jamieson DJ, et al. Maternal or Infant Antiretroviral Drugs to Reduce HIV-1 Transmission. *N Eng J Med*. 2010; 362:2271–81.
18. Thomas TK, Masaba R, Borkowf CB, et al. Triple-antiretroviral prophylaxis to prevent mother-to-child HIV transmission through breastfeeding –The Kisumu Breastfeeding Study, Kenya: a clinical trial. *PLoS Med*. 2010; 8:e1001015.
19. Lallamant M, Jourdain G, Le Coeur S, et al. A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type 1. Perinatal HIV Prevention Trial (Thailand) Investigators. *N Engl J Med*. 2000; 343:982. [PubMed: 11018164]
20. Dabis F, Bequet L, Ekouevi DK, et al. ANRS 1201/1202 DITRAME PLUS Study Group. Field efficacy of zidovudine, lamivudine and single-dose nevirapine to prevent peripartum HIV transmission. *AIDS*. 2005 Feb 18;19:309–18. [PubMed: 15718842]
21. Lallamant M, Jourdain G, Le Coeur S, et al. Single-dose perinatal nevirapine plus standard zidovudine to prevent mother-to-child transmission of HIV-1 in Thailand. *N Engl J Med*. 2004; 351:217. [PubMed: 15247338]
22. Thior I, Lockman S, Smeaton LM, et al. Breastfeeding plus infant zidovudine prophylaxis for 6 months vs formula feeding plus infant zidovudine for 1 month to reduce mother-to-child HIV transmission in Botswana: a randomized trial: the Mashi Study. *JAMA*. 2006; 296:794–805. [PubMed: 16905785]
23. Six Week extended-Dose Nevirapine (SWEN) Study Team. Extended-dose Nevirapine to 6 weeks of age for infants to prevent HIV transmission via breastfeeding in Ethiopia, India, and Uganda: an analysis of three randomized controlled trials. *Lancet*. 2008; 372:1–14. [PubMed: 18603137]
24. Kumwenda NI, Hoover DR, Mofenson LM, et al. Extended Antiretroviral Prophylaxis to Reduce Breast-Milk HIV-1 transmission. *N Eng J Med*. 2008; 359:1–11.

25. Shapiro RL, Hughes MD, Ogwu A, et al. Antiretroviral regimens in pregnancy and breast-feeding in Botswana. *N Engl J Med*. 2010; 362:2282–2294. [PubMed: 20554983]
26. de Vincenzi I. Kesho Bora Study Group. Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of mother-to-child transmission of HIV-1 (Kesho Bora study): a randomised controlled trial. *The Lancet Infect Dis*. 2011; 11:171–180. [PubMed: 21237718]
27. Nielsen-Saines K, Watts DH, Veloso VG, et al. for NICHD HPTN 040/PACTG 1043 Protocol Team. Three postpartum antiretroviral regimens to prevent intrapartum HIV infection. 2012; 366:2368–79. DOI: 10.1056/NEJMoa1108275
28. Coovadia HM, Brown ER, Fowler MG, et al. Efficacy and safety of an extended nevirapine regimen in infant children of breastfeeding mothers with HIV-1 infection for prevention of postnatal HIV-1 transmission (HPTN 046): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2012; 379:221. [PubMed: 22196945]
- 29*. Fowler MG, Qin M, Fiscus SA, et al. Benefits and Risk of Antiretroviral Therapy for Perinatal HIV Prevention. *N Engl J Med*. 2016; 375:1726. This randomized study provides the only clinical trial data available to support WHO recommendations for use of ART during pregnancy for PMTCT compared to ZDV. However it also found that Protease Inhibitor based ART was associated with increased risk of adverse pregnancy outcomes compared to antepartum ZDV alone, plus SDNVP and TDF/FTC 2 week “tail”. [PubMed: 27806243]
30. Taha TE, Flynn P, Cababasay M. , et al. Comparing Maternal Triple Antiretrovirals (mART) and Infant Nevirapine (iNVP) Prophylaxis for the Prevention of Mother-to-Child Transmission (MTCT) of HIV during Breastfeeding (BF). LBPE013, Abstract 21st International AIDS Conference; 2016, 18–22 July; Durban S. Africa. 2016.
31. Currier JS, Britto P, Hoffman R. , et al. 1077HS Randomized Trial of Stopping or Continuing ART among Postpartum Women with Pre-ART CD4 400 cells/mm³ (PROMISE 1077HS). Abstract 22nd International AIDS Conference; Paris. 2017.
32. INSIGHT START Study Group. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. *N Engl J Med*. 2015; 373:795–807. [PubMed: 26192873]
- 33*. Stranix-Chibanda L, Tierney C, Marr C, George K, Sebikari D, Dadabhai S. Impact of tenofovir-containing triple antiretroviral therapy (ART) on bone mineral density in HIV-infected breastfeeding women in sub-Saharan Africa Oral presentation O_20. 8th International Workshop on HIV Pediatrics; Durban South Africa. 15–16 July 2016; These DXA results document significant bone mineral density decreases for breastfeeding HIV infected women on TDF based ART compared to HIV infected women whose infants were on infant NVP prophylaxis during extended breastfeeding. The findings also raise the question of whether there will be BMD recovery after cessation of lactation and the impact of repeat pregnancy/breastfeeding on maternal bone health for women on lifetime ART.
34. Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate , coformulated with elvitegravir , cobicistat , and emtricitabine , for initial treatment of HIV-1 infection?: two randomised , double-blind , phase 3 , non-inferiority trials. *Lancet*. 2015; 385(9987):2606–2615. DOI: 10.1016/S0140-6736(15)60616-X [PubMed: 25890673]
35. Lockman S, Chinula L, Coletti A. IMPAACT 2010 Phase III Study of the Virologic Efficacy and Safety of Dolutegravir-Containing versus Efavirenz-Containing Antiretroviral Therapy Regimens in HIV-1-Infected Pregnant Women and Their Infants “VESTED” Virologic Efficacy and Safety of ART. http://www.impaactnetwork.org/DocFiles/IMPAACT2010/IMPAACT2010_FINALv1.0_01DEC2016.pdf
36. Lallamant M, Coeur SLE, Sirirungi W, et al. Randomized non-inferiority trial of two maternal single-dose nevirapine sparing regimens to prevent perinatal HIV in Thailand (PHPT-5). *AIDS*. 2016; 29(18):2497–2507. DOI: 10.1097/QAD.0000000000000865.Randomized
37. Nagot N, Kankasa C, Tumwine JK, et al. Extended pre-exposure prophylaxis with lopinavir – ritonavir versus lamivudine to prevent HIV-1 transmission through breastfeeding up to 50 weeks in infants in Africa (ANRS 12174): a randomised controlled trial. *Lancet* 2016. 2016; 387:566–573. (Anrs 12174). DOI: 10.1016/S0140-6736(15)00984-8

38. Cohan D, Natureeba P, Koss CA, et al. Efficacy and Safety of Lopinavir/ritonavir- versus Efavirenzbased Antiretroviral Therapy in HIV-Infected Pregnant Ugandan Women. *AIDS*. 2016; 29(2):183–191. DOI: 10.1097/QAD.0000000000000531.Efficacy
- 39*. Boerma RS, Sigaloff KCE, Akanmu AS, et al. Alarming increase in pretreatment HIV drug resistance in children living in sub-Saharan Africa: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2017; 72:365–371. This is an important timely review and meta-analyses which documents the rapidly increasing rates of antiretroviral resistant mutations being seen among HIV infected children in the past several compared to prior low levels of resistant virus in perinatal populations in Africa a decade ago.
40. Poppe LK, Chunda-Liyoka, Kwon EH, et al. HIV resistance in infants increases with changing prevention of mother-to-child transmission regimens. *AIDS*. 2017; 31:1885–1889. [PubMed: 28746086]
41. Kityo C, Sigaloff KCE, Boender TS, et al. HIV Drug Resistance among Children Initiating first-line Antiretroviral Treatment in Uganda. *AIDSs Research and Human Retroviruses*. 2016; 32:628–635.
42. Kanthula R, Rossouw TM, Feucht UD, et al. Persistence of HIV drug resistance among South African children given nevirapine to prevent mother-to-child-transmission. *AIDS*. 2107; 31:1143–48.
43. Inzaule SC, Osi S, Akinbiyi G, et al. High prevalence of HIV drug resistance among newly diagnosed infants ages <18 months: results from a national surveillance in Nigeria. *JAIDS*. 2017; ahead of PrInt. doi: 10.1097/QA00000000000001553
44. Crowell CS, Maiga A, Sylla M, et al. High rates of baseline Drug Resistance and Virologic Failure among ART Naïve HIV infected children in Mali. *The Pediatric Infectious Disease Journal*. 2017; ahead of print. doi: 10.1097/INF.00000000000001575
45. Samuel R, Julian MN, Paredes R, et al. HIV-1 Drug Resistance by Ultra-Deep sequencing following short course Zidovudine, single-Dose NVP and single dose Tenofovir with Emtricitabine for Prevention of Mother-to-Child Transmission. *J Acquir Immune Defic Syndr*. 2016; 73:384–89. [PubMed: 27327263]
46. Hauser A, Kuesherer C, Kunz A, et al. comparisons of 454 Ultra-Deep Sequencing and Allele-Specific Real-time PR with regard to the Detection of Emerging Drug-Resistant Minor HIV-1 Variants after Antiretroviral Prophylaxis for Vertical Transmission. *PLoS One*. 2015 DOI:10.1371/journal.pone.0140809.
47. Cozzi-Lepri A, Noguera-Julian M, Di Giallonardo F, et al. Low frequency drug-resistant HIV-1 and risk of virological failure to first-line NNRTI-based ART: A multicohort European case-control study using centralized ultrasensitive 454 pyrosequencing. *J Antimicrob Chemother*. 2015; 30:930–940.
48. Nachega JB, Uthman OA, Anderson J, et al. Adherence to antiretroviral therapy during and after pregnancy in low-income, middle –income and high –income countries: a systematic review and meta-analysis. *AIDS*. 2012; 26:2039. [PubMed: 22951634]
49. Matthews LT, Ribaud HB, Kaida A, et al. HIV-infected Ugandan women on antiretroviral therapy maintain HIV-1 RNA suppression across periconception, pregnancy and postpartum periods. *J Acquir Immune Defic Syndr*. 2016; 71:399–406. [PubMed: 26495883]
50. Davis NL, Miller WC, Hudgens MG, et al. Maternal and breast milk viral load: impacts of adherence on peri-partum HIV infections averted – the BAN study. *J Acquir Immune Defic Syndr*. 2016 Aug 1. [Epub ahead of print].
51. Davis NL, Miller WC, Hudgens MG, et al. Adherence to extended postpartum antiretrovirals is associated with decreased breast milk HIV-1 transmission. *AIDS*. 2014; 28:2739–49. [PubMed: 25493600]
52. Phillips T, McNairy ML, Zerbe A, Myer L, Abrams E. Implementation and operational research: postpartum transfer of care among HIV-infected women initiating antiretroviral therapy during pregnancy. *J Acquir Immune Defic Syndr*. 2015; 70:e102–9. [PubMed: 26470033]
53. Philips T, Thebus E, Bekker LG, et al. Disengagement of HIV-positive pregnant and postpartum women from antiretroviral therapy services: a cohort study. *J Int AIDS Soc*. 2014; 17:19242. [PubMed: 25301494]

54. Ngarina M, Kilewo C, Karlsson K, et al. Virologic and immunologic failure, drug resistance and mortality during the first 24 months postpartum among HIV-infected women initiated on antiretroviral therapy for life in the Mitra plus study, Dar es Salaam, Tanzania. *BMC Infect Dis.* 2015; 15:175. [PubMed: 25886277]
55. Hoffmann CJ, Cohn S, Mashabela F, et al. Treatment failure, drug resistance and CD4 T-cell count decline among postpartum women on antiretroviral therapy in South Africa. *J Acquir Immune Defic Syndr.* 2016; 71:31–7. [PubMed: 26334739]
56. Huntington S, Thorne C, Newell ML, et al. The risk of viral rebound in the year after delivery in women remaining on antiretroviral therapy. *AIDS.* 2015; 29:2269–78. [PubMed: 26544700]
57. Myer L, Phillips TK, Hsiao NY, et al. Plasma viremia in HIV-positive pregnant women entering antenatal care in South Africa. *J Int AIDS Soc.* 2015; 18:20045. [PubMed: 26154734]
58. Chen JY, Ribaud HJ, Souda S, et al. Highly Active Antiretroviral Therapy and Adverse Birth Outcomes among HIV-infected Women in Botswana. *J Infect Dis.* 2012; 206:1695–1705. [PubMed: 23066160]
59. Kourtis AP, Schmid CH, Jamieson DJ, et al. Use of antiretroviral therapy in pregnancy HIV-infected women and the risk of premature delivery: a meta-analysis. *AIDS.* 2007; 21:607–615. [PubMed: 17314523]
60. Rodriguez VK, Lacabe RP, Privette CK, et al. The Achilles heel of prevention to mother-to-child transmission of HIV: Protocol implementation, uptake and sustainability. *Sahara J.* 2017; :38–52. DOI: 10.1080/17290376.2017.1375425 [PubMed: 28922974]
61. Gill MM, Umutoni A, Hoffman HJ, et al. Understanding Antiretroviral Treatment Adherence among HIV-Positive Women at for Postpartum Time Intervals: Qualitative Results from the Kabehe Study in Rwanda. *AIDS Patient Care and STDs.* 2017; 31:153–166. [PubMed: 28358624]
62. Nance N, Prosper P, Masanja J, et al. Short-term effectiveness of a community health worker intervention for HIV infected pregnant women in Tanzania to improve treatment adherence and retention in care: a cluster-randomized trial. *PLoS One.* 2017 DOI.org10.1371/journal.pone.0181919.

Key points

Substantial progress has been made in the worldwide reduction of HIV transmission from mothers to their children over the past decade with most recent reductions related to the roll out of “Test and Treat.”

However, current ART strategies are associated with increased risk of adverse pregnancy outcomes including low birthweight and preterm delivery with use of maternal Antiretroviral Therapy compared to zidovudine regimens as highlighted with the PROMISE 1077BF/1077FF clinical trial data.

Maternal adherence to taking lifetime HIV treatment remains a major challenge: increasingly high rates of maternal HIV resistance to nonnucleoside reverse transcriptase inhibitors and nucleoside reverse transcriptase inhibitors are being documented among newly diagnosed HIV infected pregnant women; as well as among HIV infected young children being started on antiretroviral treatment.

Figure 1. Increased antiretroviral drug coverage for prevention of mother-to-child transmission of HIV, by Global Plan Priority (GPP) country in sub-Saharan Africa (2009–2015). UNAIDS data
Legend: Bar graph. Source UNAIDS 2016 data estimates. Based on [3] http://www.unaids.org/sites/default/files/media_asset/GlobalPlan2016_en.pdf (last accessed Oct 18, 2017). PMTCT ARV maternal uptake for 20 UNAIDS GPP countries in sub-Saharan Africa. The presented 2016 estimates do not include Ethiopia. Country-level data were based on proportion of HIV-infected pregnant women who received antiretroviral medicines (excluding single-dose nevirapine only regimens) for PMTCT. Botswana, Mozambique, Namibia, South Africa, Swaziland, and Uganda achieved the UNAIDS 90% coverage by 2015 target set in 2009.

Figure 2. Antiretroviral Therapy Randomized Control Trials for Prevention of mother to child transmission of HIV (1994–2017)

Legend: Presentation of Key Perinatal HIV Prevention Trials, modified from power point slide by Dr. James McIntyre. Key: Lamivudine (3TC); Antiretroviral therapy (ART); US Centers for Disease Control and Prevention (CDC); HIV Prevention Trials Network (HPTN); Nelfinavir (NFV); Nevirapine (NVP); Pediatric AIDS Clinical Trials Group (PACTG); Post-Exposure Prophylaxis (PEPI); Promoting Maternal and Infant Survival Everywhere (PROMISE); Single dose Nevirapine (sdNVP); Six Weeks of Nevirapine (SWEN); Zidovudine (ZDV)

Figure 3. Overall design of the PROMISE 1077BF trial including the Antepartum, Postpartum and Maternal Health components. N=3490

PROMISE Trial 1077 Schema: In the Antepartum Component, pregnant HIV infected women were randomized to one of three regimens: either maternal Zidovudine (ZDV) or one of two Maternal Antepartum Triple Antiretroviral Regimens: antepartum Zidovudine/Lamivudine/Lopinavir/Ritonavir or Tenofovir/emtricitabine/Lopinavir/Ritonavir. In the Postpartum Component, HIV infected mothers or their newborns were randomized to either receive daily maternal triple antiretroviral prophylaxis, Tenofovir/Emtricitabine/Lopinavir/Ritonavir; or to daily infant nevirapine, using WHO weight adjusted dosing through 18 months post delivery or cessation of breastfeeding, whichever occurred sooner. In the Maternal Health Component, HIV infected mothers who had been randomized to postpartum Triple ARVs were randomized at entry into Maternal Health Component to either continue or stop triple antiretrovirals at 18 months post delivery; or at the cessation of breastfeeding, whichever occurred sooner. The mothers were then followed to the end of PROMISE.

Based on [19].

Table 1**PROMISE 1077 EFFICACY AND SAFETY FINDINGS**

	ARV regimens Compared and N	Efficacy Findings	Safety Comparisons
Antepartum Component	ZDV plus SD NVP at labor/delivery and 2 week tail of TDF/FTC	0.56% ZDV/3TC/Lop/r or TDF/FTC/Lop/r ART vs 1.8% for ZDV regimen at 1 week post delivery visit. Repeated CI difference -1.3 (-2.1 to -0.4)	Maternal ART associated with significantly increased Adverse Pregnancy Outcomes compared to ZDV :
			LBW 12% ZDV arm vs 23% ART arm, P<001;
			PTD 13.1% ZDV arm vs 23 vs 23% ART arm; p<001
			Composite adverse outcome 27.5% ZDV arm vs 40% ART arm; p <001.
Post partum Component	Maternal daily TDF/FTC/Lop/r ART versus daily infant NVP throughout BF or 18 months of age, whichever comes sooner	0.57% transmission for maternal ART and 0. 58% for infant NVP regimens by 18 months post delivery or end of breastfeeding which came first. No Significant (NS) differences efficacy or seen at 18 months by study arm. Overall 24 month survival 97.1% mat ART arm vs 97.8% infant NVP arm. NS difference.	No significant differences in maternal 13.1% mat ART arm vs 13.4% infant NVP arm or grade 3 or higher lab toxicities; or for infant grade 3 or higher lab toxicity 34.9% maternal ART and 35.1% infant NVP arm.
Maternal Health Component	Continuation of TDF/FTC/Lop/r or stopping of ART after cessation of Breastfeeding	NS differences in progression to AIDS or death with continuation vs stopping ART 15.3 vs 13.9 per 100/PY (HR, 1.03 0.8–1.3)	WHO stage 2 and 3 events were reduced with continuing ART, 2.7 continued d ART vs 4.7 rate stopped ART per 100/PY (HR 0.60, 95%CI 0.39–0.90, p=0.01).Composite time to grade 3 or higher lab event:

Details of abbreviations/acronyms. ARV (antiretrovirals); ART (antiretroviral therapy); ZDV/3TC/Lop/r (zidovudine/ lamivudine/lopinavir/ritonavir); TDF/FTC/Lop/r (tenofovir/emcitrabine/lopinavir/ritonavir); CI (95% Confidence Interval); PTD (preterm delivery <37 weeks); LBW (low birth weight <2500grams); PY (person years).