Prevention of new pediatric HIV infections: A work in progress

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This activity is jointly provided by Physicians' Research Network and the Medical Society of the State of New York.

A **work in progress**

- Basics of preventing new pediatric infections
- The story at home – epi update, key issues in treatment of pregnant women living with HIV and their infants
- The global picture – epi update, root cause analysis for failure to reach targets
- COVID-19: impact on pregnancy, vertical transmission, HIV service delivery

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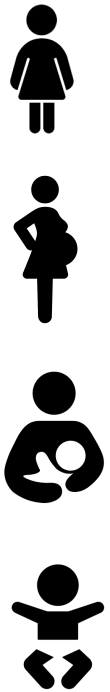
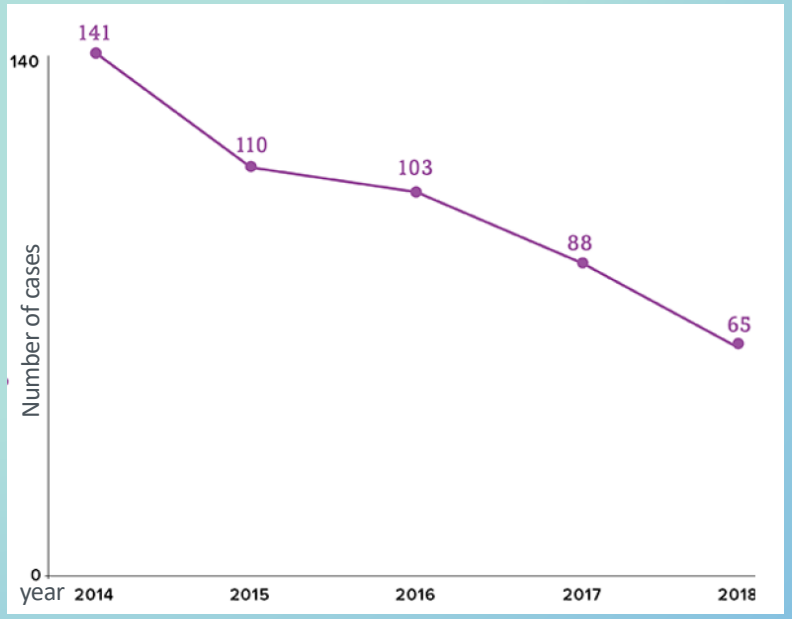
What have we learned over the last 35 years?

- Terminology has evolved: prevention of mother-to-child HIV transmission to prevention of perinatal or vertical transmission.
- Perinatal transmission can occur during pregnancy (in utero), labor & delivery (intrapartum), and breastfeeding (postnatal).
- Maternal plasma HIV RNA viral load (VL) is the **major determinant** of risk of perinatal transmission.
- Suppressive antiretroviral treatment (ART) to the mother, coupled with infant antiretroviral (ARV)prophylaxis, **reduces the risk** of perinatal transmission, preventing new pediatric infections and preserving maternal health.
    - Lowest perinatal transmission rates are among women on suppressive ART begun prior to conception.
    - Sustained undetectable maternal VL is associated with very low risk of perinatal infection.
    - Whether Undetectable = Untransmissible (U=U) applies fully to perinatal transmission, particularly postnatal transmission, is still under discussion.
- Effectively we have the knowledge to prevent new child HIV infections.
    - Recognize critical importance of **maximizing maternal health**

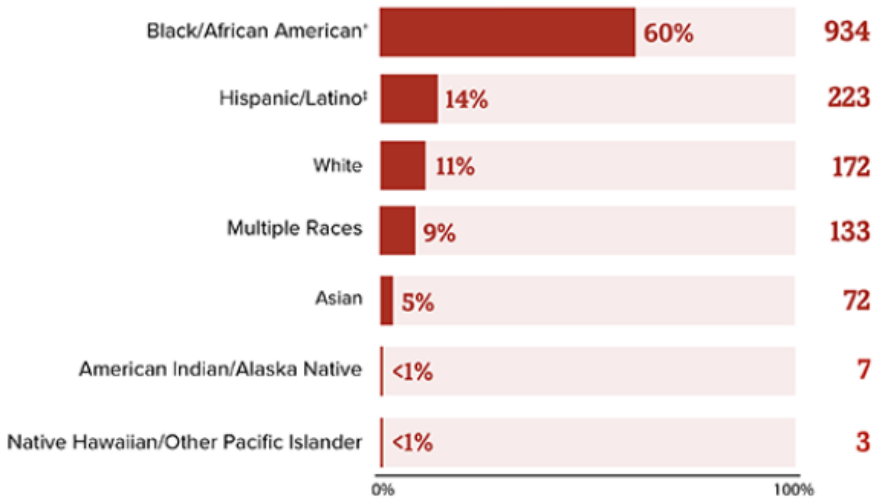


Diagnoses of Perinatal HIV Infections in the US and Dependent Areas, 2014-2018

- Of 37,968 new HIV diagnoses in the US and dependent areas in 2018, <1% (65) were attributed to perinatal transmission
- HIV diagnoses declined 54% among children overall from 2014 to 2018

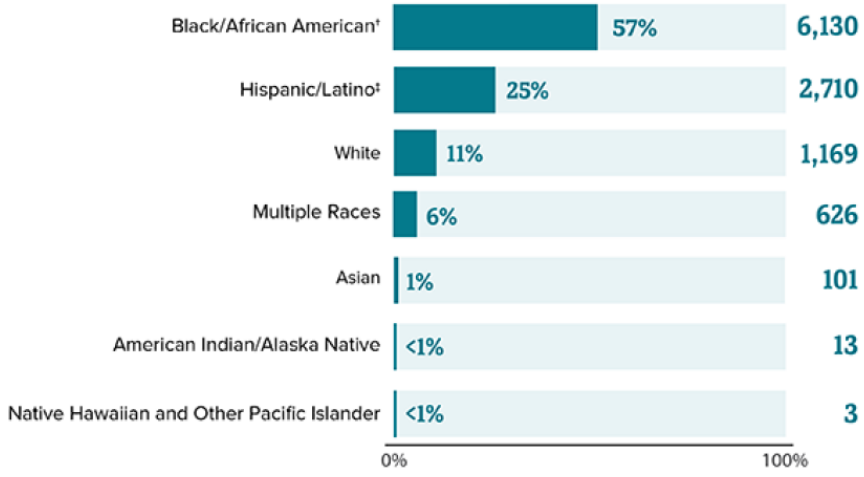


Source: CDC. Surveillance Report 2020;31



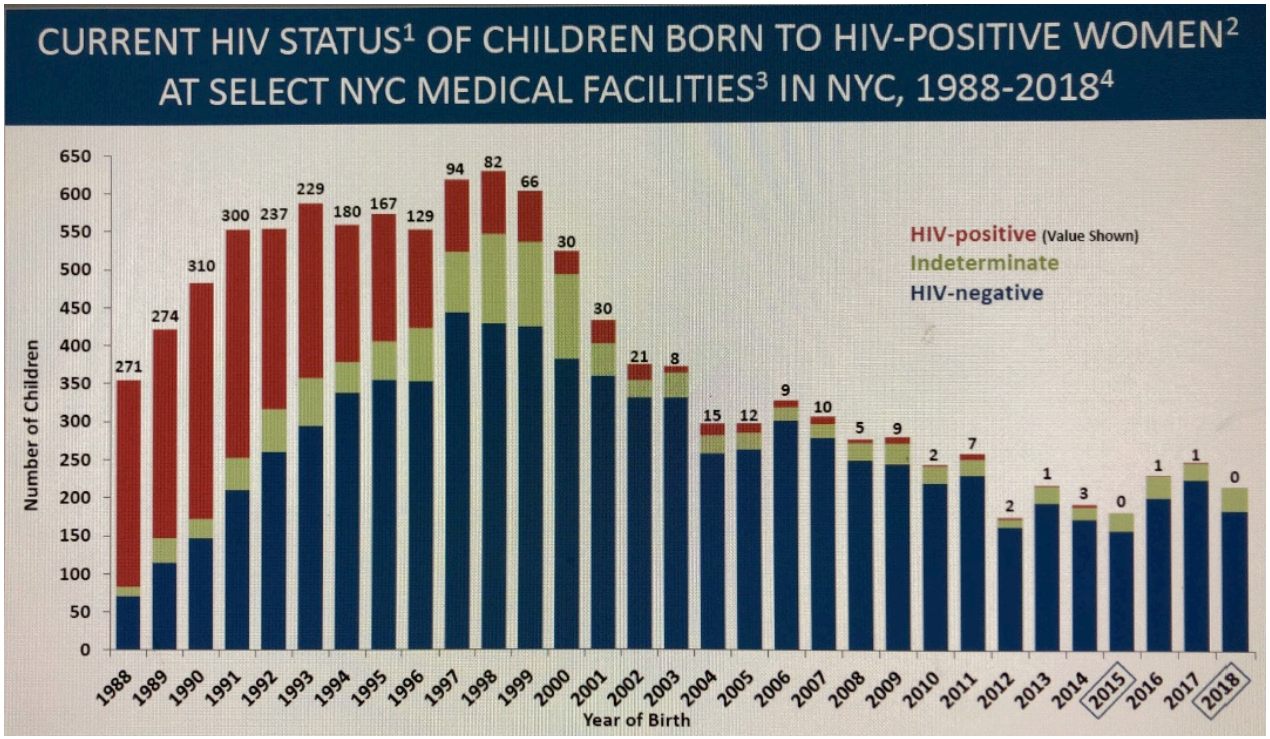
1544 children <13 years of age living with HIV in the US, 2018. Most are Black/African American

10,752 adults and adolescents with diagnosed perinatal HIV in the US, 2018. Most are Black/African American



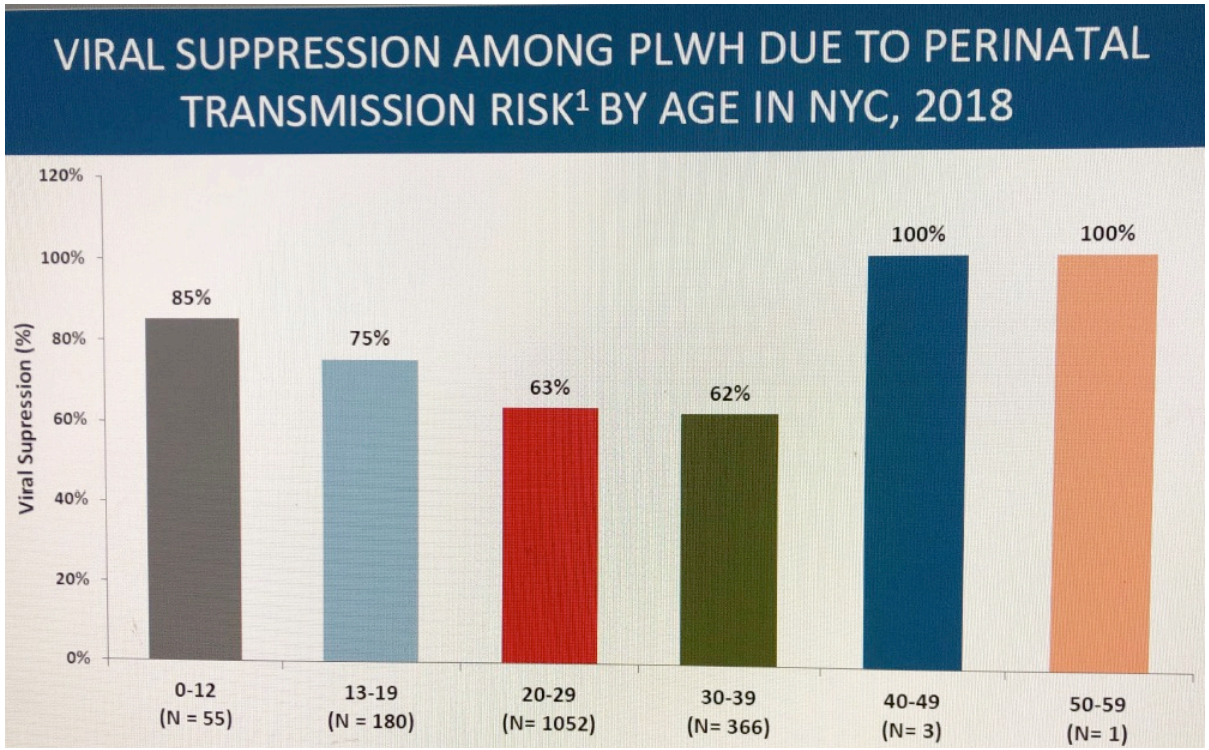
Source: CDC. Surveillance Report 2020;31

Perinatal HIV among children in NYC, 2018



https://www1.nyc.gov/site/doh/data/data-sets/epi-surveillance-slide-sets.page

Perinatal HIV among children in NYC, 2018



https://www1.nyc.gov/site/doh/data/data-sets/epi-surveillance-slide-sets.page

Why are we still seeing new pediatric infections in the US?

While increasingly rare, new infections among children are associated with:

- Poor access to prenatal care and routine HIV testing
- Poor adherence and engagement in care
    - Including substance use and mental illness
- New maternal infections during pregnancy and breastfeeding

Key issues in the treatment of pregnant women living with HIV and their infants

ARV choices for treatment during pregnancy

PrEP during pregnancy and breastfeeding

Reexamination of breastfeeding practices

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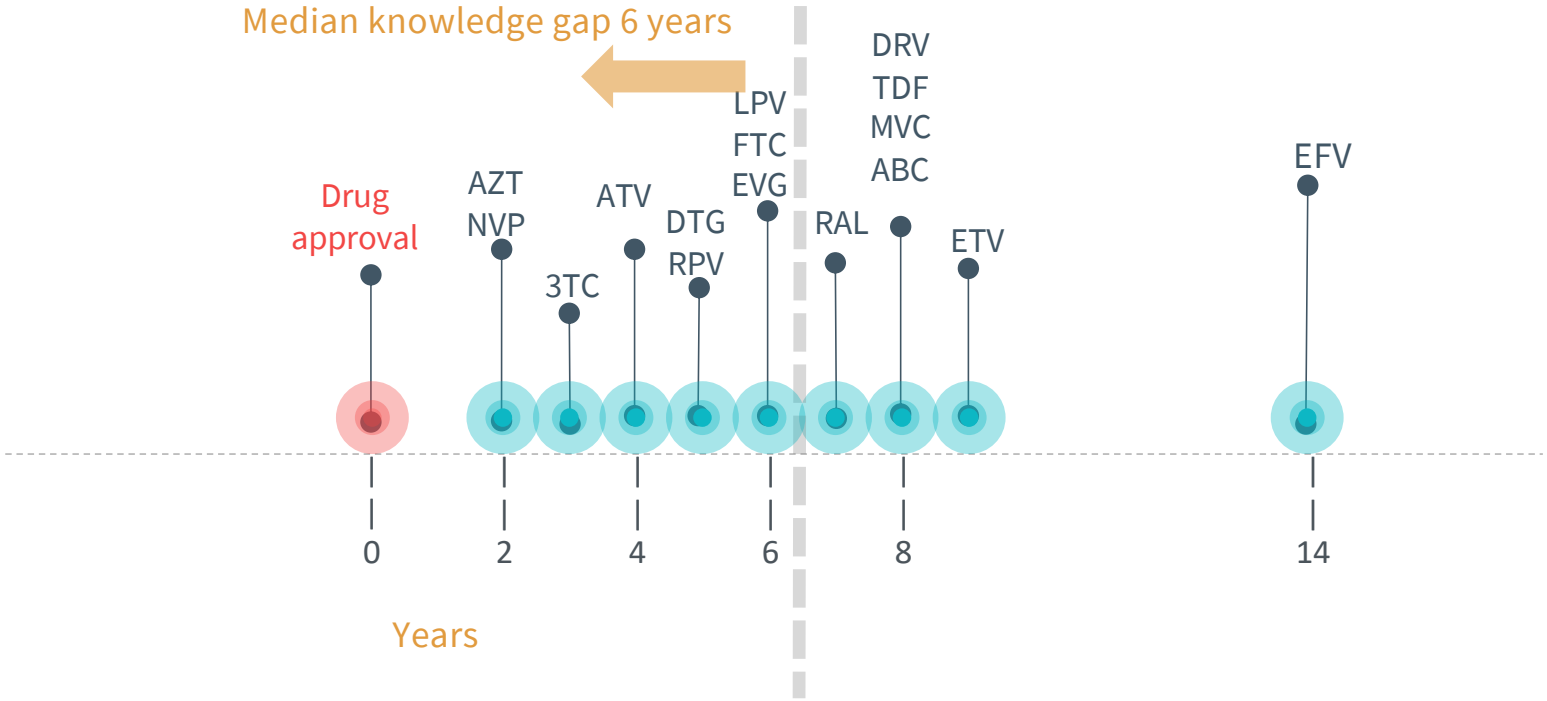
Evolving research paradigm

- Historically research has focused on ARV studies to reduce perinatal transmission rates.
  - Starting with monotherapy (AZT, single dose nevirapine), incremental increases in duration of exposure, ARV number and combinations
  - Calibrating interventions to maternal health status
- Transition in guidance and approaches to HIV treatment.
  - Endorsement of universal treatment and general agreement that all individuals living with HIV, *including pregnant and breastfeeding women*, should receive lifelong suppressive ART.
  - Introduction of 'optimized' regimens for HIV treatment in LMIC.

Focus for prevention of perinatal transmission research

- Decreased emphasis on testing regimen efficacy to reduce the risk of perinatal transmission.
  - Most new regimens are highly efficacious and transmission rates among women on traditional RCTs are very low.
  - Still a need to document viral efficacy during pregnancy conditions.
- Enhanced attention to establishing proper dosing in pregnancy and determining the safety profile.
  - Maternal health outcomes
  - Pregnancy outcomes
  - Child health outcomes (birth – 1000 days)

Time-to-first published pharmacology data in pregnancy



https://globalhealthtrainingcentre.tghn.org/research-toolkit-paediatric-antiretroviral-drug-and-formulation-development/

Why the long delay?

- Pregnant women are *excluded* from Phase II and III trials of new agents
  - To protect the fetus from potential harm
- Data on new agents in pregnancy generally obtained through post-marketing opportunistic studies
  - PK and safety studies among women who become pregnant while on ART with the new agent
  - Post-market surveillance including the Antiretroviral Pregnancy Registry (APR)
- However, once a drug is on the market it can be used during pregnancy
  - May lead to **greater harm** if there are no data in the population using the agent
  - Increasing recognition that exclusion of pregnant women from research does NOT remove risk, but simply **shifts risk** from a setting with informed consent and intensive monitoring to routine clinical setting

Excluding pregnant women from ARV trials can lead to greater harm

- Reproductive toxicity studies of efavirenz (EFV) identified a possible association with neural tube defects (NTD). Reports of NTD in infants with first trimester EFV exposure led to a label change to Pregnancy Class D. EFV was introduced as an optimal regimen by WHO in 2010 but restricted during pregnancy. Pregnant women were expected to receive nevirapine, a more toxic agent.
  - The risk of NTD was determined NOT to be elevated only after adequate numbers of non-pregnant women conceived on EFV-based ART (off label).
    - *21 studies, 2156 EFV 1st trimester exposures, 2026 live births, 44/2026 birth defects (1.6%), 1/2026 NTD(0.05%)*
  - APR 2019; 27 (2.4%, 95% CI, 1.6%, 3.4%) among the 1,142 infants with 1st trimester EFV exposure including only 1 NTD (0.09%) consistent with expected background prevalence
- Despite cobicistat-containing regimens being potent, convenient, and well-tolerated, cobicistat exposure and its boosting effect are substantially reduced during pregnancy resulting in the recommendation that cobicistat-containing fixed-dose combinations should not be initiated during pregnancy.

Ford N et al. AIDS 2014;28 Supp 2:S123-31; Eke AC, et al. Expert opinion on drug metabolism & toxicology. 2019;15(7):523-525 ;.Boyd SD, et al. AIDS. 2019;33(6):1089-1093.

Birth surveillance and the Botswana Tsepamo Study

- *Designed to evaluate the risk of NTD with preconception EFV exposure*
- Prospective birth outcomes surveillance for major surface birth defects, 8 large maternity wards, including 45% of Botswana births
  - Trained hospital-based midwives to do surface exams
  - Research assistant consent mother for photo
  - Clinical geneticist reviews all diagnoses
- Good denominator with control groups and ability to distinguish between ARV regimens, timing of ART initiation, infant HIV exposure status
- *In May 2016, the Botswana government shifted 1st line ART from tenofovir + lamivudine + efavirenz (TLE) to tenofovir + lamivudine + dolutegravir (TLD)*

Zash R. IAS, Amsterdam July 2018 Late Breaker; Zash R et al. N Engl J Med 2018 July 24 epub

Botswana Tsepamo Study Reported NTD outcomes, May 2018

- **86 NTDs identified in 88,755 births - 0.10% (95% CI 0.08%, 0.12%)**
  - 42 meningocele/myelomeningocele, 30 anencephaly, 13 encephalocele and 1 iniencephaly
- 22 (25%) NTDs occurred among stillbirths
- Among live-born babies with NTDs, 25 (39%) died within 28 days, and 1 had unknown vital status
- **Estimated prevalence of NTD in 2015 globally was 0.19% (95% CI 0.15% to 0.23%)** [18.6 (15.3–23.0)/10,000] live births, with varied distribution geographically, **~0.09-0.14% in Sub Saharan Africa**

Deliveries up to 1 MAY 2018

Dolutegravir (DTG) at conception:

4/426 (0.94%; 95%CI 0.37%, 2.4%)

Non-DTG ART at conception:

14/11,300 (0.12%; 95%CI 0.07%, 0.21%)

EFV at conception:

3/5,787 (0.05%; 95%CI 0.02%, 0.15%)

DTG started during pregnancy:

0/2,812 (0.00%; 95%CI 0.0%, 0.13%)

Non-DTG ART started during pregnancy:

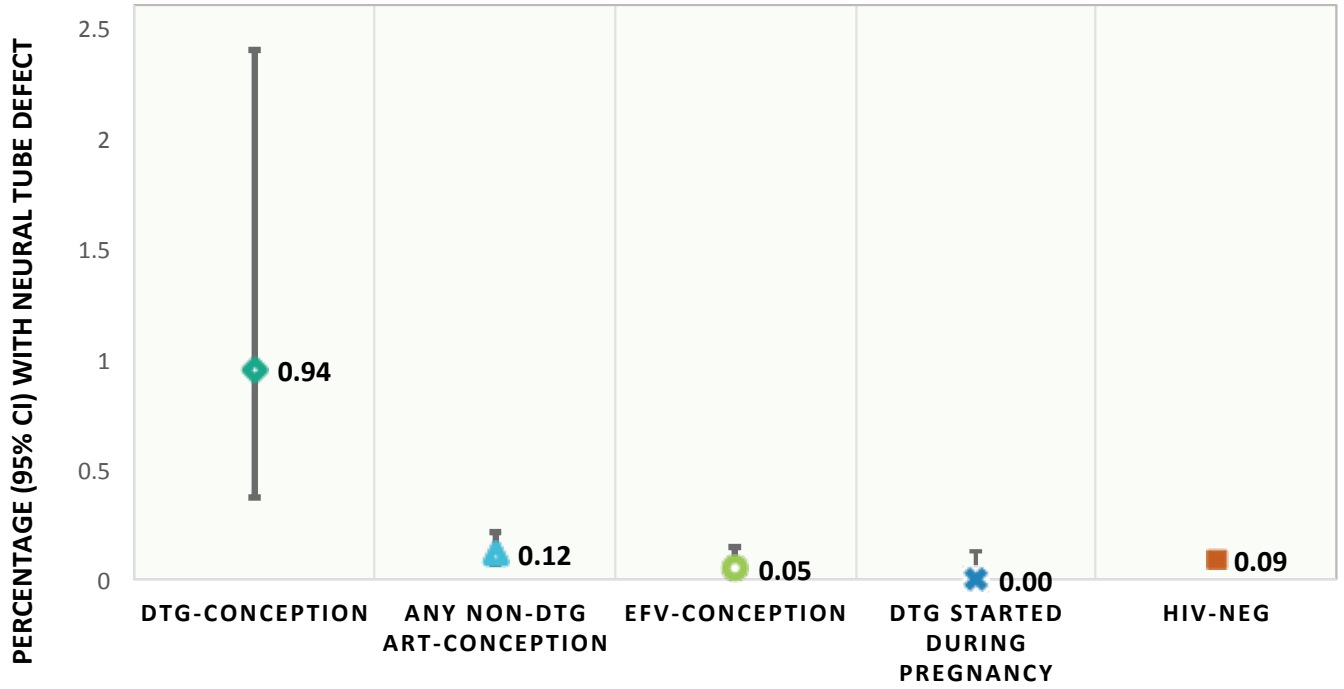
3/5,624 (0.05%, 95% CI 0.02%, 0.16%)

HIV-uninfected

61/66,057 (0.09%, 95%CI 0.07%, 0.12%)

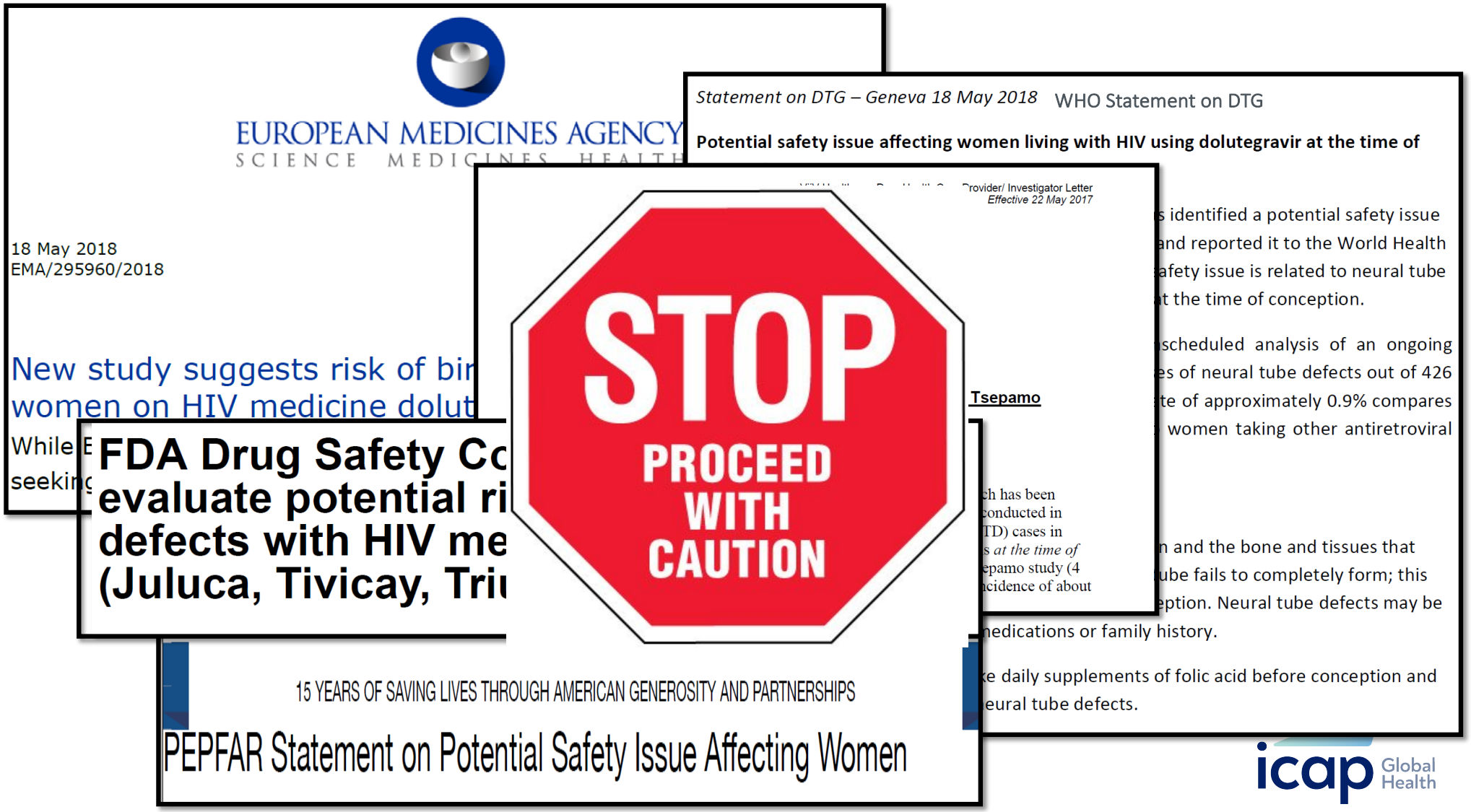
Zash R. IAS, Amsterdam July 2018 Late Breaker;
Zash R et al. N Engl J Med 2018 July 24 epub

Neural Tube Defect prevalence by exposure, 2018



NTDs/Exposures	4/426	14/11,300	3/5,787	0/2.812	61/66,057
% with NTD (95% CI)	0.94% (0.37%, 2.4%)	0.12% (0.07%, 0.21%)	0.05% (0.02%, 0.15%)	0.00% (0.00%, 0.13%)	0.09% (0.07%, 0.12%)
Prevalence Difference (95% CI)	**ref**	**-0.82% (-0.24%, -2.3%)**	**-0.89% (-0.31%,- 2.3%)**	**-0.94% (-0.35%, -2.4%)**	**-0.85% (-0.27%, -2.3%)**

Zash R. IAS, Amsterdam July 2018 Late Breaker; Zash R et al. N Engl J Med 2018 July 24 epub


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH
18 May 2018
EMA/295960/2018
New study suggests risk of bir
women on HIV medicine dolut
While E
seeking
FDA Drug Safety Co
evaluate potential ri
defects with HIV me
(Juluca, Tivicay, Tri
Statement on DTG – Geneva 18 May 2018
WHO Statement on DTG
Potential safety issue affecting women living with HIV using dolutegravir at the time of
s identified a potential safety issue
and reported it to the World Health
afety issue is related to neural tube
t the time of conception.
scheduled analysis of an ongoing
es of neural tube defects out of 426
te of approximately 0.9% compares
women taking other antiretroviral
n and the bone and tissues that
ube fails to completely form; this
eption. Neural tube defects may be
nedications or family history.
e daily supplements of folic acid before conception and
eural tube defects.
Provider/ Investigator Letter
Effective 22 May 2017
Tsepamo
ch has been
conducted in
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epamo study (4
ncidence of about
STOP
PROCEED
WITH
CAUTION
15 YEARS OF SAVING LIVES THROUGH AMERICAN GENEROSITY AND PARTNERSHIPS
PEPFAR Statement on Potential Safety Issue Affecting Women
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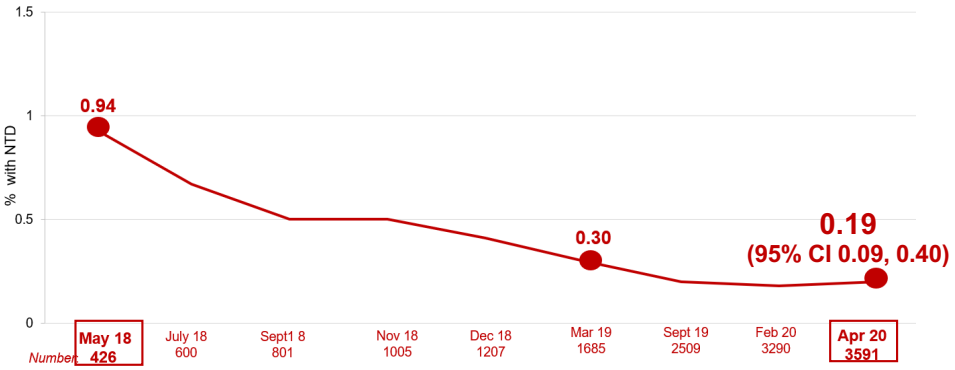
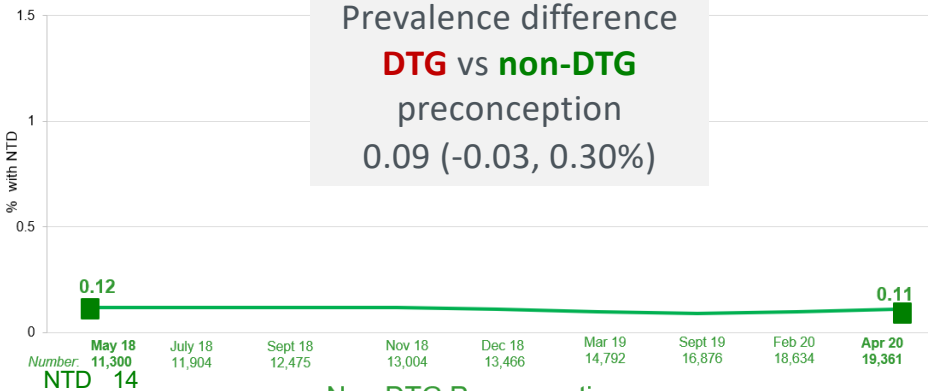
NTD Prevalence by exposure over time

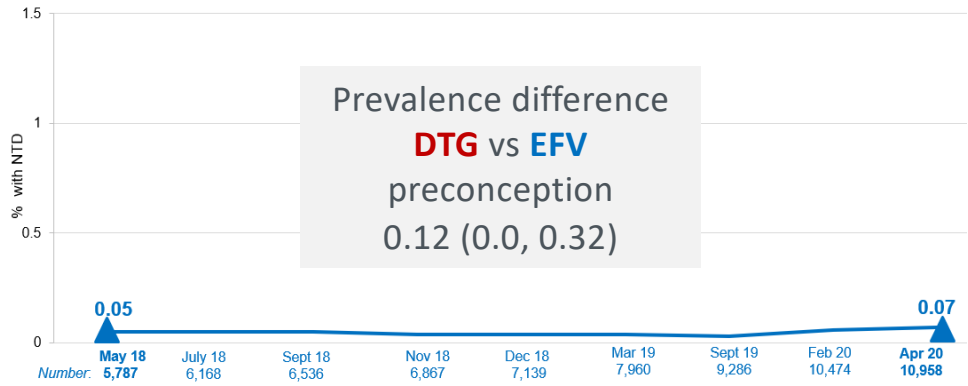


NTD 4 — DTG Preconception — 7



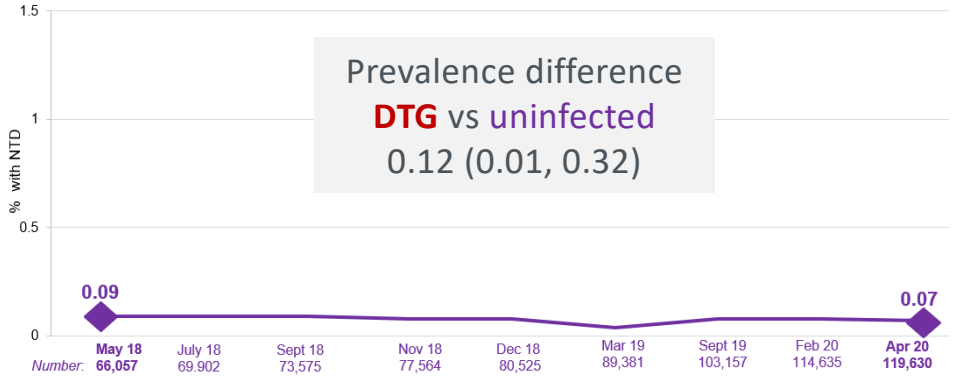
Prevalence difference
DTG vs **non-DTG**
preconception
0.09 (-0.03, 0.30%)

NTD 14 — Non-DTG Preconception — 17



Prevalence difference
DTG vs **EFV**
preconception
0.12 (0.0, 0.32)

NTD 3 — EFV Preconception — 8



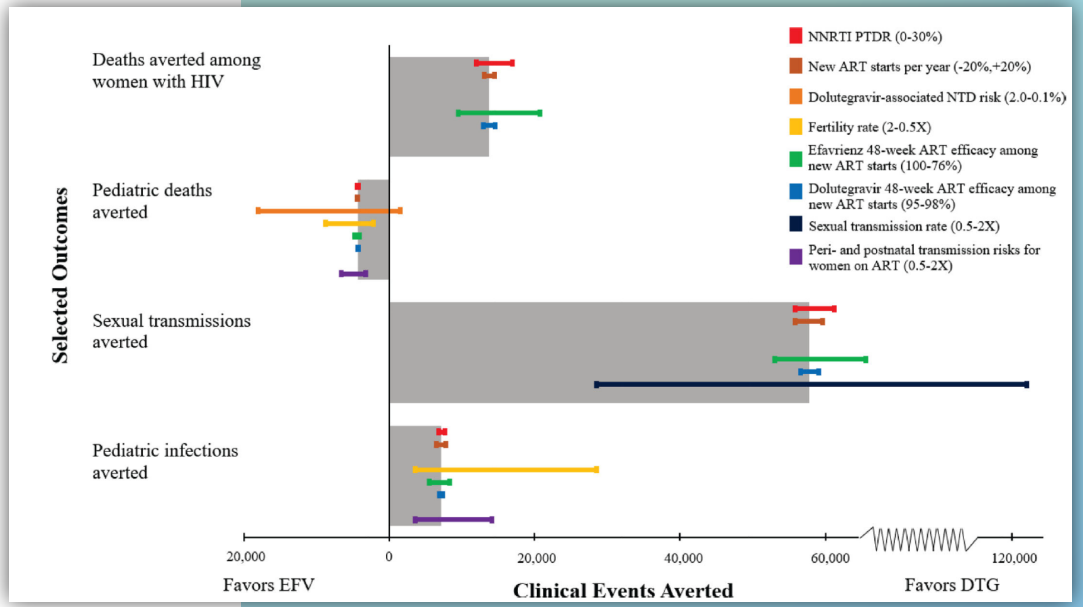
Prevalence difference
DTG vs uninfected
0.12 (0.01, 0.32)

NTD 61 — HIV-Uninfected — 87

Zash R et al. IAS Virtual July 2020 Abs. OAXLB0102

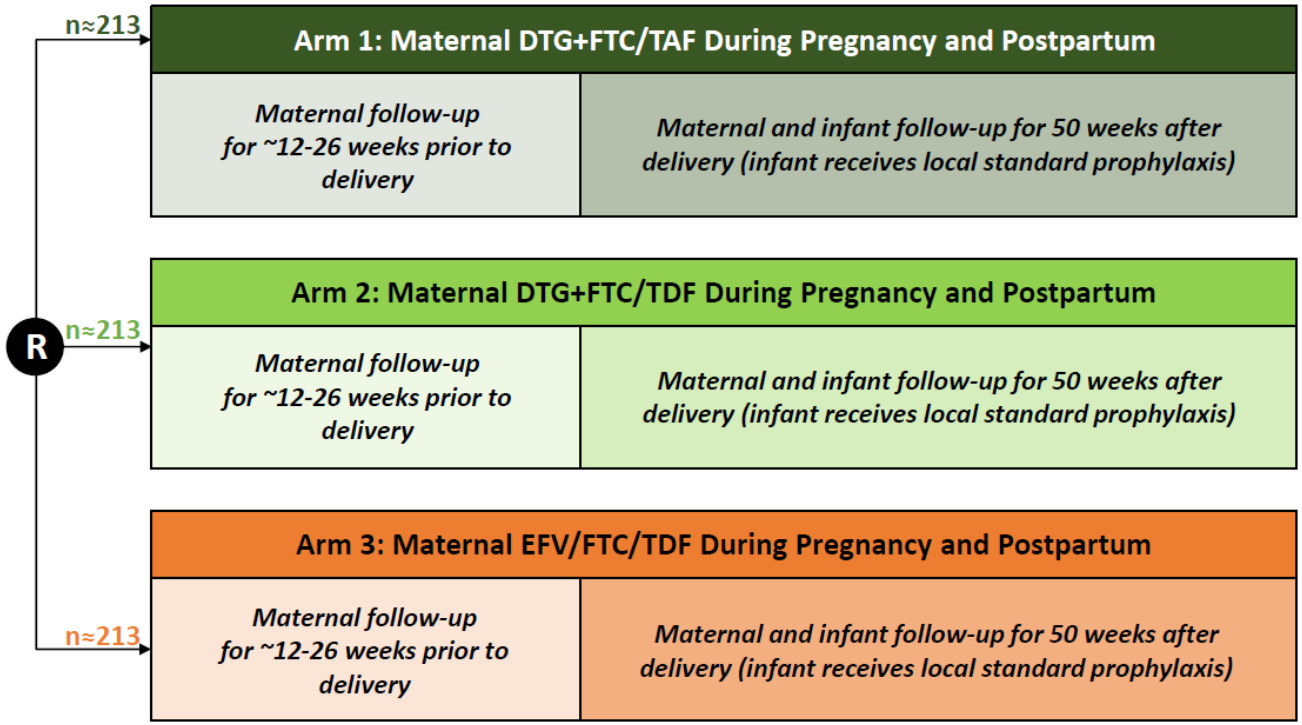
Learning from the DTG story

- Reconsideration of the paradigm for evaluating the risks and benefits of ARV agents and strategies during pregnancy beyond fetal safety
  - Deaths averted among women with HIV
  - Pediatric deaths averted
  - Sexual transmissions averted
  - Pediatric infections averted



Dugdale C. et al. Ann Intern Med 2019

Safety and Efficacy of DTG vs EFV and TDF vs TAF in Pregnancy: IMPAACT 2010 Trial

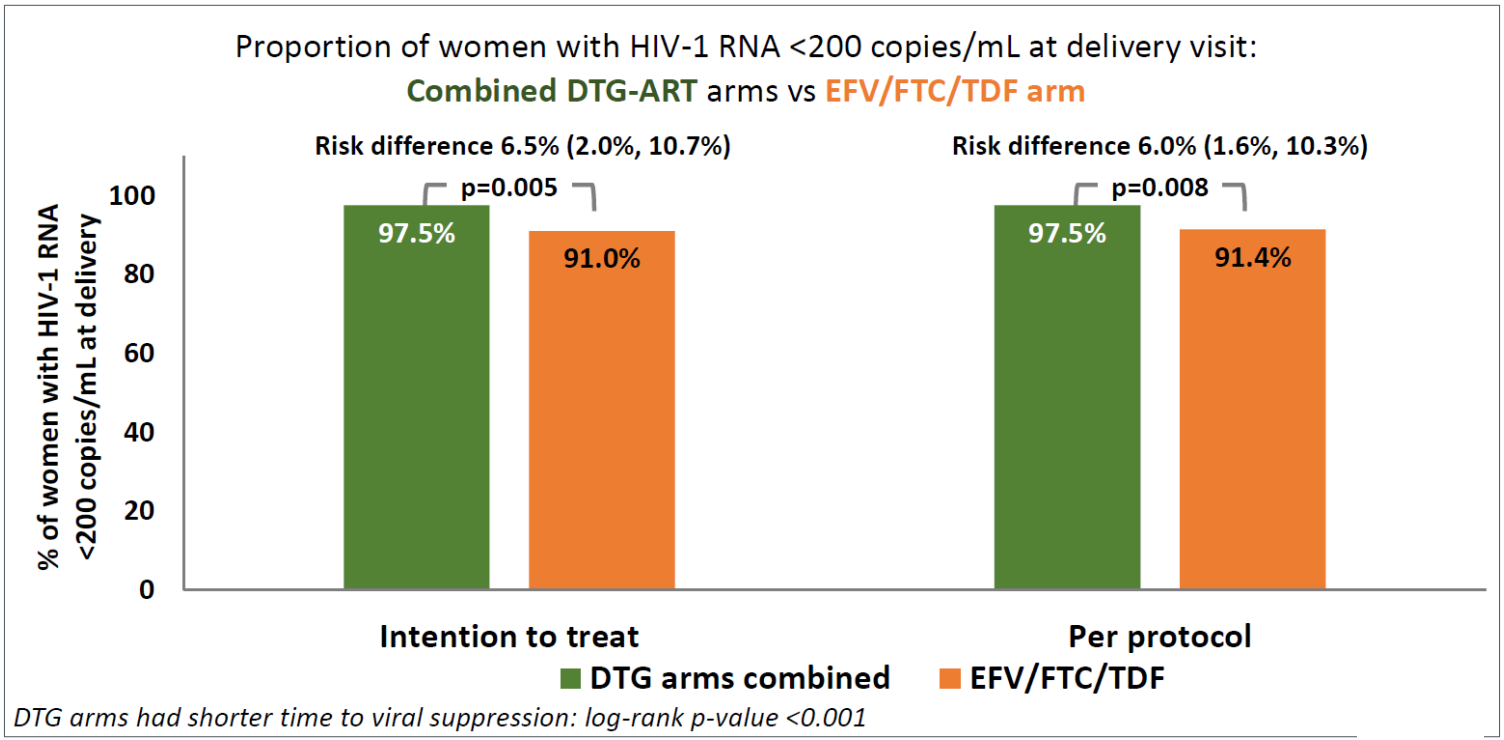


ART naïve pregnant women were randomized to one of three ART regimens

- 22 sites, 9 countries
- Median age 26.6 years
- Median gestation 22 weeks

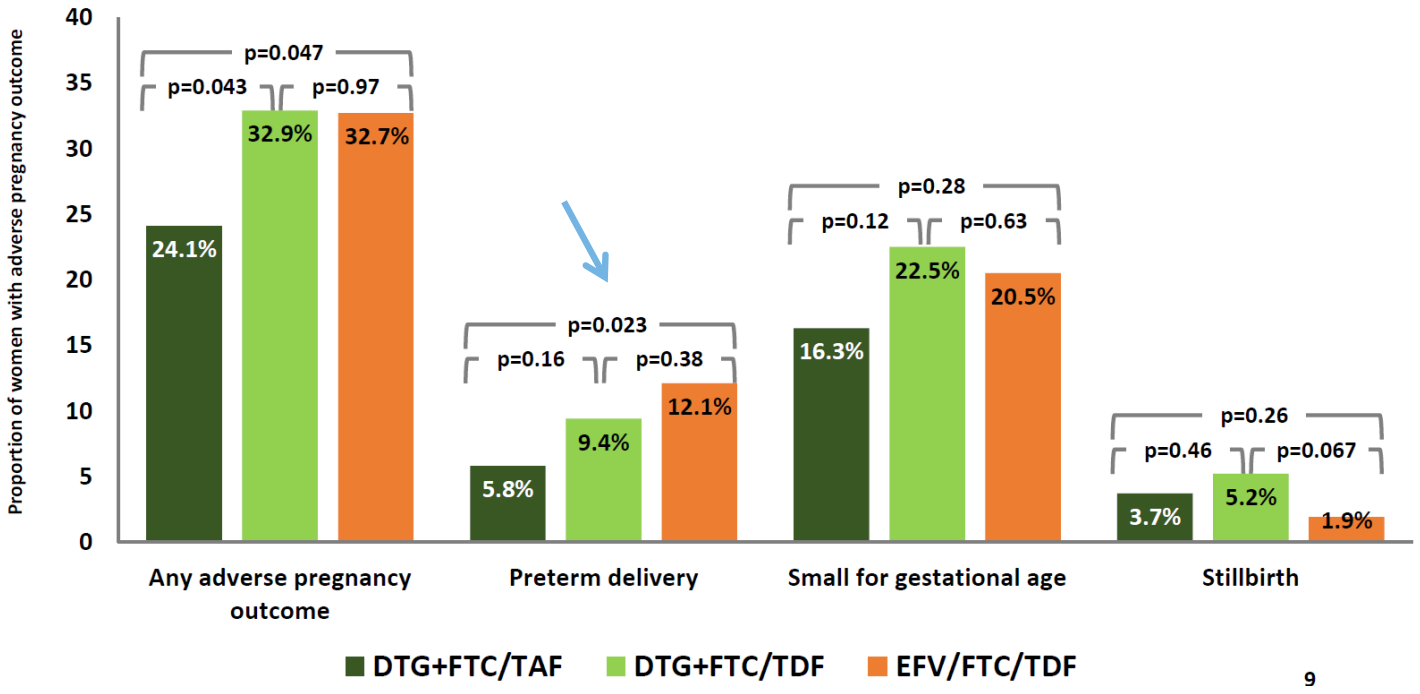
Chinula L et al. CROI, 2020 Boston Abs. 130LB

DTG-containing ART had superior virologic efficacy at delivery compared to EFV/FTC/TDF



Chinula L et al. CROI, 2020 Boston Abs. 130LB

DTG+FTC/TAF was associated with significantly fewer adverse pregnancy outcomes compared with EFV/FTC/TDF



No difference in adverse events between study arms.

Fewer neonatal deaths with DTG arms than EFV/FTC/TDF.

2 infant infections, both in DTG arms

Chinula L et al. CROI, 2020 Boston Abs. 130LB

Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant Women and Nonpregnant Women Who Are Trying to Conceive, Dec 2019

ART Regimen Component	ART for Pregnant Women Who Have Never Received ARV Drugs and Who Are Initiating ART for the First Time	Continuing ART for Women Who Become Pregnant on a Fully Suppressive, Well-Tolerated Regimen	ART for Pregnant Women Who Have Received ARV Drugs in the Past and Who Are Restarting ART[a]	New ARV Regimen for Pregnant Women Whose Current Regimen is Not Well Tolerated and/or is Not Fully Suppressive[a]	ART for Nonpregnant Women Who Are Trying to Conceive[a,b]
INSTIs Used in combination with a dual-NRTI backbone[c]					
DTG[d]	Preferred	Continue	Preferred	Preferred	Alternative
RAL	Preferred	Continue	Preferred	Preferred	Preferred
BIC	Insufficient data	Insufficient data	Insufficient data	Insufficient data	Insufficient data
EVG/c[e]	Not recommended	Consider switching, or continuing the same regimen with frequent viral load monitoring	Not recommended	Not recommended	Not recommended
PIs Used in combination with a dual-NRTI backbone[c]					
ATV/r	Preferred	Continue	Preferred	Preferred	Preferred
DRV/r	Preferred	Continue	Preferred	Preferred	Preferred
LPV/r	Alternative	Continue	Alternative	Alternative	Alternative
ATV/c[e]	Not recommended	Consider altering the regimen, or continuing the same regimen with frequent viral load monitoring	Not recommended	Not recommended	Not recommended
DRV/c[e]	Not recommended	Consider altering the regimen, or continuing the same regimen with frequent viral load monitoring	Not recommended	Not recommended	Not recommended
NNRTIs					

Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Transmission in the United States. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines

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NNRTIs Used in combination with a dual-NRTI backbone[c]					
NVP[g]	Not recommended	Continue	Not recommended, except in special circumstances	Not recommended, except in special circumstances	Not recommended, except in special circumstances
NRTIs[c,h]					
ABC[i]	Preferred	Continue	Preferred	Preferred	Preferred
FTC	Preferred	Continue	Preferred	Preferred	Preferred
3TC	Preferred	Continue	Preferred	Preferred	Preferred
TDF	Preferred	Continue	Preferred	Preferred	Preferred
ZDV	Alternative	Continue	Alternative	Alternative	Alternative
TAF[i]	Insufficient data	Continue	Insufficient data	Insufficient data	Insufficient data

Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Transmission in the United States. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines

Key issues in the treatment of pregnant women living with HIV and their infants

ARV choices for treatment during pregnancy

PrEP during pregnancy and breastfeeding

Reexamination of breastfeeding practices

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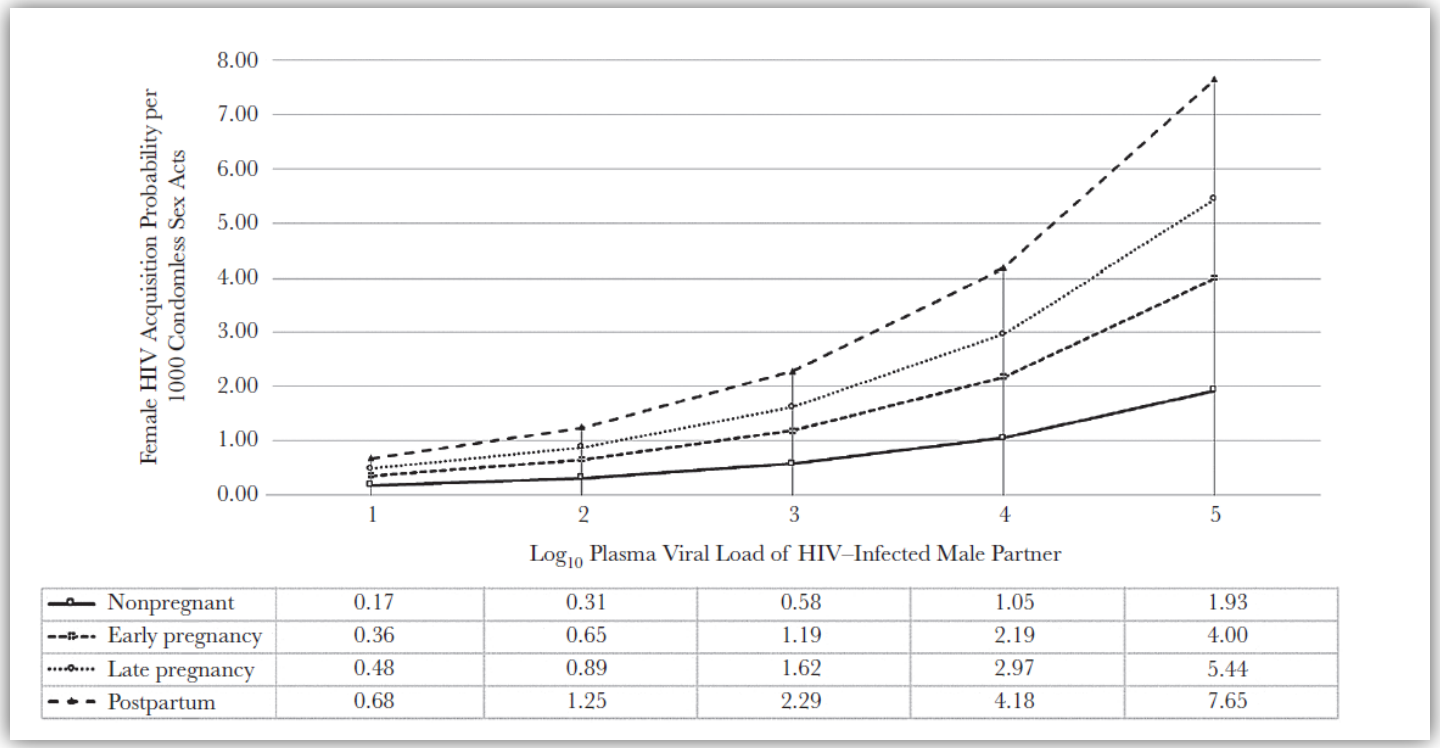
Increased Per-Coital-Act risk of HIV Acquisition throughout Pregnancy and Postpartum



Nonpregnant	0.17	0.31	0.58	1.05	1.93
Early pregnancy	0.36	0.65	1.19	2.19	4.00
Late pregnancy	0.48	0.89	1.62	2.97	5.44
Postpartum	0.68	1.25	2.29	4.18	7.65

Thompson et al , JID 2018

Pregnant women generally excluded from studies of ARVs for PrEP

- Like ARVs for treatment, data generally obtained through opportunistic pharmacology and safety studies among women taking PrEP who become pregnant
  - Several large studies of PrEP in Africa provided preliminary data for TDF
- HPTN 084 (Long-acting cabotegravir) excluded pregnant women and required women to use contraception while on study. The few women who became pregnant had to stop study drug.
- DISCOVER Trial (F/TAF) did not include women
- The dapivirine ring is being studied in pregnancy

TFV-DP levels in pregnancy considerably lower than postpartum, IMPAACT 2009

Interpretation	DBS TFV-DP fmol/punch	
	Pregnancy	Postpartum
~ 7 doses/wk	≥ 650	≥ 950
2-6 doses/wk	200-649	250-949
< 2 doses/wk	< 200	< 250

Based on 25th percentile

Interpretation	DBS TFV-DP fmol/punch	
	Pregnancy	Postpartum
~ 7 doses/wk	≥ 600	≥ 1000
2-6 doses/wk	200-599	400-999
< 2 doses/wk	< 200	< 400

Based on ROC analysis

IMPAACT 2009, Chi, Stranix-Chibana, CROI 2020

PrEP for pregnant and breastfeeding women

- Pilot programs in high HIV prevalence settings
- Interest and uptake increasing globally with recognition of potential increased risk of acquisition
- Challenges in identifying pregnant women at ‘high risk’
- Delayed study of ARV agents for PrEP in pregnancy limit available options
  - Adherence to daily PrEP has been suboptimal among women, particularly young women, in many studies

Key issues in the treatment of pregnant women living with HIV and their infants

ARV choices for treatment during pregnancy

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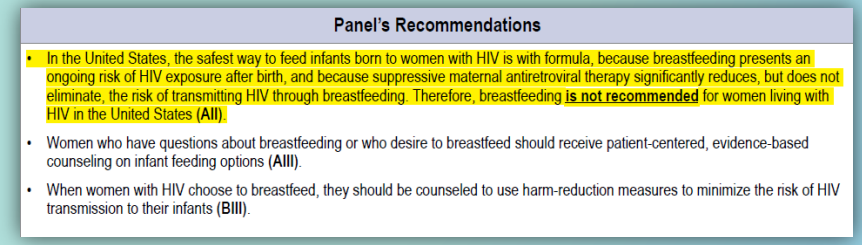
Breastfeeding among women living with HIV in the US

Historically breastfeeding (BF) has not been recommended in US guidelines

Recently US guidance has evolved considering:

- Use of more robust ART regimens
  - Increasing evidence of efficacy of suppressive ART to reduce the risk of postnatal transmission
  - Multiple benefits of BF for mother and child (psychological, early and late health outcomes)
  - Acknowledgement of the desires and voices of mothers who want to BF
  - Breastfeeding is the recommended mode of infant feeding for women on ART in LMIC
- There is significant controversy the applicability of U=U to BF
- The appropriate infant prophylaxis regimen and infant diagnosis algorithm to use during BF has not been determined



Panel's Recommendations

- In the United States, the safest way to feed infants born to women with HIV is with formula, because breastfeeding presents an ongoing risk of HIV exposure after birth, and because suppressive maternal antiretroviral therapy significantly reduces, but does not eliminate, the risk of transmitting HIV through breastfeeding. Therefore, breastfeeding **is not recommended** for women living with HIV in the United States (**AII**).
- Women who have questions about breastfeeding or who desire to breastfeed should receive patient-centered, evidence-based counseling on infant feeding options (**AIII**).
- When women with HIV choose to breastfeed, they should be counseled to use harm-reduction measures to minimize the risk of HIV transmission to their infants (**BIII**).

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Does U=U apply to transmission perinatal transmission?

U=U signifies that an HIV-infected individual on antiretroviral therapy who achieves and maintains an undetectable viral load cannot transmit HIV to their partner.

Principles of U=U

- In order for antiretroviral therapy (ART) to provide maximum benefit, taking medication as prescribed is essential.
- Achieving an undetectable viral load can take up to 6 months of ART. Once achieved, continued adherence is required.
- According to guidelines from the Department of Health and Human Services, viral load testing should be performed every 3-4 months after the plasma HIV-1 RNA level reaches undetectable (<200 copies/mL). If viral suppression and stable immunologic status are maintained for >2 years, the viral load testing can be extended to every 6 months thereafter.
- Stopping therapy negates the validity of assuming that U = U.

In Utero/Intrapartum transmission in Non-Breastfeeding Women Starting ART Prior to Conception

Cohort (Location)	First author (Year)	Viral Load at Delivery			
		Transmission at <50 c/mL	Transmission at 50-400 c/mL	Transmission at 400-1,000 c/mL	Transmission at >1000 c/mL
France	Mandelbrot* (2015)	0% (0/2,651) 95% CI 0 - 0.1%	0.3% (1/301)	2.2% (≥400 copies/mL, 5/230)	
United Kingdom & Ireland (NSHPC)	Townsend (2014)	0% (0/1,894) 95% CI 0 - 0.2%	2.0% (≥50 copies/mL, 3/151)		
Total		0% (0/4,545) 95% CI 0 - 0.8%	1.3% (≥50 copies/mL, 9/682)		

Mandelbrot L et al. *Clin Infect Dis.* 2015;61:1715-25
Townsend CL et al. *AIDS* 2014;28:1049-57

*312 women on preconception ART had ART interruption in first trimester; 4/312, 1.3%, transmitted to infant, despite 2/4 having VL <50 at delivery.

In Utero/Intrapartum transmission in Non-Breastfeeding Women Starting ART During Pregnancy

Cohort (Location)	First author (Year)	Viral Load at Delivery			
		Transmission at <50 c/mL	Transmission at 50-400 c/mL	Transmission at 400-1,000 c/mL	Transmission at >1000 c/mL
France	Mandelbrot* (2015)	0.5% (14/2,694)	2.0% (17/873)	3.1% (≥400 copies/mL, 18/588)	
United Kingdom & Ireland (NSHPC)	Townsend* (2014)	0.1% (2/1,965)	2.2% (≥50 copies/mL, 17/783)		
Total		0.3% (16/4,659)	2.3% (52/2,244)		

Mandelbrot L et al. *Clin Infect Dis.* 2015;61:1715-25
Townsend CL et al. *AIDS* 2014;28:1049-57

*In both studies, MTCT risk associated with **duration of ART** prior to delivery

In Utero/Intrapartum/Early Breastfeeding Transmission in Breastfeeding Women

Location ART start	First author (Year)	Delivery Viral Load			
		Transmission at <50 c/mL	Transmission at 50-400 c/mL	Transmission at 400-1,000 c/mL	Transmission at >1000 c/mL
South Africa 100% start during pregnancy	Myer (2017) MTCT 6 wk	0.25% (1/406)	2.0% (50-1,000 c/mL, 2/102)		8.5% (4/47)
Malawi 50% before pregnancy	Landes (2019) MTCT 4-24 wk	0.9% (8/902)	7.0% (6/86)		14.0% (19/136)
South Africa Likely most preconception	Moyo (2020) MTCT birth	0.3% (3/946)*	3.2% (6/187)		7.9% (25/316)

Myer L et al. HIV Med. 2017;18:80-88; Landes M et al. JIAS. 2019;22:e25290; Moyo et al. JAIDS.2020;83:390-6;Davies NL et al. JAIDS. 2016;73:572-80.

*2 no prior VL, 1 VL >1,000 3 mo before delivery; ** Undetectable plasma and breast milk RNA

Late Breastfeeding Transmission, ART, and Maternal VL

First Author (Year)	Study location	Findings
Flynn (2018)	Multi-country (PROMISE study)	2 infant infections in mothers who initiated ART postpartum with subsequent viral load <40 copies/mL
Luoga (2018)	Tanzania	1 infant infection where the maternal viral load was <1000 copies/mL but mother had a disruption in therapy
Giuliano (2013)	Malawi	1 infant infection where mother initiated ART during pregnancy and had a subsequent viral load <37 copies/mL

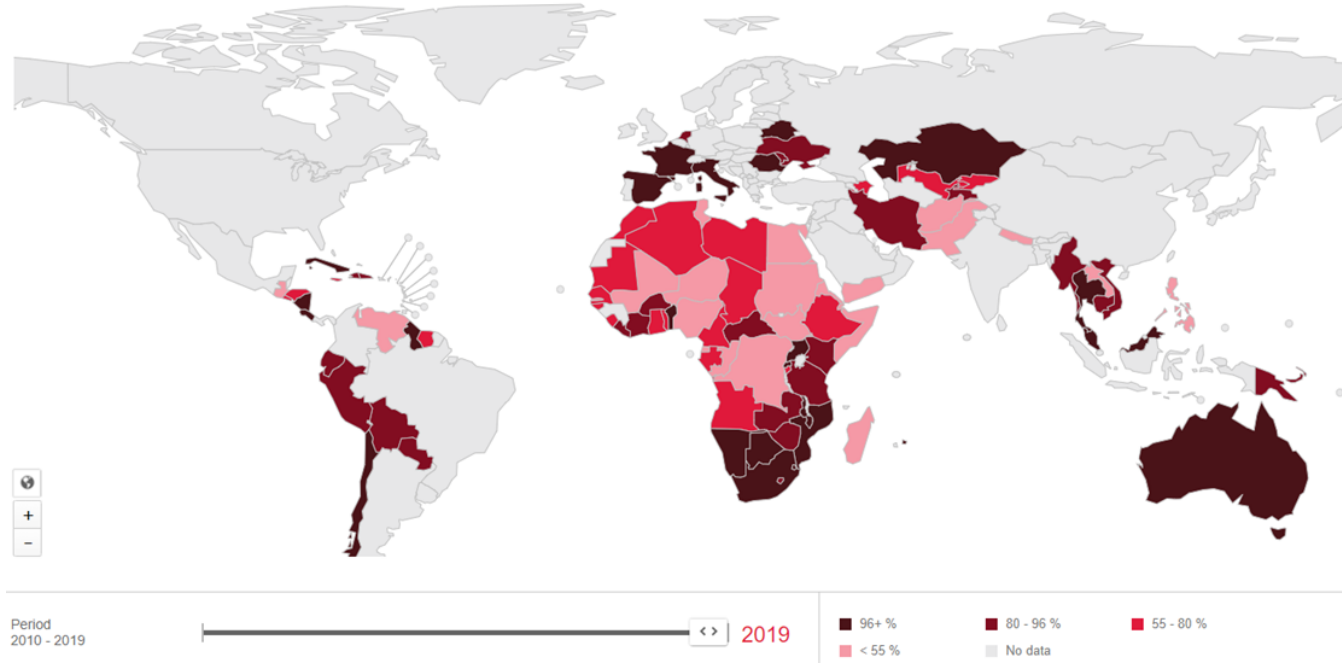
Does U=U apply to perinatal transmission? Not perfectly….

- Likely need to use <50 c/mL rather than <200c/mL
  - Women on effective ART prior to conception, no breastfeeding - yes
  - Women starting ART during pregnancy, no breastfeeding – almost (very low risk)
  - Women on ART and breastfeeding – less certain
    - *Early transmissions (first six weeks) documented among women starting ART before and during pregnancy virally suppressed at delivery*
    - *Limited data on late transmissions (through 12-24 months) but transmissions have been reported among virally suppressed women*
- While U=U may not be a perfect fit for prevention of perinatal transmission, it is clear that the risk of transmission during pregnancy, delivery and breastfeeding is **extremely low** when the mother's viral load is undetectable

- Likely to see a shift in practice and guidance to a more nuanced, patient-centered approach, balancing the risks and benefits of breastfeeding
- Urgent need to define optimal infant prophylaxis regimens in the context of suppressive maternal ART and breastfeeding

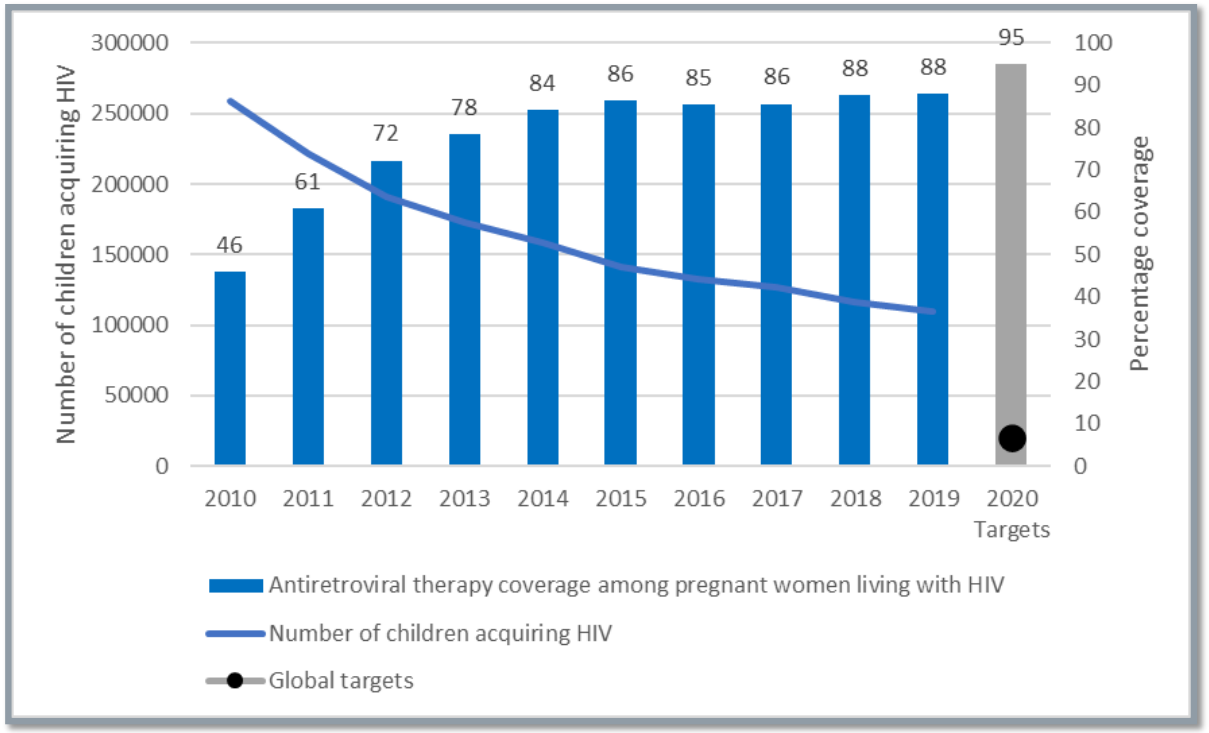
Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Transmission in the United States. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines

Global coverage of pregnant women with HIV who receive ARVs for prevention of vertical transmission



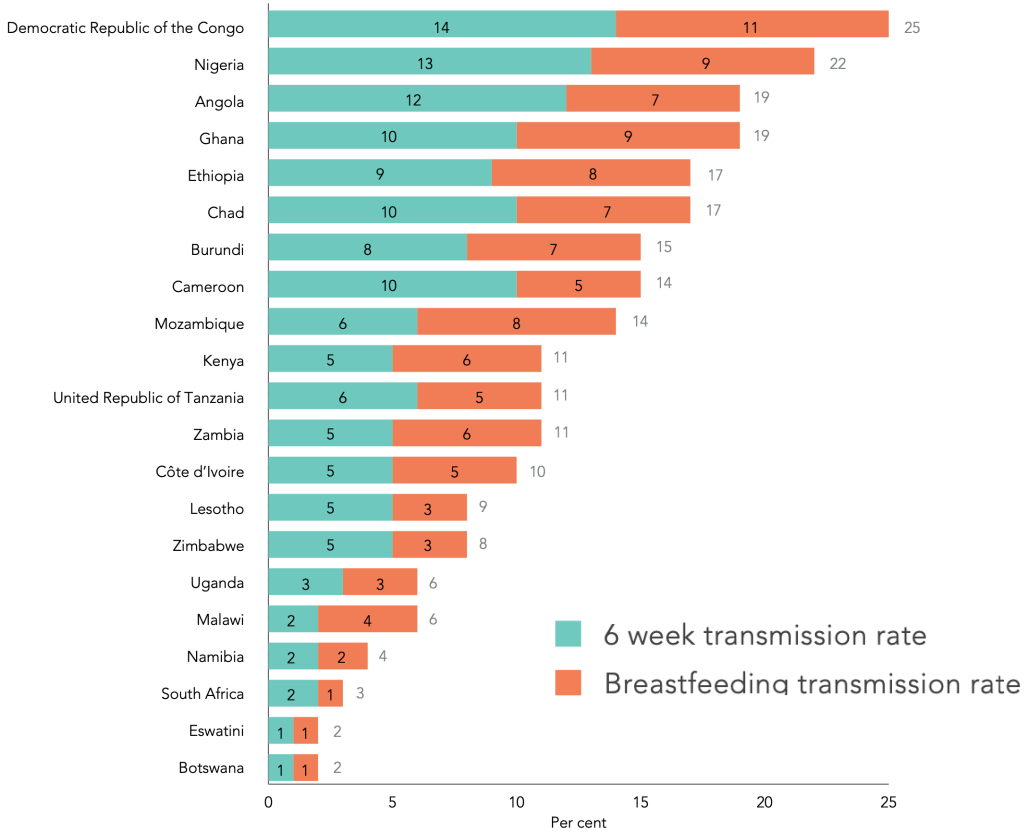
https://aidsinfo.unaids.org/

In 2019 there were 150,000 new pediatric HIV infections



Source: UNAIDS 2020 Estimates

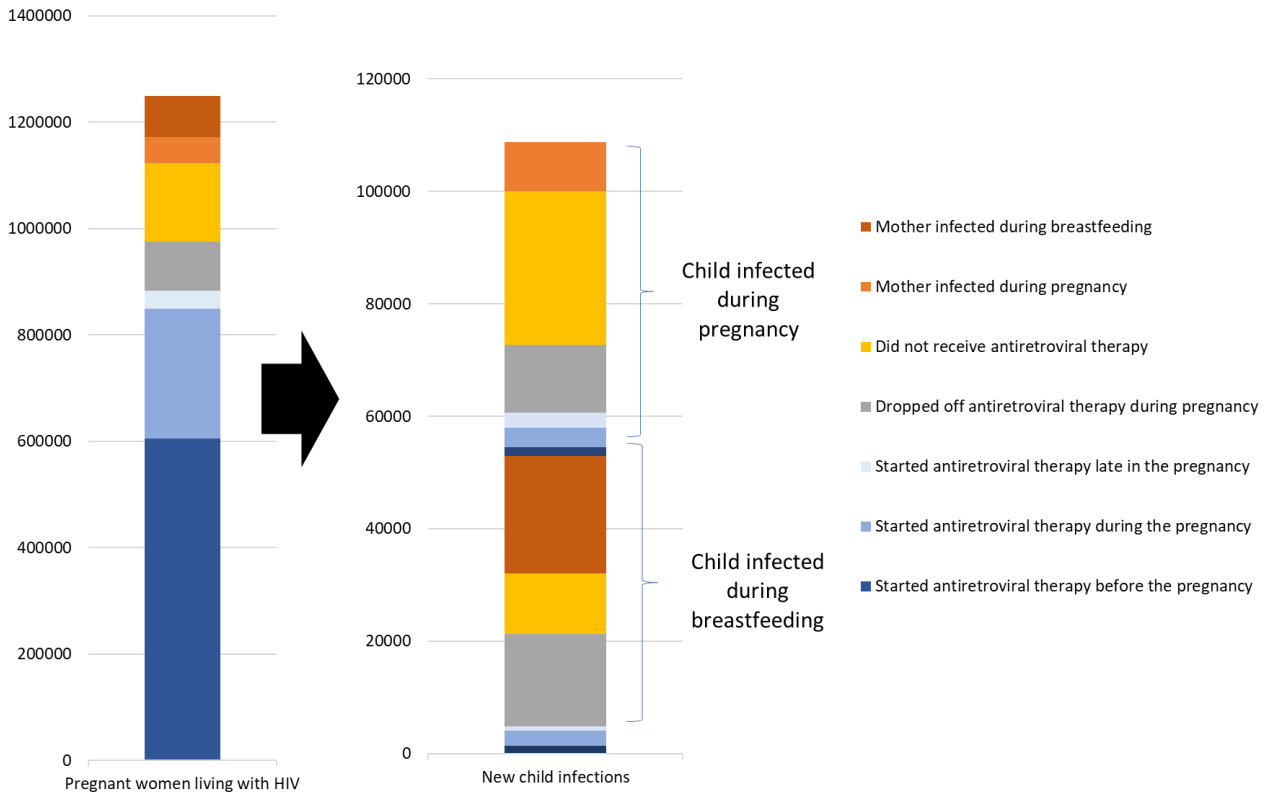
Six-week vertical transmission and final transmission rate in 21 focus countries, 2019



- Many countries have persistently high transmission rates
  - 13 countries with >10% perinatal transmission rate
- Some countries have reduced perinatal transmission rates substantially but because of high HIV seroprevalence, many children continue to acquire HIV infection

Source: UNAIDS epidemiological estimates, 2020.

New child infections due to gaps in the perinatal prevention cascade

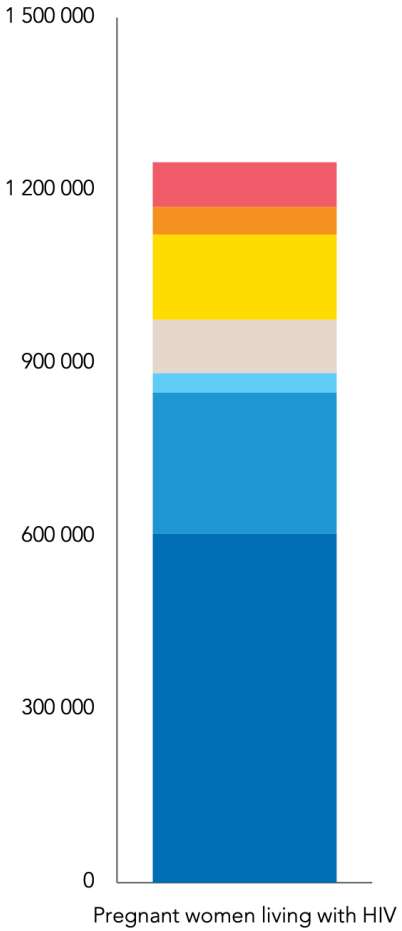


Parameters assessed:

- Timing of ART initiation
- Retention on ART
- Incident maternal HIV infection

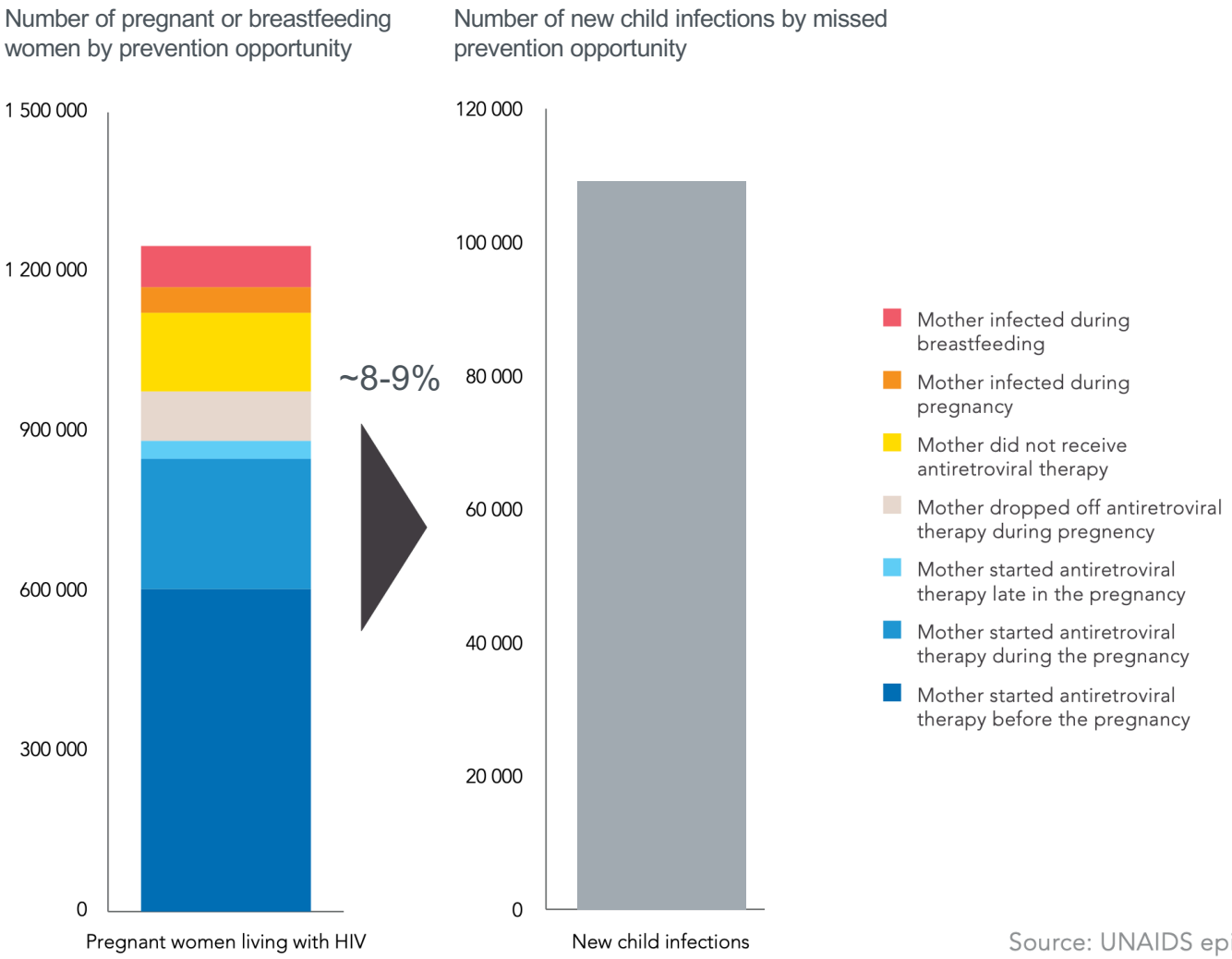
UNAIDS epidemiological estimates, 2020

Number of pregnant or breastfeeding women by prevention opportunity



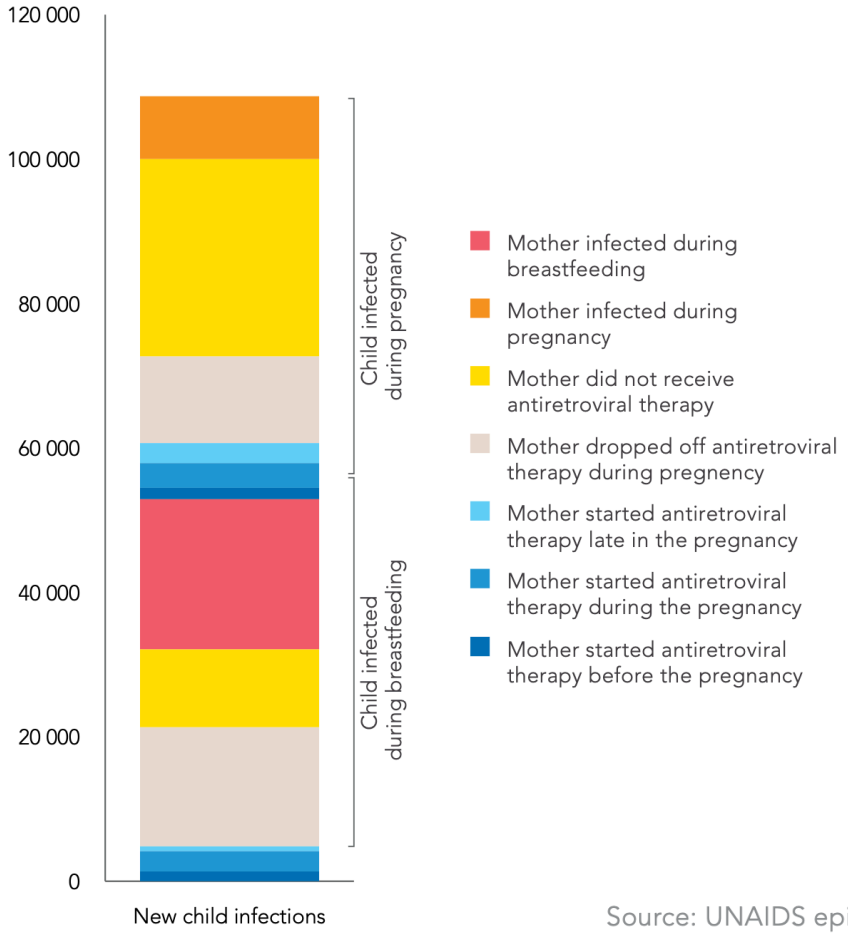
- Mother infected during breastfeeding
- Mother infected during pregnancy
- Mother did not receive antiretroviral therapy
- Mother dropped off antiretroviral therapy during pregnency
- Mother started antiretroviral therapy late in the pregnancy
- Mother started antiretroviral therapy during the pregnancy
- Mother started antiretroviral therapy before the pregnancy

Source: UNAIDS epidemiological estimates, 2020.



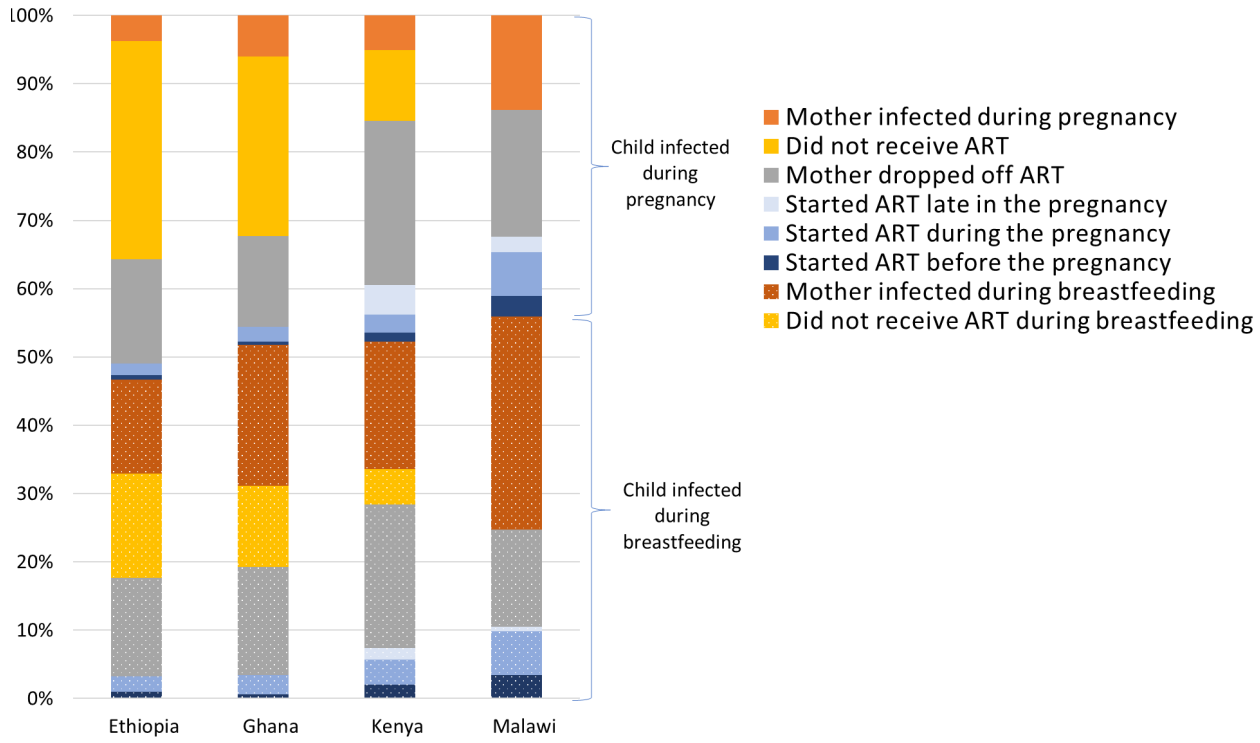
Source: UNAIDS epidemiological estimates, 2020.

Number of new child infections by missed prevention opportunity



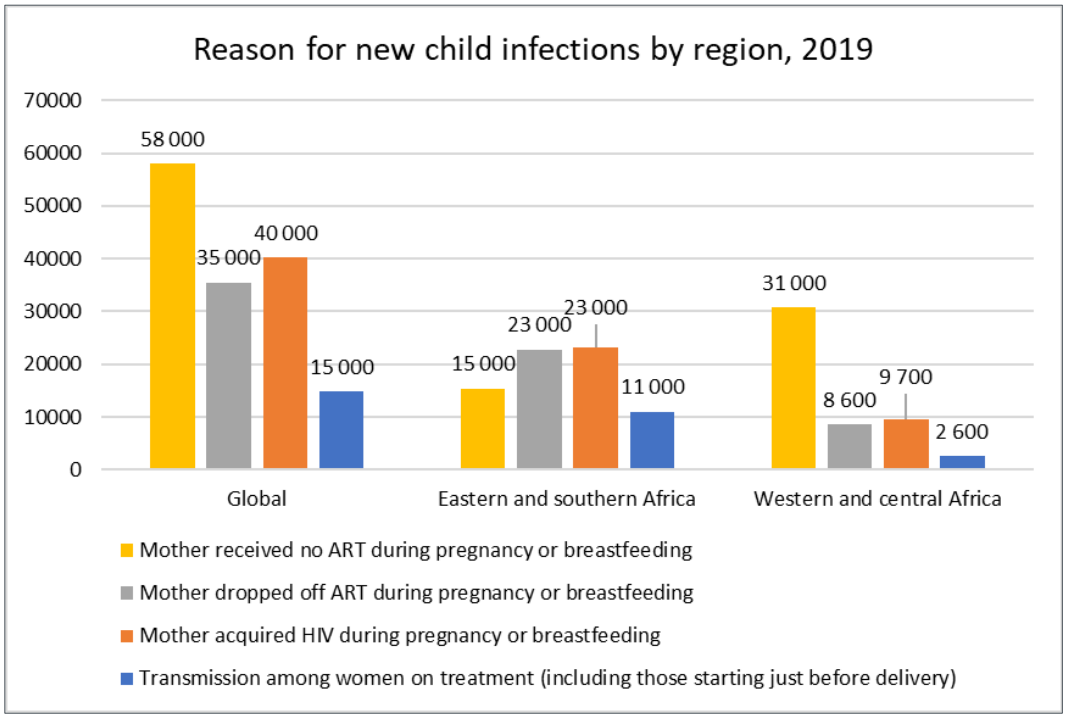
Source: UNAIDS epidemiological estimates, 2020.

Stacked bar analysis for four countries



UNAIDS epidemiological estimates, 2020

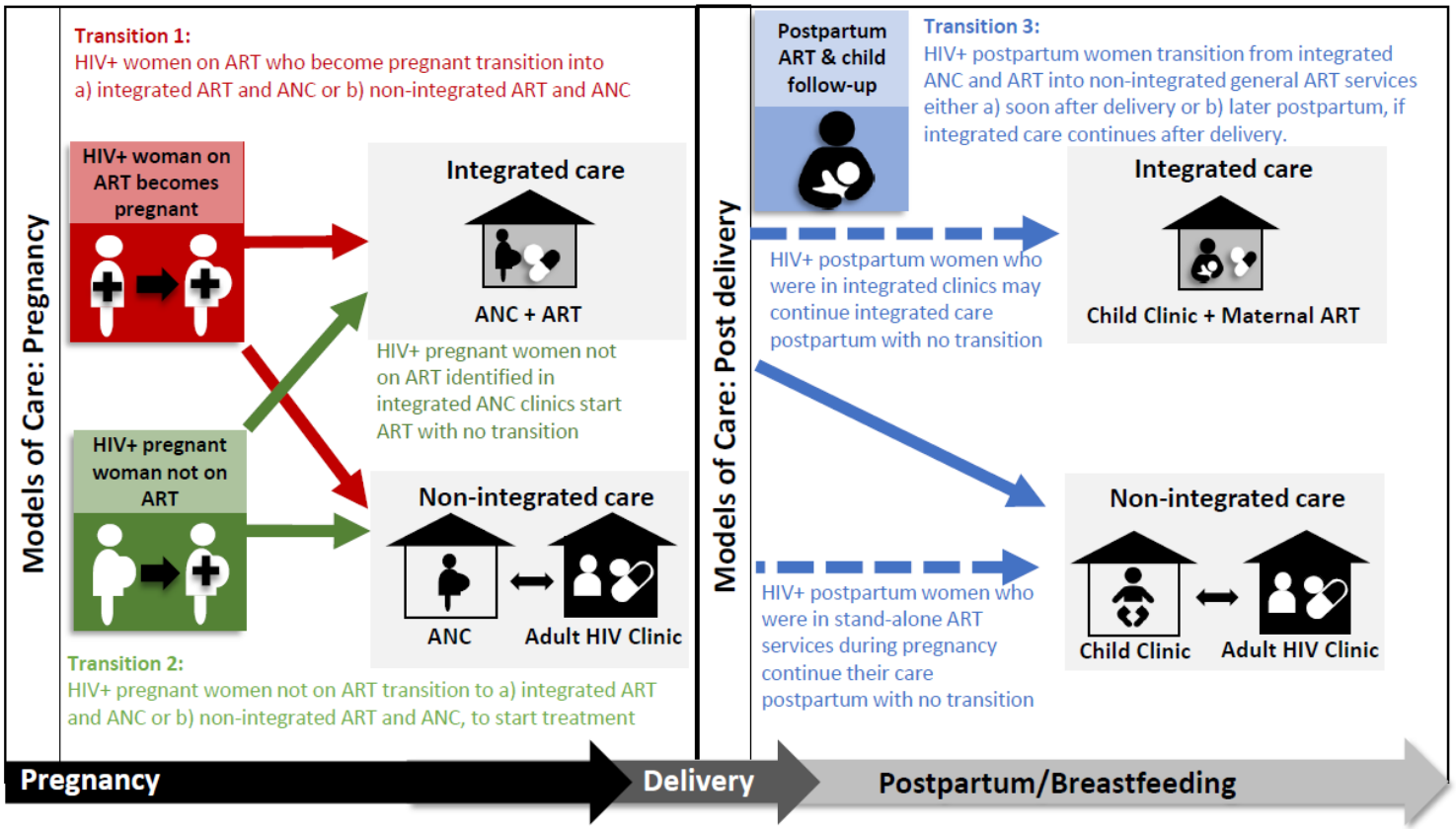
Primary reasons for new child infections, 2019



- **39%** linked to lack of maternal ART during pregnancy or breastfeeding
- **24%** linked to inadequate maternal retention on ART
- **27%** linked to acute infection during pregnancy or breastfeeding
- **10%** among women **on ART**

UNAIDS epidemiological estimates, 2020

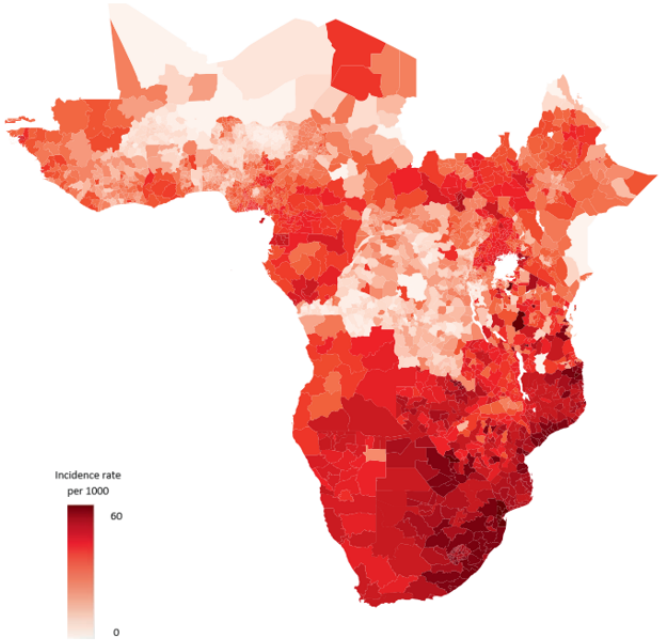
The HIV Care Cascade for pregnant and breastfeeding women and their infants



Phillips T, Teasdale C, et al JIAS, in press

What have we learned?

- Despite ART scale-up, inadequate retention in care and ART adherence remain significant barriers to effective maternal treatment and perinatal prevention.
- Half of new infections occur during breastfeeding.
  - Shift from early epidemic reflecting increased ART during pregnancy.
- Incident maternal HIV infections account for an increasing proportion of new pediatric infections.
  - Increased risk of HIV acquisition during pregnancy and breastfeeding.
  - High risk of perinatal transmission associated with acute maternal infection.
  - 43% of the incident infections among pregnant and breastfeeding women are among adolescent girls and young women, 15-24 years, underscoring the need NOT to exclude this population from HIV prevention services and research.



HIV incidence in female 15-24 years
UNAIDS epidemiological estimates, 2020

icap Global Health

COVID-19: impact on pregnancy, vertical transmission, HIV service delivery

SARS-CoV-2 and pregnancy

- As of December 3, 2020, there were 42,268 cases of COVID-19 and 55 deaths in pregnant women reported to the CDC
- Pregnant women do not appear to be at higher risk of acquiring COVID-19
  - Risk linked to sociodemographic factors; disproportionally impacts Black and Latino women
- Pregnant women may be at higher risk for more severe disease manifestations
  - In an analysis of approximately 400,000 women aged 15–44 years with symptomatic COVID-19, intensive care unit admission, invasive ventilation, extracorporeal membrane oxygenation, and death were more likely in pregnant women than in nonpregnant women.

Outcomes among women with symptomatic, laboratory confirmed SARS-CoV-2, Jan 22- Oct 3, 2020

	No. (per 1,000 case) of symptomatic women		Risk ratio (95% CI)	
	Pregnant n-23,434	Nonpregnant n=386,028	Crude	Adjusted
ICU admission	245 (10.5)	1492 (3.9)	2.7 (2.4-3.1)	2.7 (2.4-3.1)
Invasive ventilation	67(2.9)	412(1.1)	2/7(2.1-3.5)	2.9(2.2-3.8)
ECMO	17(0.7)	120(0.3)	2/3(1.4-3.9)	2.4(1.5-4/0)
Death	34 (1.5)	447 (1.2)	1.3(0.9-1.8)	1.7(1.2-2.4)

Zambrano LD, et al. Update:. MMWR 2020;69:1641–1647.
DOI: http://dx.doi.org/10.15585/mmwr.mm6944e3

SARS-CoV2 and birth outcomes

- There may be a higher risk of adverse pregnancy outcomes to mothers with CoV-2 infection during pregnancy
- Severe outcomes seen with other viruses (congenital anomalies, stillbirths) have not been reported
- Recent CDC study reported higher rate of preterm delivery, 12.9%, among 3,912 infants of mothers with COVID-19 during second/third trimester of pregnancy, higher than national estimates of 10.2% in 2019 (SET-NET study)
  - Not a nationally representative:46% were Hispanic or Latina, and 45% underlying medical condition, most often obesity
- Two more recent studies show no temporal increase in stillbirth or preterm deliveries in the US and UK associated with COVID-19 pandemic

Table. Birth Outcomes by Race/Ethnicity Before (March-June 2018 and 2019) and During (March-June 2020) the Severe Acute Respiratory Syndrome Coronavirus 2 Pandemic in 2 Philadelphia Hospitals[a]

Birth outcome	No. (%) Prepandemic epoch (n = 5907)	Pandemic epoch (n = 3007)	Unadjusted *P* value[b]	Adjusted absolute risk difference (95% CI), %[c]
Preterm birth[d]	617 (10.5)	283 (9.5)	.12	−1.1 (−2.4 to 0.2)
Non-Hispanic Black	323 (13.1)	157 (12.4)	.57	−0.7 (−3.0 to 1.5)
Non-Hispanic White	177 (7.9)	73 (6.8)	.26	−1.0 (−2.8 to 0.9)
Other race/ethnicity	117 (9.9)	53 (8.2)	.24	−1.7 (−4.4 to 1.0)
Spontaneous preterm birth[e]	315 (5.7)	135 (4.7)	.09	−0.8 (−1.8 to 0.2)
Non-Hispanic Black	150 (6.6)	77 (6.5)	.99	0.1 (−1.6 to 1.9)
Non-Hispanic White	96 (4.5)	30 (2.9)	.04	−1.4 (−2.8 to −0.1)
Other race/ethnicity	69 (6.1)	28 (4.5)	.16	−1.6 (−3.7 to 0.6)
Medically indicated preterm birth[f]	302 (5.4)	148 (5.2)	.65	−0.3 (−1.4 to 0.6)
Non-Hispanic Black	173 (7.5)	80 (6.7)	.45	−1.0 (−2.7 to 0.8)
Non-Hispanic White	81 (3.8)	43 (4.1)	.70	0.4 (−1.1 to 1.9)
Other race/ethnicity	48 (4.3)	25 (4.0)	.80	−0.3 (−2.3 to 1.7)
Stillbirth (per 1000 births)	32 (0.54)	15 (0.50)	.88	−0.03 (−0.34 to 0.29)
Non-Hispanic Black	25 (1.01)	9 (0.71)	.47	−0.29 (−0.90 to 0.31)
Non-Hispanic White[g]	4 (0.18)	2 (0.19)	.99	
Other race/ethnicity[g]	3 (0.25)	4 (0.61)	.26	

MMWR Morb Mortal Wkly Rep 2020;69:1635–1640.
DOI: http://dx.doi.org/10.15585/mmwr.mm6944e2external icon.; Stowe et al, Dec 7, 2020 doi:10.1001/jama.2020.21369; Handley H, Dec 7, 2020. doi:10.1001/jama.20991

Much is still unknown about the risks of COVID-19 to the newborn but vertical transmission is uncommon

Intrauterine infection – *very rare*

Viremia is rare; virus rare in amniotic fluid, placental infection is rare

1 or possible 2 case of 'confirmed' in utero infection

Perinatal Infection – *possible but very uncommon*

Vaginal secretions rarely positive; potential exposure to maternal fecal virus or virus in respiratory secretions during delivery

Breast Milk Infection – *possible but unlikely*

Virus rarely found in milk; SARS-CoV-2 IgA and IgG detected in milk

Mother		Neonate	
Sample	**Viral load (Log)**	**Sample**	**Viral load (Log)**
Nasopharyngeal swab	4.22	Blood	1.15
Vaginal swab	0.63	Nasopharyngeal swab (DOL1)	2.21
Placenta	11.15	Rectal swab	4.71
Amniotic fluid	2.09	Nasopharyngeal swab (DOL3)	7.30
Blood	4.87	Nasopharyngeal swab (DOL18)	4.54

*SARs-CoV-2 viral load maternal and infant samples

*https://www.nature.com/articles/s41467-020-17436-6

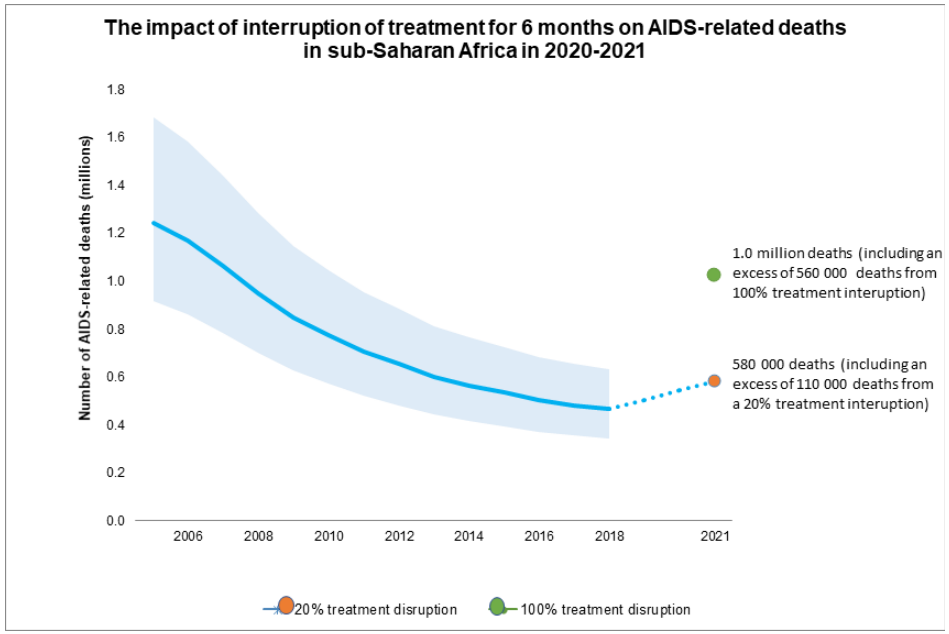
Newborn management

American Academy of Pediatrics

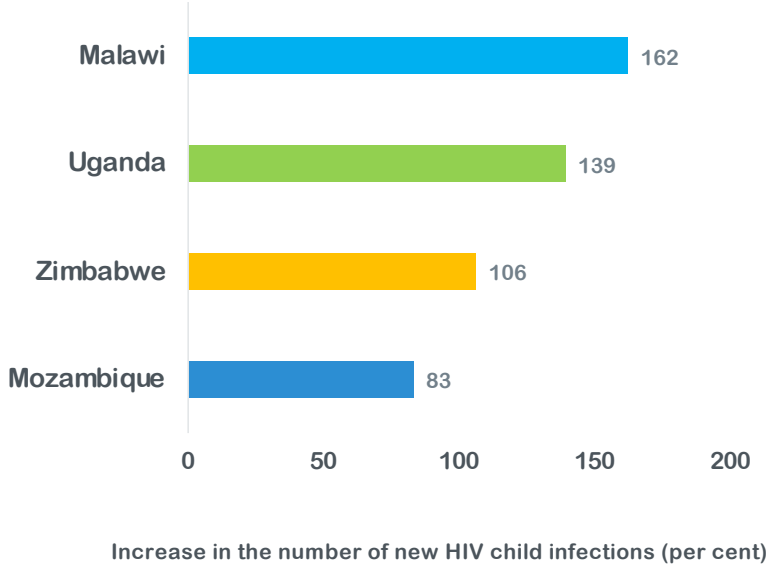
- Mothers and newborns may room-in according to usual center practice.
- During the birth hospitalization, the mother should maintain a reasonable distance from her infant when possible. When a mother provides hands-on care to her newborn, she should wear a mask and perform hand-hygiene. Use of an isolette may facilitate distancing and provide the infant an added measure of protection from respiratory droplets. If using an isolette, care should be taken to properly latch doors to prevent infant falls.
- The AAP strongly supports breastfeeding as the best choice for infant feeding. Several published studies have detected SARS-CoV-2 nucleic acid in breast milk. Currently, however, viable infectious virus has not been detected in breast milk. One study demonstrated that pasteurization methods (such as those used to prepare donor milk) inactivate SARS-CoV-2. It is not established whether protective antibody is found in breast milk. Given these findings and uncertainties, direct breastfeeding is encouraged at this time.
- Mothers should perform hand hygiene before breastfeeding and wear a mask during breastfeeding

Projected impact of COVID-19 on HIV – collateral damage

Interruption of HIV treatment for 6 months could result in 1 million AIDS-related deaths in sub-Saharan Africa in 2020/2021

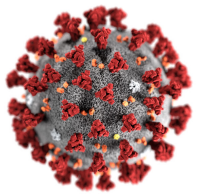


Suspension of prevention of mother to child transmission services for 6 months could result in dramatic increases in new HIV infections among children in 2020/2021



Source: UNAIDS 2019 estimates. Projected estimated HIV related deaths and child new HIV infections derived from mathematical modelling by 5 research groups exploring a complete disruption of HIV prevention and treatment services over 3- and 6-months on HIV mortality and incidence in sub-Saharan Africa. Pre-print manuscript available at: Jewell B, Mudimu E, Stover J, et al for the HIV Modelling Consortium, Potential effects of disruption to HIV programmes in sub-Saharan Africa caused by COVID-19: results from multiple models. The Lancet HIV Volume 7 Issue 9 Pages e629-e640 (September 2020) .

The COVID-19 pandemic: reasons to worry about prevention of perinatal infections



- Disruption of the product supply chain
- Disruption of health services
- Rapid, unplanned transition to multi-month ART dispensing
- Delayed roll-out of optimized ARVs
- Decreased utilization of health services for antenatal and delivery care
- Increased violence against women
- Decreased access to reproductive health services
- Food insecurity
- Economic disruption
- Social unrest
- Increased risk of adverse pregnancy with COVID-19 infection
- Increased risk of adverse birth outcomes with COVID-19 infection
- Shift of laboratory resources to COVID-19 testing

Thank you

Thank you for your attention

Thanks to the many colleagues who contributed their work, slides and ideas including Lynne Mofenson, Martina Penazzato, and Mary Mahy


Thank You for Your Attendance!
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