2022 Update: HIV & Pregnancy

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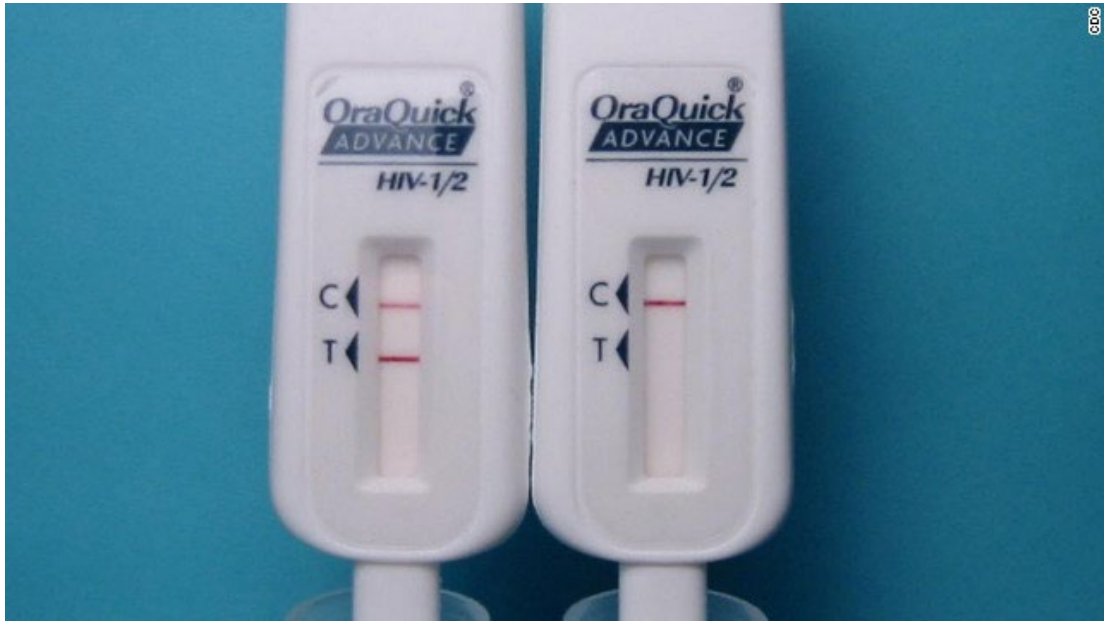
Conflicts of Interest

- none

Outline

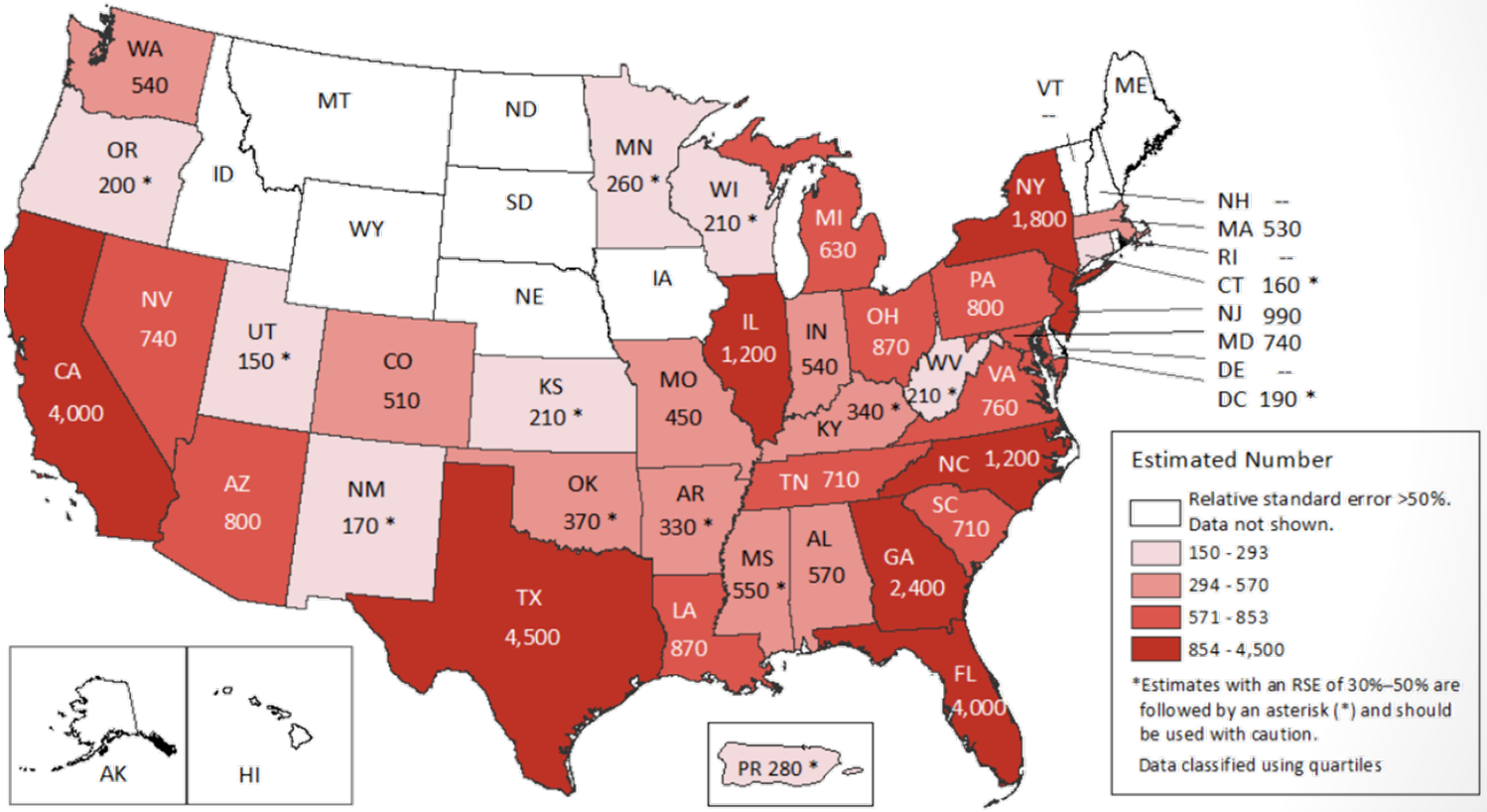
- Epidemiology
- HIV Screening
- Benefits/Risks of ART in Pregnancy
- Management
- Resources
- Key Research Questions

HIV Epidemiology – United States



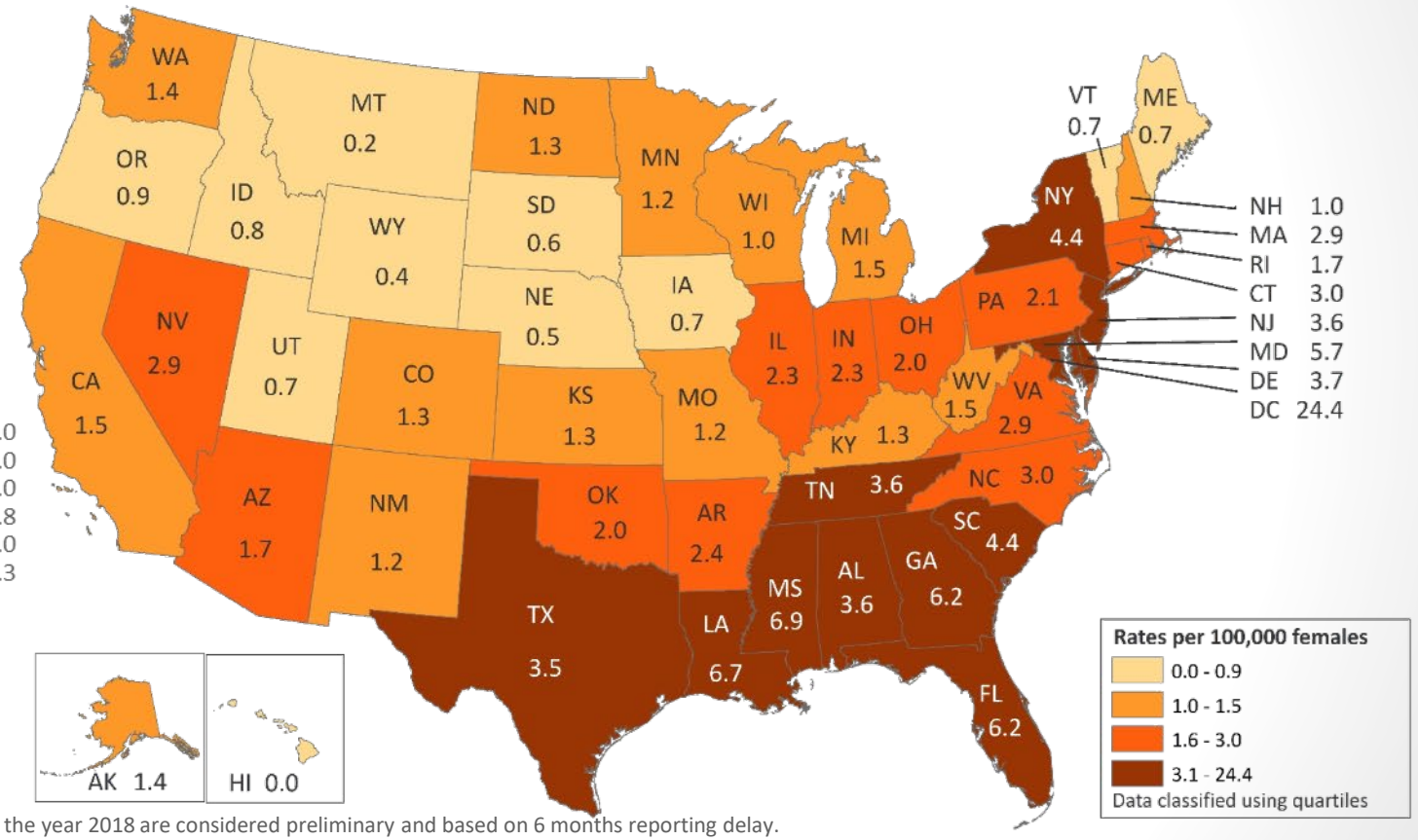
Estimated HIV Incidence among Persons Aged ≥13 Years, by Area of Residence 2019

Total = 34,800



Rates of Stage 3 (AIDS) Classifications among Female Adults and Adolescents with Diagnosed HIV Infection, 2018

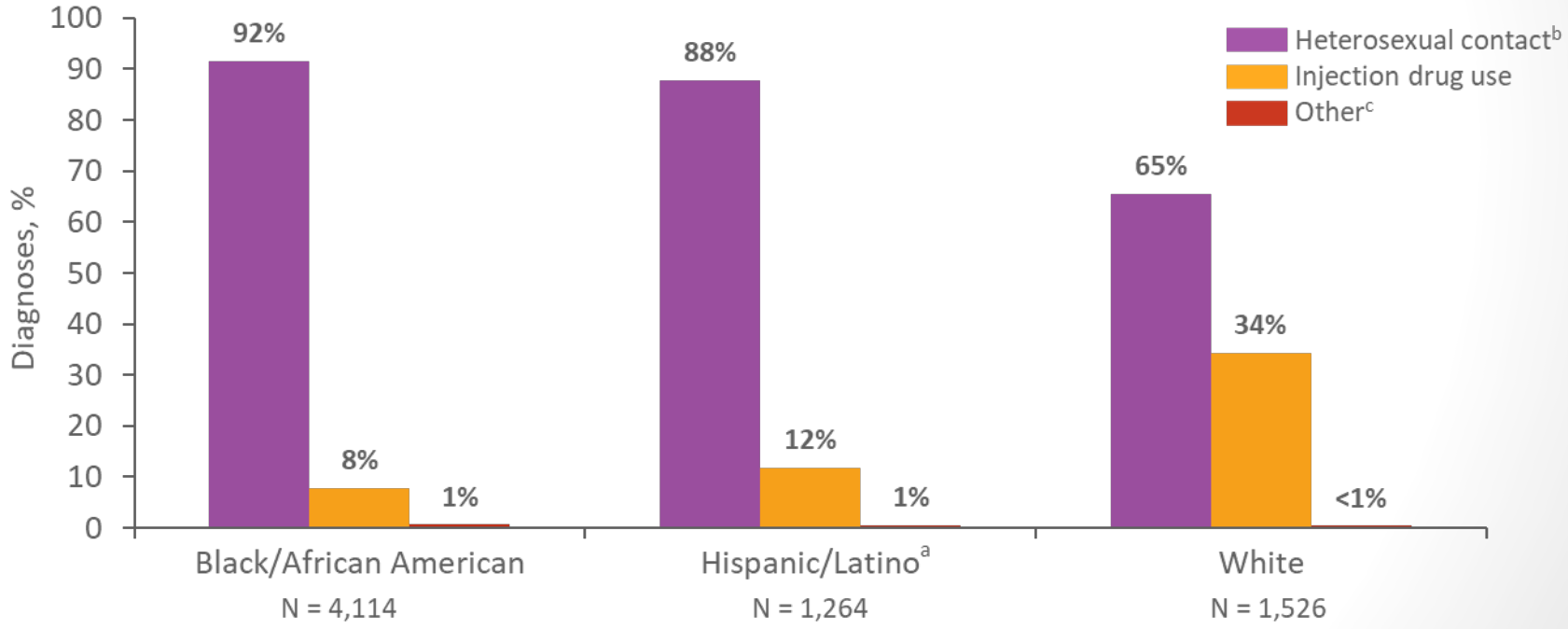
N = 4,149 Total Rate = 2.9



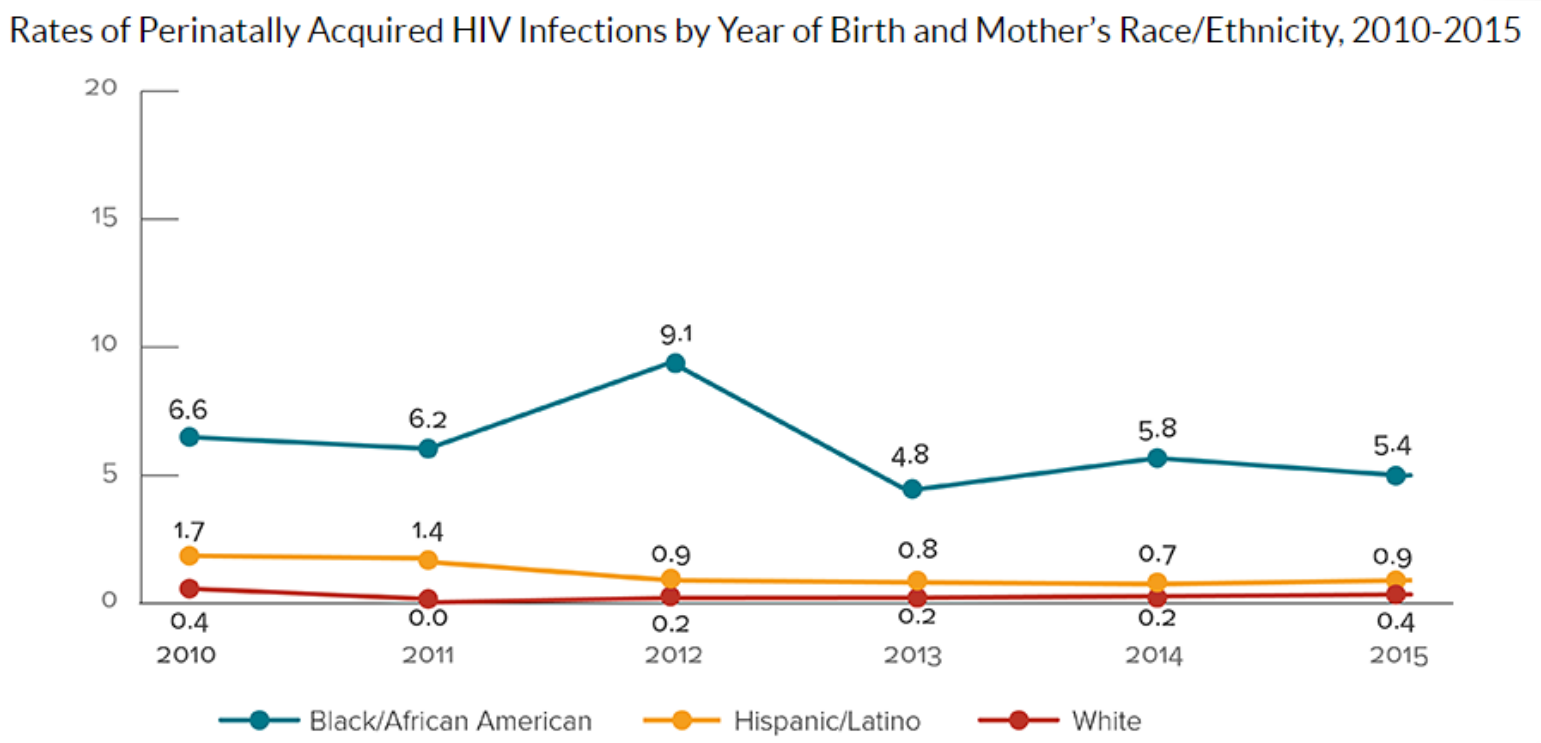
American Samoa	0.0
Guam	0.0
Northern Mariana Islands	0.0
Puerto Rico	2.8
Republic of Palau	0.0
U.S. Virgin Islands	4.3

Note. Data for the year 2018 are considered preliminary and based on 6 months reporting delay.

Diagnoses of HIV Infection among Female Adults and Adolescents, by Race/Ethnicity and Transmission Category, 2018



Perinatal HIV Infections in the US



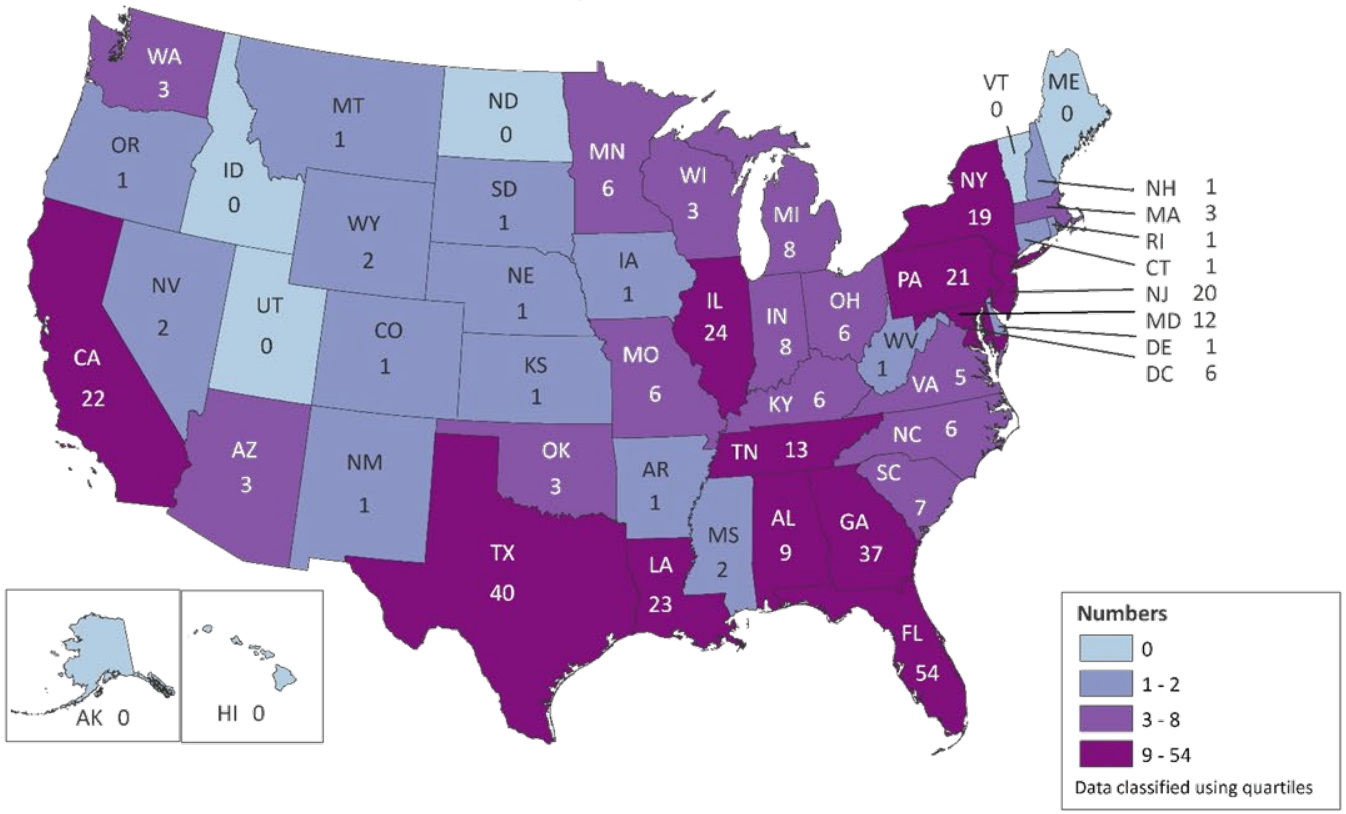
- An estimated 5000 women with HIV give birth each year in the US.
- Perinatal HIV cases decreased 41% between 2012 and 2016
  - 73 children (<13 years old) were diagnosed with perinatally acquired HIV in 2017.

www.cdc.gov

Diagnoses of Perinatally Acquired HIV Infection among Children Born in the United States and Puerto Rico, Birth Years 2010–2016, by Area of Residence

N = 407

Puerto Rico 1



Alabama Department of Public Health (ADPH)
Alabama Emergency Response Technology (ALERT)
Health Alert Network (HAN)
March 23, 2021

Increase in Perinatal HIV Cases in Alabama

The Alabama Department of Public Health is collaborating with University of Alabama at Birmingham (UAB) Family Clinic, UAB 1917 Clinic, Medical Advocacy and Outreach, UAB Departments of OB/Gyn and Pediatrics and the Alabama Perinatal Quality Collaborative to investigate a recent increase in the number of cases of perinatal HIV infections in Alabama.

In the four-year period from December 2015 through January 2020, there were a total of three identified cases of perinatal HIV infection in the state. However, since January 1, 2020, five infants have acquired HIV through perinatal transmission. These infants were diagnosed between January 1, 2020 and December 31, 2020. While these cases are still under investigation, preliminary data suggest that all women had presented for prenatal care during their pregnancies.

It is imperative that providers remain vigilant in their efforts to prevent perinatal HIV infection by adhering to the following guidelines:

- HIV testing is standard of care for all pregnant women and is a routine component of preconception care.
- Consistent with CDC and American Academy of Pediatrics guidelines, all pregnant women in Alabama should receive both **first trimester and third trimester HIV screening. Third trimester HIV screening should occur at <36 weeks gestational age to allow time to intervene.**

Not all people with HIV are getting the care they need. ‡‡

At the end of 2018, an estimated **1,173,900 people** had HIV.

86%
of all people with HIV knew they had the virus. ***

It is important for people to know their HIV status so they can take medicine to treat HIV if they have the virus. Taking medicine every day can make the viral load undetectable. People who get and keep an undetectable viral load (or stay virally suppressed) have effectively no risk of transmitting HIV to HIV-negative sex partners.

Although more than half of adults and adolescents with HIV are virally suppressed, more work is needed to increase these rates. For every **100 adults and adolescents with HIV in 2018:** ‡‡

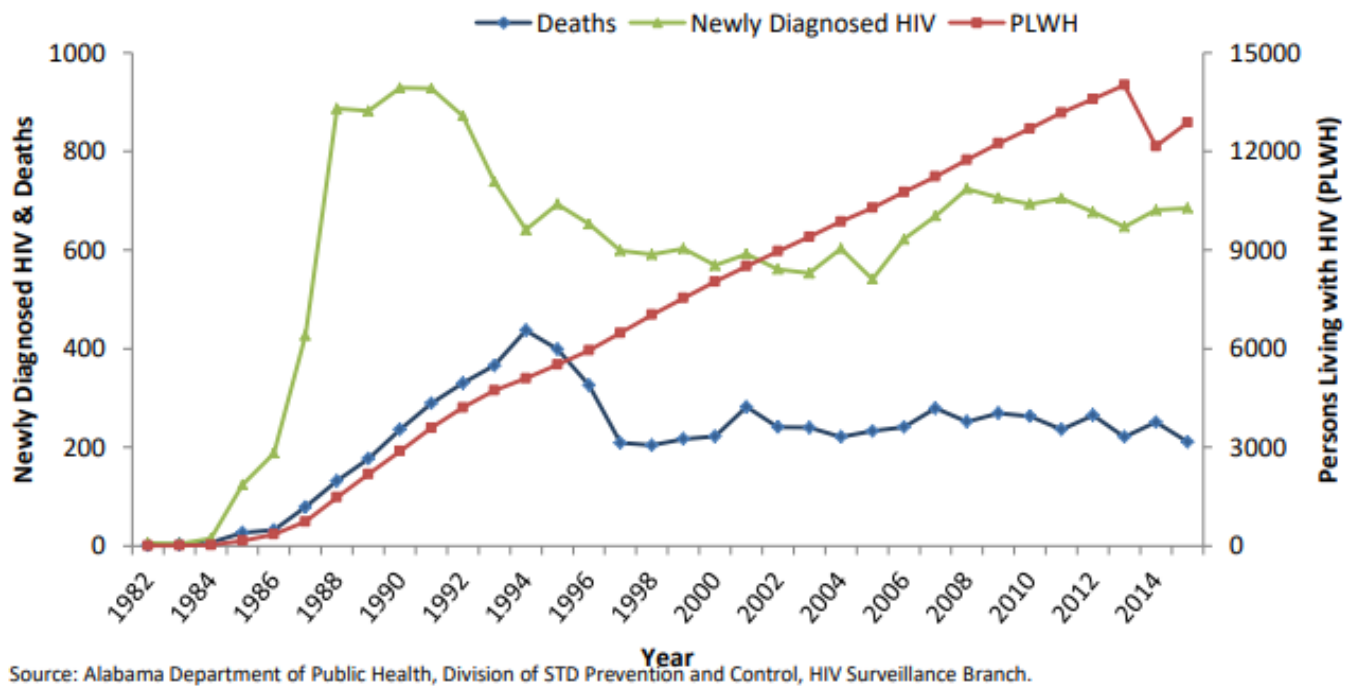
65 received some HIV care

50 were retained in care

56 were virally suppressed

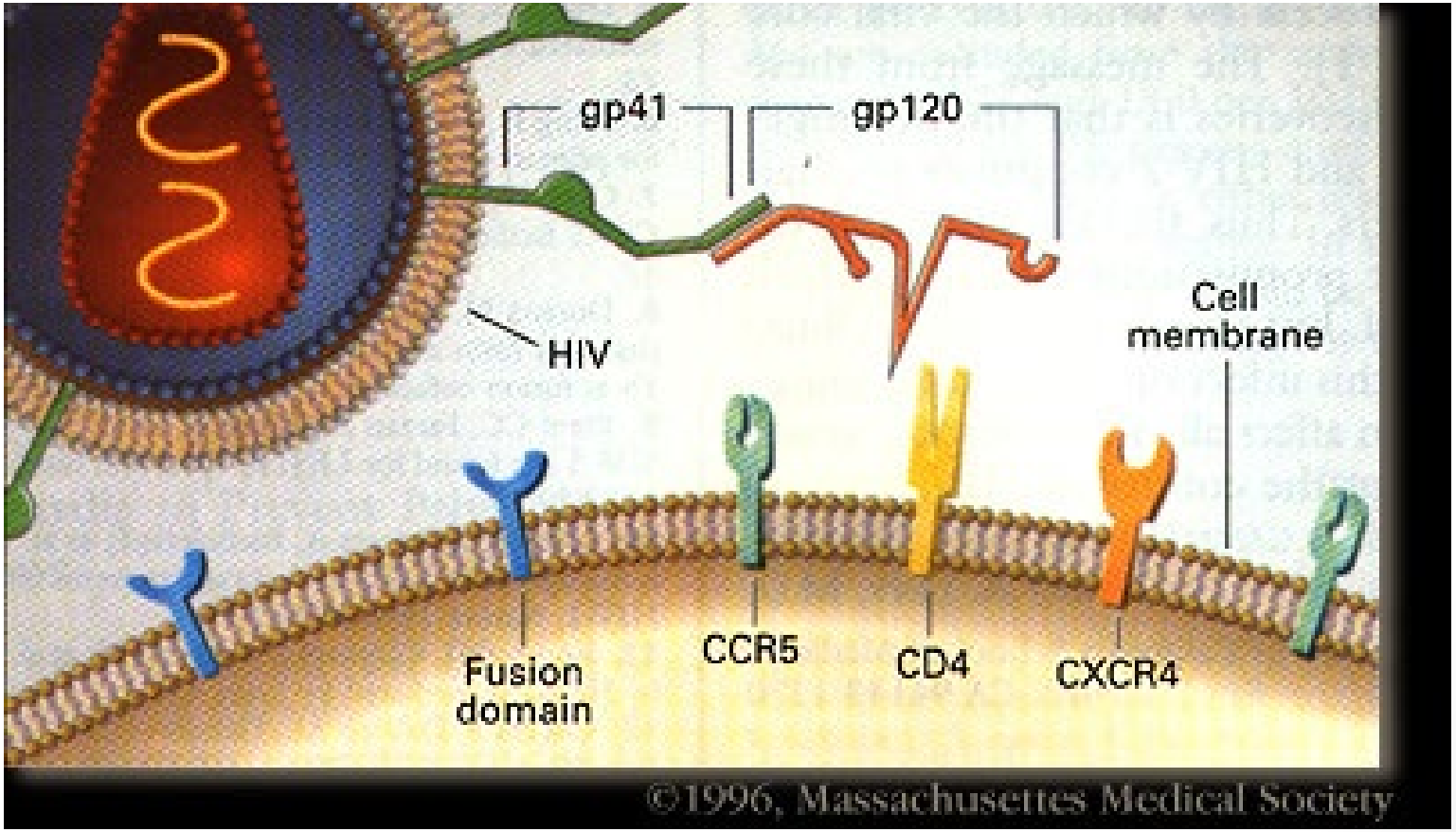
cdc.gov

Figure 1. Persons Living with HIV, Newly Diagnosed HIV, and Deaths, Alabama 1982-2015

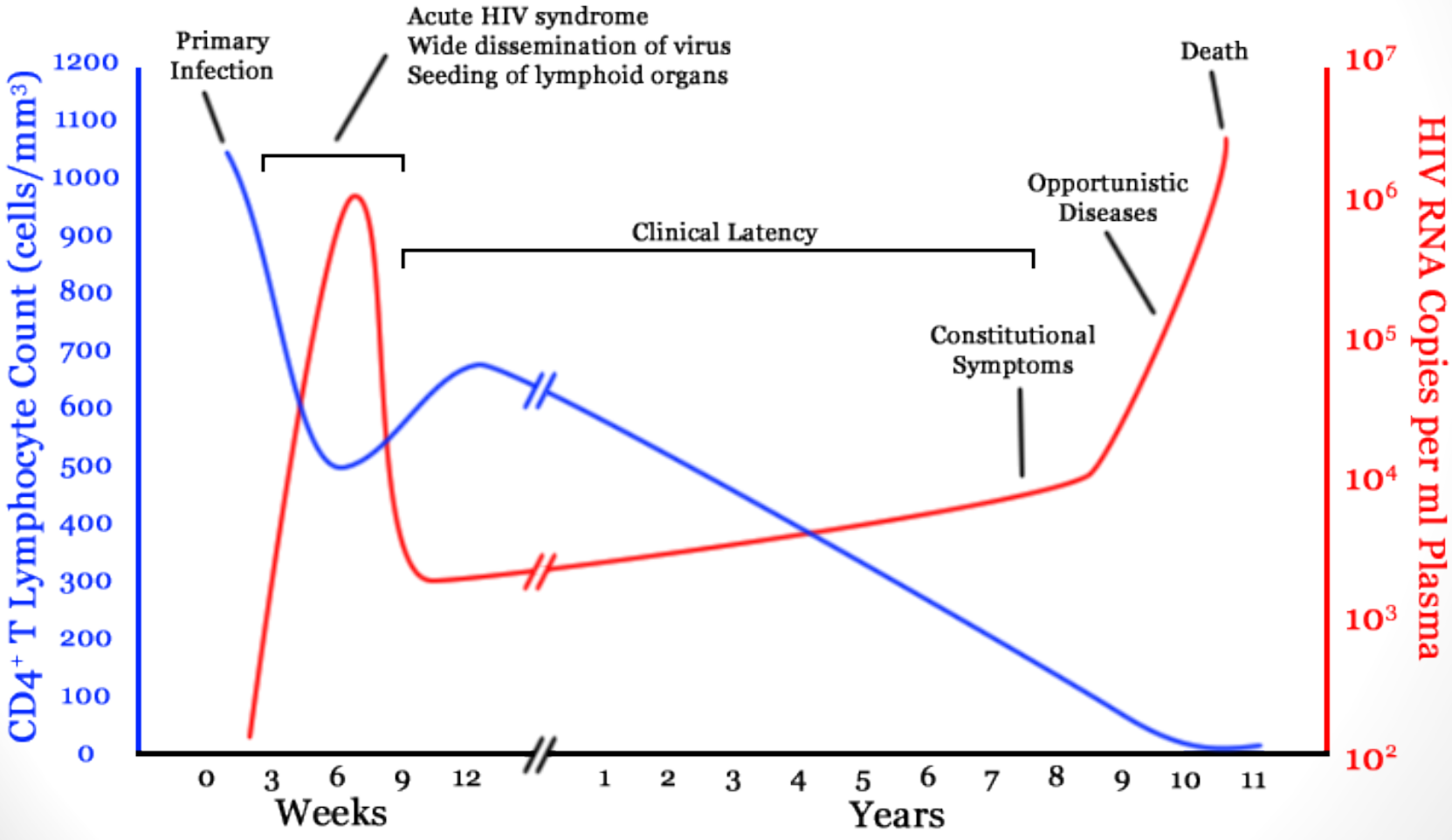


Source: Alabama Department of Public Health, Division of STD Prevention and Control, HIV Surveillance Branch.
Note: PLWH include persons living with HIV infection (non-AIDS) and Stage 3 (AIDS) as of December 31st for the year reported.

HIV Infection – Cell Entry



Natural History of HIV



HIV Screening and Diagnosis

2018 ACOG HIV Testing Guidelines

- Human immunodeficiency virus testing using the opt-out approach, which is currently permitted in every jurisdiction in the United States, should be a routine component of care for women during prepregnancy and as early in pregnancy as possible.

- Repeat HIV testing in the third trimester, preferably before 36 weeks of gestation, is recommended for pregnant women with initial negative HIV antibody tests who are known to be at high risk of acquiring HIV infection; who are receiving care in facilities that have an HIV incidence in pregnant women of at least 1 per 1,000 per year; who are incarcerated; who reside in jurisdictions with elevated HIV incidence; or who have signs or symptoms consistent with acute HIV infection (eg, fever, lymphadenopathy, skin rash, myalgias, arthralgias, headache, oral ulcers, leukopenia, thrombocytopenia, or transaminase elevation).

- Rapid screening during labor and delivery or during the immediate postpartum period using the opt-out approach should be done for women who were not tested earlier in pregnancy or whose HIV status is otherwise unknown. Results should be available 24 hours a day and within 1 hour.

Testing and Diagnosis

- 14% of adults with HIV in the US are unaware of their infection
- In past - 3rd generation HIV testing
  - Tests for antibodies (IgM/IgG)
  - 3-4 week window period
- Currently – 4th generation HIV-1/2 Testing
  - Tests for antibodies and HIV P24 antigen.
  - 2 week window period.
  - Sensitivity and specificity approach 100%
- Molecular virologic testing - HIV RNA PCR
  - Not recommended for screening
  - Useful if acute HIV infection is suspected

Testing and Diagnosis

- All currently available tests look for HIV-1 and HIV-2 antibodies.
- False positive screening tests can occur with autoantibodies of pregnancy.
- Reactive 3rd/4th generation test without confirmation is a “reactive test”, but not a “positive test”.
- Confirmatory testing via a different method is needed.
  - Many labs have reflex confirmatory testing.
  - ie - HIV differentiation assay
- Western blot is no longer recommended for confirmatory testing (longer window period for detection).

Testing and Diagnosis

- Once HIV infection has been confirmed, follow up testing includes HIV viral load, CD4 and CBC with differential.
- HIV Genotype to look for resistance is recommended.
  - HIV VL must be >500 copies/mL
- If HIV diagnosis is confirmed, discuss results in person.

Case #1

- 36 yo AAF G5P4 6.1 wga admitted with T102.6, HA, N/V, possible pyelonephritis (Ucx negative).

Laboratory	2/13/2018 15:30	2/13/2018 2:59	2/12/2018 11:15	2/12/2018 0:56	2/11/2018 8:25	2/11/2018 1:30	2/10/2018 23:55	2/10/2018 22:37
HB Core Ab-Total			Non-Reactiv					
HBS Ab			0.5 *					
HBsAb Interp			Non-Reactiv					
Hep B Surface Ag			Non-Reactiv					
Treponema Ab	Negative *							
Toxo IgM			Non-Reactiv					
Toxo IgG			<6.5 *					
HIV 1/2 Ag/Ab	Reactive * A							
HIV Confirm	See Note *							See Note *
CDC HIV								Reactive * C
CDC Hep C Ab								Non-Reactiv

Result History

Value	Valid From	Valid Until
Reactive	2/11/2018 0:26	Current

Result | Specimen | **Comments** | Action List

```
1.)  (Medium Importance) Result Comment by Stallworth, Cody Koi on February 11, 2018 0:21
Extreme high value verified.
TECH Cody Stallworth CALLED Robinson Taylor, MD AT 2/11/2018 00:26:24 CST .  Read back policy enforced.

2.)  (Medium Importance) Interpretive Data by Stallworth, Cody Koi on February 11, 2018 0:21
Reactive result will be sent for confirmation. Test performed in UED Lab.
```

Result | Specimen | **Comments** | Action List

1.) (Medium Importance) Result Comment by Stallworth, Cody Koi on February 11, 2018 1:19
HIV-2 INDETERMINATE (HIV-1 Negative/HIV-2 Indeterminate): HIV-2 band(s) detected but did not meet the criteria for HIV-2 Positive. Recommend additional HIV molecular testing.
Tech Cody Stallworth called Patrick Siler, MD at 2/11/2018 01:15:03 CST.
Read back policy enforced.
The specimen was REACTIVE at very low levels on the 4th Generation HIV antibody/antigen assay. Supplemental testing on a rapid antibody assay was NONREACTIVE. This result is highly suggestive of a FALSE POSITIVE, and patients should be counseled accordingly. This could also represent acute HIV infection if fitting with the patient's history and clinical presentation. HIV1 QNT has been ordered for confirmation.

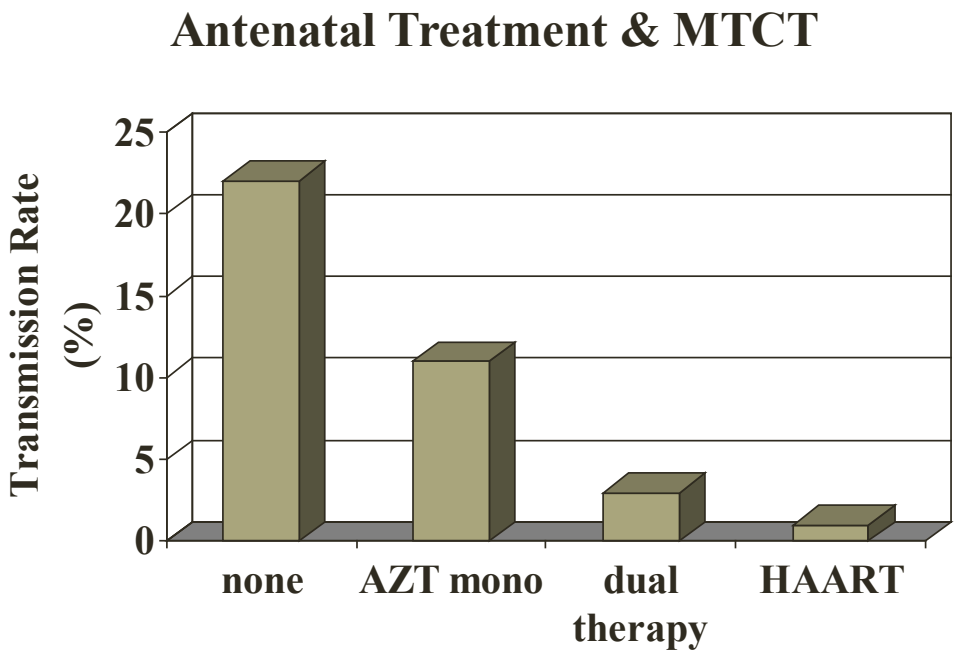
2.) (Medium Importance) Interpretive Data by Stallworth, Cody Koi on February 11, 2018 1:19
Normal value is Negative.
Test performed using the Geenius HIV 1/2 Supplemental Assay

Last 999 Results in the Past 3 Years

Laboratory	2/12/2018 11:15	2/12/2018 0:56	2/11/2018 8:25	2/11/2018 1:30	2/10/2018 23:55	2/10/2018 22:37	2/10/2018 16:30
CD4 Percent		40.0 *					
CD4 Absolute		1,404					
Infection Serology							
Rflu							Negative
HBcIgM	Non-Reactiv						
HB Core Ab-Total	Non-Reactiv						
HBS Ab	0.5 *						
HBsAb Interp	Non-Reactiv						
Hep B Surface Ag	Non-Reactiv						
Treponema Ab							
Toxo IgM	Non-Reactiv						
Toxo IgG	<6.5 *						
HIV 1/2 Ag/Ab							
HIV Confirm						See Note *	
CDC HIV						Reactive * C	
CDC Hep C Ab						Non-Reactiv	
Molecular Diagnostic							
U GC RNA	Negative *						
U Chlam RNA	Negative *						
U Trich RNA							
HIV1QNTX				7,687,554 * H			
Other High Risk -HPV DNA							
Type 16 -HPV DNA							

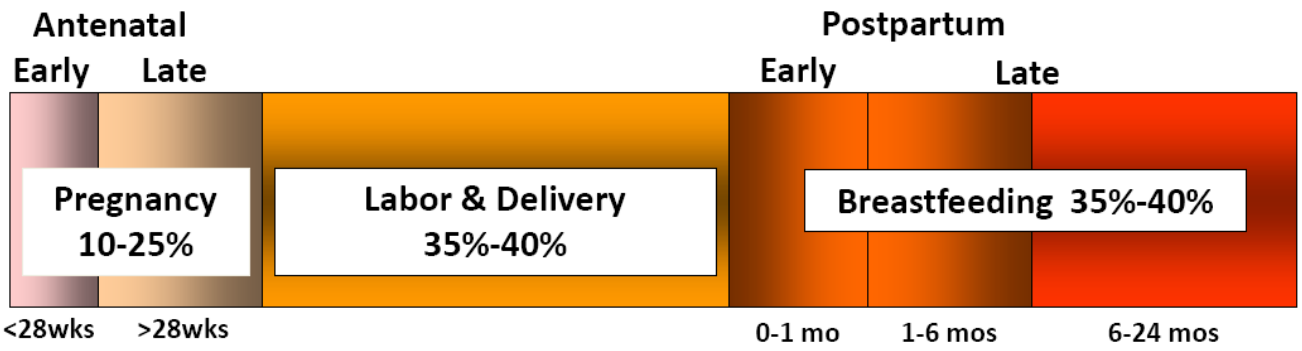
Benefits of ART in Pregnancy

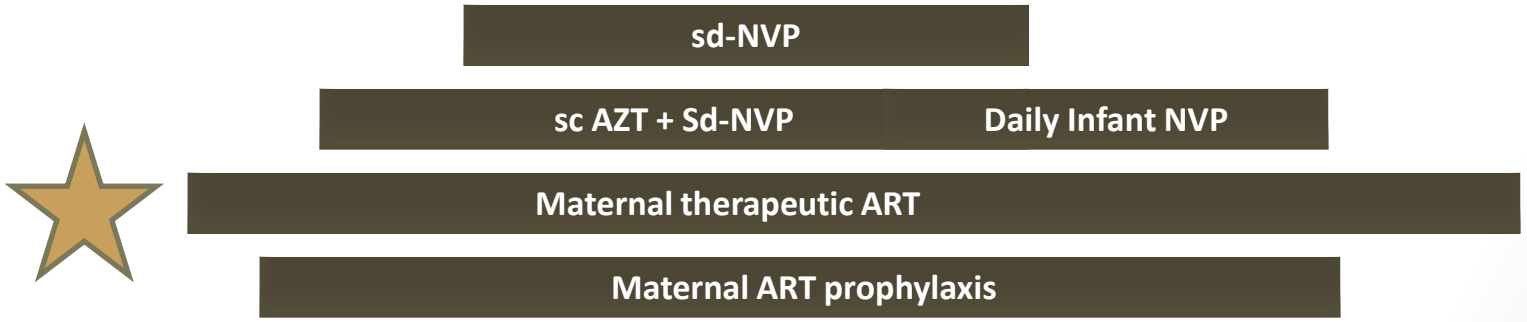
HIV Vertical Transmission Rates



Cooper JAIDS 2002;29

ART duration, timing and complexity impacts efficacy





Courtesy of Lynne Mofenson, NICHD

Goal of ART Therapy

Table 1. Perinatal transmission of human immunodeficiency virus type 1 from mothers with virus loads <1000 copies/mL at time of delivery or at the last measurement closest to delivery.

Study team	Mothers receiving ART	Mothers without ART	RR (95% CI)[a]
French[b]	1/346 (0.3)	4/37 (10.8)	0.03 (0.00–0.24)
PACTS	2/154 (1.3)	6/56 (10.7)	0.12 (0.03–0.59)
PACTG 076	1/62 (1.6)	0/47 (0.0)	2.29 (0.10–54.9)
PACTG 185	1/135 (0.8)	—	—
Ariel	3/44 (6.8)	1/14 (7.1)	0.95 (0.11–8.46)
ECS	0/56 (0.0)	24/141 (17.0)	0.05 (0.00–0.82)
MICS	—	1/24 (4.2)	—
WITS	0/22 (0.0)	0/35 (0.0)	1.57 (0.03–76.2)
Fang et al. [8]	—	0/1 (0.0)	—
Melvin et al. [11]	0/5 (0.0)	0/2 (0.0)	0.50 (0.01–19.6)
Dickover et al. [9]	0/10 (0.0)	0/11 (0.0)	1.09 (0.02–50.4)
Total	8/834 (1.0)	36/368 (9.8)	0.10 (0.05–0.21)

Table 2. Timing of Mother-to-Child Transmission of Human Immunodeficiency Virus Among the International Site Development Initiative Population (n=916)

Timing of Neonatal HIV Transmission	EGA: 40 Wk or Greater	EGA: Less than 40 Wk	Total
In utero	2	1	3
Intrapartum	0	2	2
Intrapartum or postnatal	0	1	1
Total	2	4	6

Ioannidis JID 2001; Scott OBGYN 2017

Case #2

- 24 year old G2P1 is 16.3 weeks pregnant and presenting for routine follow up care (visit #2).

- Her intake medical labs are notable for newly diagnosed HIV infection (4th generation screen, confirmatory test positive).
  - CD4 is 455 cells/mm3, CD4 % is 38
  - HIV Viral Load is 95,000 copies/mL
  - Remainder of labs and STI screen are unremarkable

- She feels well and has no complaints.

- Male partner is being tested today.

Questions

- What additional labwork do you need to order today?

- Does she need to start antiretroviral therapy?
- Does she need PCP prophylaxis?
- Does she need medications today?
  - Which medications do you want to begin ?

When to Initiate Therapy?

No Perinatal HIV-1 Transmission From Women With Effective Antiretroviral Therapy Starting Before Conception

Laurent Mandelbrot,[1,2,5,8] Roland Tubiana,[9,10] Jerome Le Chenadec,[2] Catherine Dollfus,[11] Albert Faye,[5,12] Emmanuelle Pannier,[8,13] Sophie Matheron,[5,14] Marie-Aude Khuong,[17] Valerie Garrait,[18] Veronique Reliquet,[19] Alain Devidas,[20] Alain Berrebi,[21] Christine Allisy,[22] Christophe Elleau,[23] Cedric Arvieux,[24] Christine Rouzioux,[6,15] Josiane Warszawski,[2,3,4] and Stéphane Blanche[7,16]; for the ANRS-EPF Study Group[a]

- 8075 mother-infant pairs
- Followed prospectively in France 2000-2011.
- Cohort analyzed according to maternal viral load at delivery and timing of ART initiation.
- 56/8075 vertical transmissions (0.7%).
- Zero MTCT among 2651 women with VL <50 before conception

Mandelbrot CID 2015

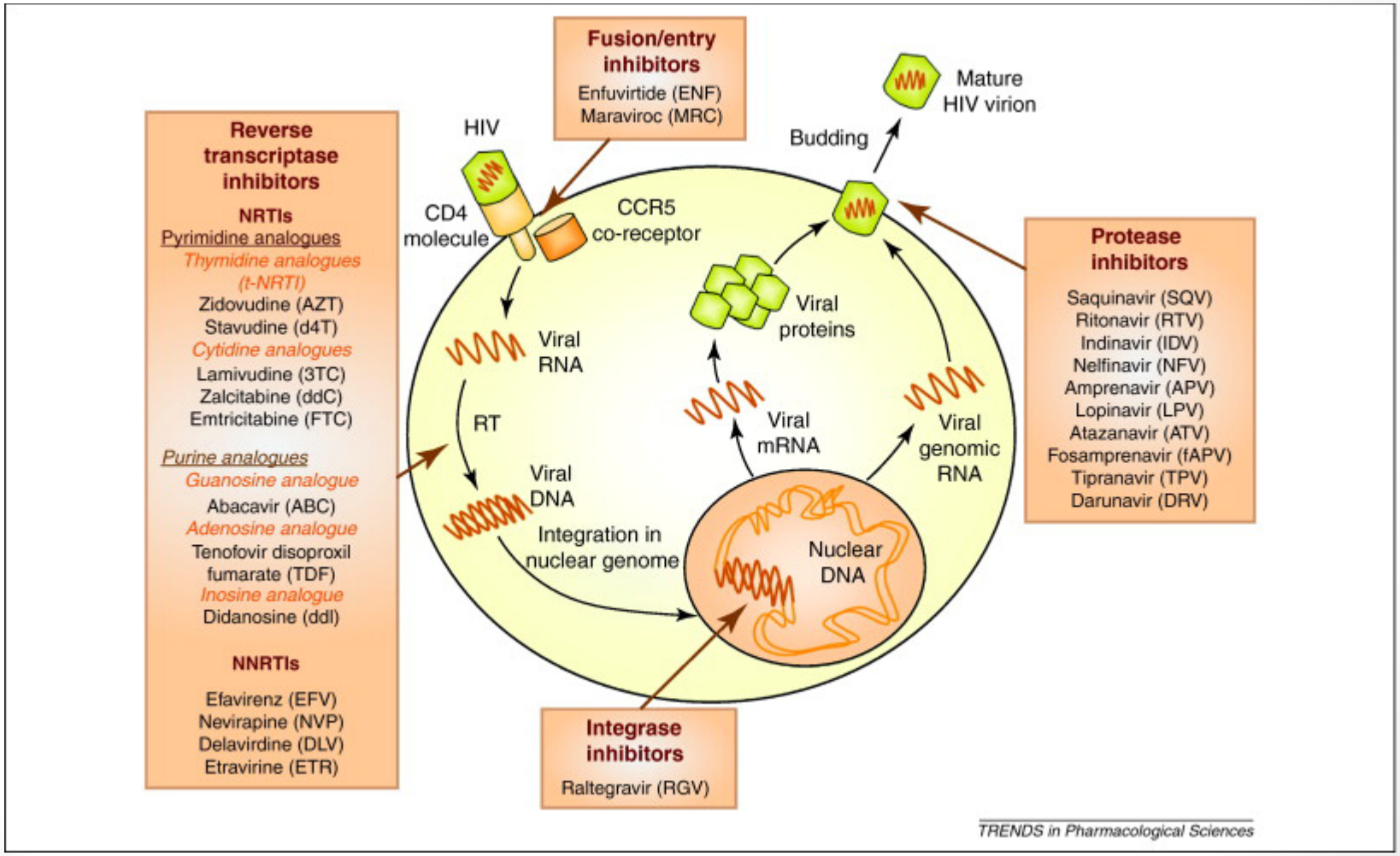
Principles of HIV Treatment

Drug names		Recommended adult dose *	Total daily pills
Fixed dose combinations			
Atripla (efavirenz 600 mg + emtricitabine 200 mg + tenofovir DF 300 mg)		One tablet, once-daily. Take at night and not with a high fat meal. See info on separate drugs.	1
Eviplera (rilpivirine 25 mg + emtricitabine 200 mg + tenofovir DF 300 mg)		One tablet, once-daily, with food (400 kcal). See separate drug info.	1
Odefsey (rilpivirine 25 mg + emtricitabine 200 mg + TAF 25 mg)		One tablet, once-daily, take with food. See info on separate drugs.	1
Triumeq (dolutegravir 50 mg + abacavir 600 mg + lamivudine 300 mg)		One tablet, once-daily. Take with or without food. See info on separate drugs.	1
Genvoya (elvitegravir 150 mg + cobicistat 150 mg + emtricitabine 200 mg + TAF 10 mg)		One tablet, once-daily. Take with food. See info on separate drugs.	1
Stribild (elvitegravir 150 mg + cobicistat 150 mg + emtricitabine 200 mg + tenofovir DF 300 mg)		One tablet, once-daily, take with food. See info on separate drugs.	1
Nukes: nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs)			
Dual nukes			
Truvada (tenofovir DF 300 mg + emtricitabine 200 mg)		One tablet, once-daily.	1
Descovy (TAF 10 mg OR 25 mg + emtricitabine 200 mg)		One tablet, once-daily.	1
Kivexa (abacavir 600 mg + lamivudine 300 mg)		One tablet, once-daily.	1
Single nukes			
lamivudine (3TC) ** (Epivir [pictured] - or generic)		1 x 300 mg or 2 x 150 mg (150 mg shown), (taken as a once-daily or twice-daily dose).	1 if 300 mg 2 if 150 mg
abacavir (Ziagen)		2 x 300 mg tablets (taken as a once-daily or twice-daily dose).	2
emtricitabine (FTC) (Emtriva)		1 x 200 mg capsule, once-daily.	1
tenofovir DF * (Viread)		1 x 300 mg tablet, once-daily.	1

* Different doses and formulations might be used - always check the dose with your doctor and pharmacist.
** Generic versions of lamivudine, nevirapine, efavirenz and TDF may be a different colour and shape. Some drugs are not recommended for first-line therapy. Smaller pills are for children or if larger pills are difficult to swallow. Some syrups are available. Pictures approximate to actual size

Drug names		Recommended adult dose *	Total daily pills
NNRTIs: non-nucleoside reverse transcriptase inhibitors (non-nukes)			
efavirenz ** (Sustiva) 600 mg or 200 mg		1 x 600 tablet (or 3 x 200 caps) once-daily; at night, not with high fat meal.	1 tablet (or 3 capsules)
nevirapine ** 200 / 400 mg	 200 mg  400 mg	1 x 200 mg twice-daily; or 2 x 200 mg once a day; or 1 x 400 mg once a day.	1 x 400 mg or 2 x 200 mg
etravirine (Intelence)		1 x 200 mg tablet, twice daily, take with food. Dispersible in water.	2
rilpivirine (Edurant)		1 x 25 mg tablet, once-daily, take with main meal (500 kcal).	1
INIs: integrase inhibitors			
raltegravir (Isentress)		1 x 400 mg tablet, twice-daily. Take with or without food.	2
dolutegravir (Tivicay) *		1 x 50 mg tablet, once-daily (or 1 x 50 mg twice -daily). With food if twice-daily but with or without otherwise.	1 or 2
elvitegravir – only available in fixed dose combinations – see Stribild and Genvoya.			1
CCR5 inhibitors (entry inhibitor)			
maraviroc * (Celsentri)		150 mg or 300 mg or 600 mg, as directed, depending on other ARVs in the combination.	1 or 2 or 4
b/PI: boosted protease inhibitors			
atazanavir * (Reyataz)		1 x 300 mg cap + booster, once-daily. Take with food. 150 mg and 200 mg capsules also available.	1 (+ 1 booster)
darunavir * (Prezista)		1 x 800 mg + booster once-daily (or 1 x 600 mg + 100 mg booster twice-daily if resistance). Take with food.	1 or 2 (+ 1 or 2 boosters based on dose)
atazanavir/cobicistat (Evotaz)		1 tablet, once-daily. Take with food.	1
darunavir/cobicistat (Rezolsta)		1 tablet, once-daily. Take with food.	1
PK (pharmacokinetic) boosters			
cobicistat (/c) (Tybost)		150 mg tablet, once daily. Used to boost atazanavir, darunavir and elvitegravir.	depends on boosted drug
ritonavir (/r) * (Norvir)		100 mg tablets used at different doses to boost other PIs.	depends on PI

ART - Mechanism of Action



General Principles of Drug Selection

- Guidelines for use of ART for maternal health during pregnancy generally are the same as for women who are not pregnant
  - Some modifications based on concerns about specific ARVs during pregnancy

- Consider benefits vs risks of ARV drug use during pregnancy .
- Consider co-infection (hepatitis B, tuberculosis)

- Ensure that at least 1 NRTI with high placental transfer is included in cART regimen for sufficient infant preexposure prophylaxis

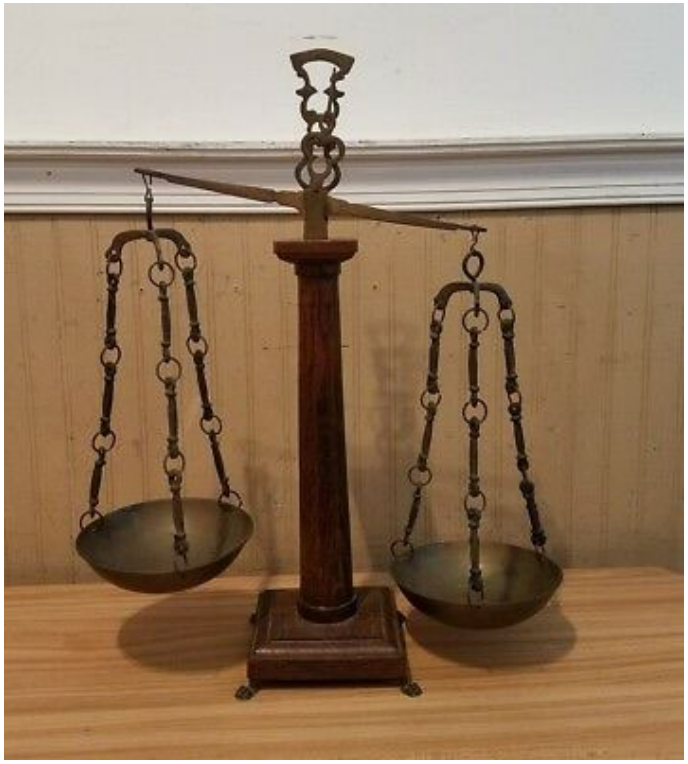
- Counsel women on the importance of close adherence to ARV regimen.

- Coordinate care between OB/GYN, ID/HIV and Pediatric specialists.

Optimizing ART Management

- Support ART adherence
- Address comorbidities
  - HBV/HCV
  - MTB
  - Drug Use
  - Mental Health
- Assess support network
- Address social determinants of health
- Discuss postpartum infant care and HIV care retention

Risks of ART in Pregnancy



Adverse Pregnancy Outcomes Associated with Medication Use

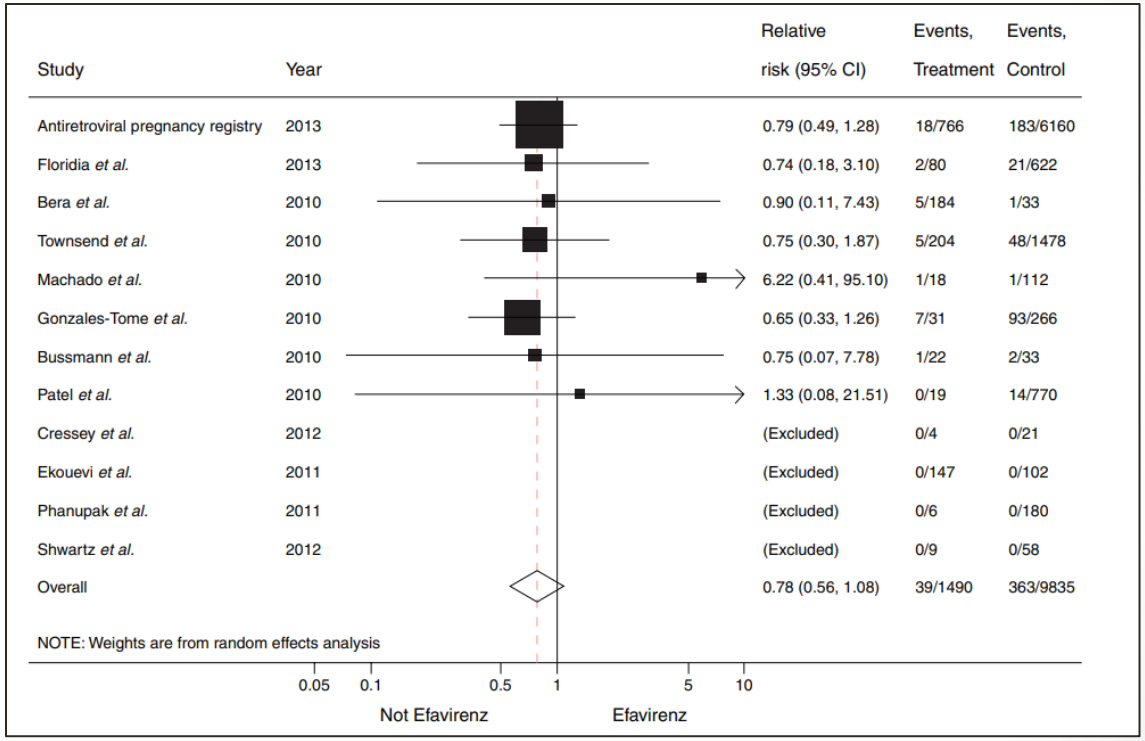
- Congenital Malformation
- Stillbirth
- Low Birth Weight
- Preterm Delivery

Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis

Nathan Ford[a], Lynne Mofenson[b], Zara Shubber[c], Alexandra Calmy[d,e], Isabelle Andrieux-Meyer[e], Marco Vitoria[a], Nathan Shaffer[a] and Françoise Renaud[a]

NTD Background

- Form by 7 weeks gestational age (GA)
- 0.1% prevalence in general population
- Case reports of NTD association with EFZ
- FDA 2005: Avoid EFZ in 1st trimester.
- WHO 2012: EFZ 1st line. Benefit > risk.



Ford AIDS 2014

Newsroom – Published on: May 21, 2018

FDA Warns of Neural Tube Birth Defects From HIV Drug Dolutegravir

Jaime Rosenberg

The FDA has warned of serious cases of neural tube birth defects involving the brain, spine, and spinal cord affecting babies born to women with HIV being treated with dolutegravir.

The FDA has issued an alert to the public on neural tube defects affecting babies born to women with HIV being treated with dolutegravir.

According to the agency, there have been serious cases of neural tube birth defects involving the brain, spine, and spinal cord. Neural tube defects occur early in pregnancy when the brain, spinal cord, and related structures do not develop properly.

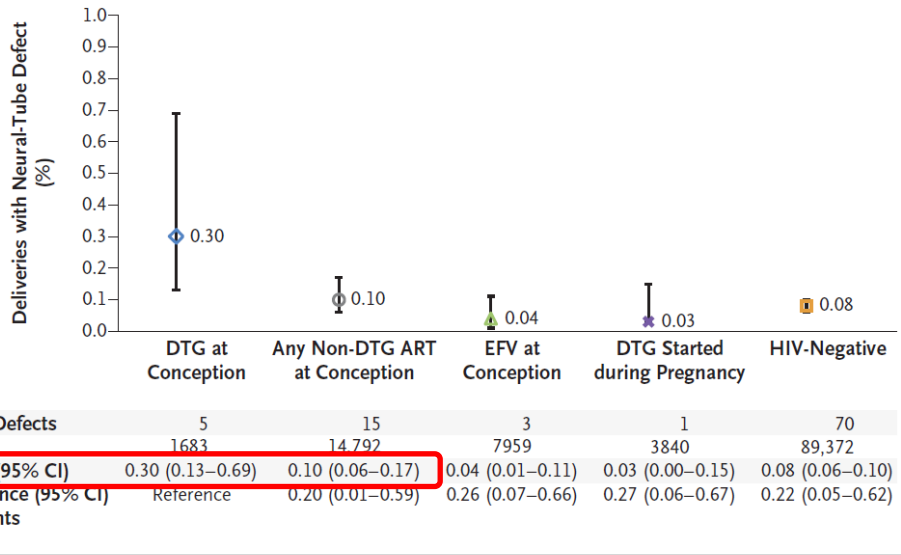
Preliminary results from an ongoing study in Botswana found that women being treated with dolutegravir at the time of becoming pregnant or early in the first trimester are at a higher risk for the defects. There are no reported cases of babies born with these defects to women who started taking dolutegravir later in their pregnancy.

ORIGINAL ARTICLE

Neural-Tube Defects and Antiretroviral Treatment Regimens in Botswana

Rebecca Zash, M.D., Lewis Holmes, M.D., Modiegi Diseko, B.P.H., Denise L. Jacobson, Ph.D., M.P.H., Sean Brummel, Ph.D., Gloria Mayondi, B.Sc., Arielle Isaacson, B.A., Sonya Davey, M.Phil., Judith Mabuta, Mompati Mmalane, M.D., Tendani Gaolathe, M.D., M. Essex, D.V.M., Ph.D., Shahin Lockman, M.D., Joseph Makhema, M.B., B.S., and Roger L. Shapiro, M.D., M.P.H.

- TSEPAMO Study
- Botswana adopted DTG as 1st line ART in 2016
- 119,033 deliveries with surface examination (2014-2019).
- 1683 pregnancies with DTG exposure at conception.
- Overall 98 NTD (0.08%)



	DTG at Conception	Any Non-DTG ART at Conception	EFV at Conception	DTG Started during Pregnancy	HIV-Negative
No. of Neural-Tube Defects	5	15	3	1	70
No. of Exposures	1683	14,792	7959	3840	89,372
Percent with Defect (95% CI)	0.30 (0.13–0.69)	0.10 (0.06–0.17)	0.04 (0.01–0.11)	0.03 (0.00–0.15)	0.08 (0.06–0.10)
Difference in Prevalence (95% CI) — Percentage Points	Reference	0.20 (0.01–0.59)	0.26 (0.07–0.67)	0.27 (0.06–0.67)	0.22 (0.05–0.62)

Figure 2. Neural-Tube Defects According to Maternal ART and HIV Infection Status, August 2014–March 2019.

Zash NEJM 2019

ORIGINAL RESEARCH

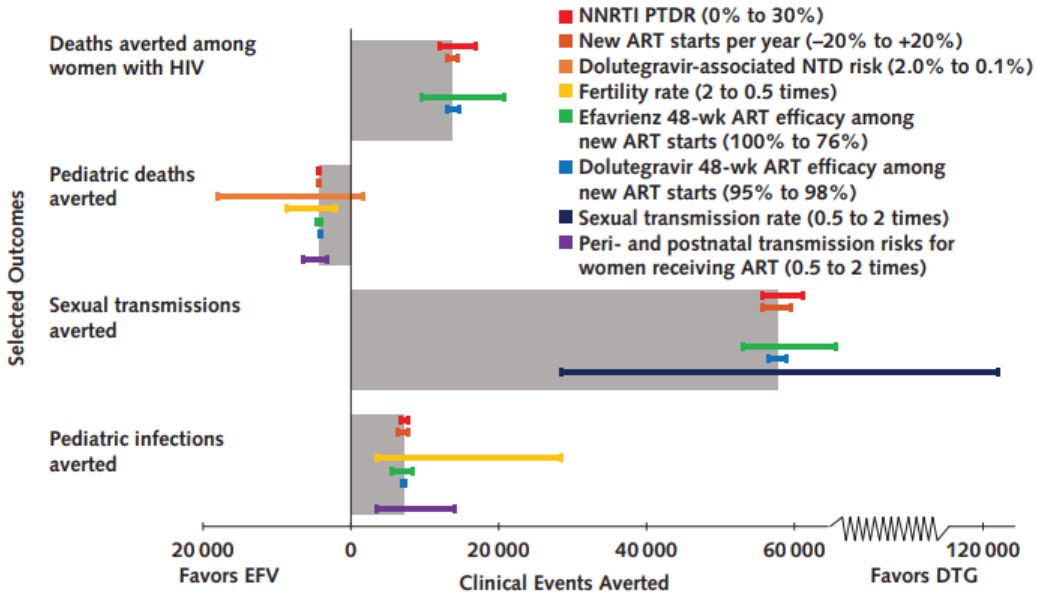
Annals of Internal Medicine

Risks and Benefits of Dolutegravir- and Efavirenz-Based Strategies for South African Women With HIV of Child-Bearing Potential

A Modeling Study

Caitlin M. Dugdale, MD; Andrea L. Ciaranello, MD, MPH; Linda-Gail Bekker, MD, PhD; Madeline E. Stern, BA; Landon Myer, MBChB, PhD; Robin Wood, MMed, DSc (Med); Paul E. Sax, MD; Elaine J. Abrams, MD; Kenneth A. Freedberg, MD, MSc; and Rochelle P. Walensky, MD, MPH

Figure 1. Tornado diagram of model-based outcomes for the comparison of EFV versus DTG.



Dugdale Annals 2019

ATTENTION HEALTHCARE PROVIDERS

Please visit our website at www.APRegistry.com for data forms or contact our Registry Call Center at SM_APR@APRegistry.com for additional information on how to report to the APR.

The Antiretroviral Pregnancy Registry (APR) recognizes the significant participation of the following 100% Healthcare Providers (HCPs) (listed alphabetically). We greatly appreciate the contributions of all HCPs who report to the APR and we encourage all registered reporters to submit all of their cases to the Registry. Contact the Registry at SM_APR@APRegistry.com or visit www.APRegistry.com to learn more about becoming a 100% Healthcare Provider.

Andrews, Mary-Margaret MD *(Dartmouth-Hitchcock Medical Center)*

Badell, Martina MD *(Grady Memorial Hospital)*

Balt, Christine DNP *(Eskenazi Health)*

Cecchini, Diego MD *(Hospital Cosme Argerich)*

Cejtin, Helen MD *(Ruth M. Rothstein CORE Center)*

Chokephaibulkit, Kulkanya MD *(Faculty of Medicine Siriraj Hospital, Mahidol University)*

Cohan, Deborah MD *(UCSF-Bay Area Perinatal AIDS Center)*

Deville, Jaime MD *(UCLA Care-4-Families Clinic)*

Dionne-Odom, Jodie MD *(UAB Department of Pediatrics)*

Fearnley, Nicola MD *(Bradford Teaching Hospitals NHS Foundation Trust)*

Galang, Minerva MD *(Mercy Health-Special Immunology Services, Saint Mary's Hospital)*

Garcia, Patricia MD *(Northwestern University/Prentice Women's Hospital)*

Han, Guorong MD *(Second Affiliated Hospital of the Southeast University)*

Hayes, Erick MD *(St. Louis Children's Hospital /Washington University School of Medicine)*

Hitti, Jane MD *(University of Washington Medical Center)*

Hüfner, Anja *(Ambulanzzentrum Infektiologie des UKE GmbH - Hamburg, Germany)*

Ivalo, Silvina MD *(Hospital General de Agudos J. M. Ramos Mejía - Buenos Aires, Argentina)*

Kedem, Eynat MD *(Rambam Health Care Center)*

Kinzie, Kay FNP-BC *(Children's Hospital Colorado CHIP Program)*

Lad, Madhuri DO *(Oklahoma State University Center for Health Sciences)*

Lazenby, Gweneth MD *(Medical University of South Carolina)*

Levison, Judy MD *(Harris Health System/ Baylor College of Medicine)*

Levy, Miriam MD *(Liverpool Hospital, Sydney Australia)*

Momplaisir, Florence MD *(Drexel College of Medicine)*

Nerette-Fontain, Sandy MD *(Les Centres GHESKIO - Haiti)*

Nielsen, Natalie PharmD *(Nationwide Children's Hospital)*

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Reid, Christopher MD *(Orange County HIV Clinic)*

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Schut, Ronald MD *(Positive Care Center at Hennepin County Medical Center)*

Sha, Beverly MD *(Rush University Medical Center)*

Short, William MD, MPH *(University of Pennsylvania, Division of Infectious Diseases)*

Sidi, Leon MD *(Hospital dos Servidores do Estado)*

Smok, Dorothy MD *(New York Presbyterian Hospital)*

Stek, Alice MD *(MCA Program at Los Angeles County + University of Southern California Medical Center)*

Szabo, Susan MD *(Christiana Care Health System)*

Taylor, Graham MD *(Imperial College Healthcare NHS Trust)*

Tedaldi, Ellen MD *(Temple General Internal Medicine)*

Tkatch, Lisa MD *(PinnacleHealth REACCH Program)*

Tyler, Charles MD *(Rural HIV Model Clinic)*

Vande Waa, John DO *(University of South Alabama Family Specialty Clinic)*

Verlinghieri, Gwen CRNP *(AIDS Care Group)*

Wait, Brenton MD *(Homerton Sexual Health Services, Homerton Hospital)*

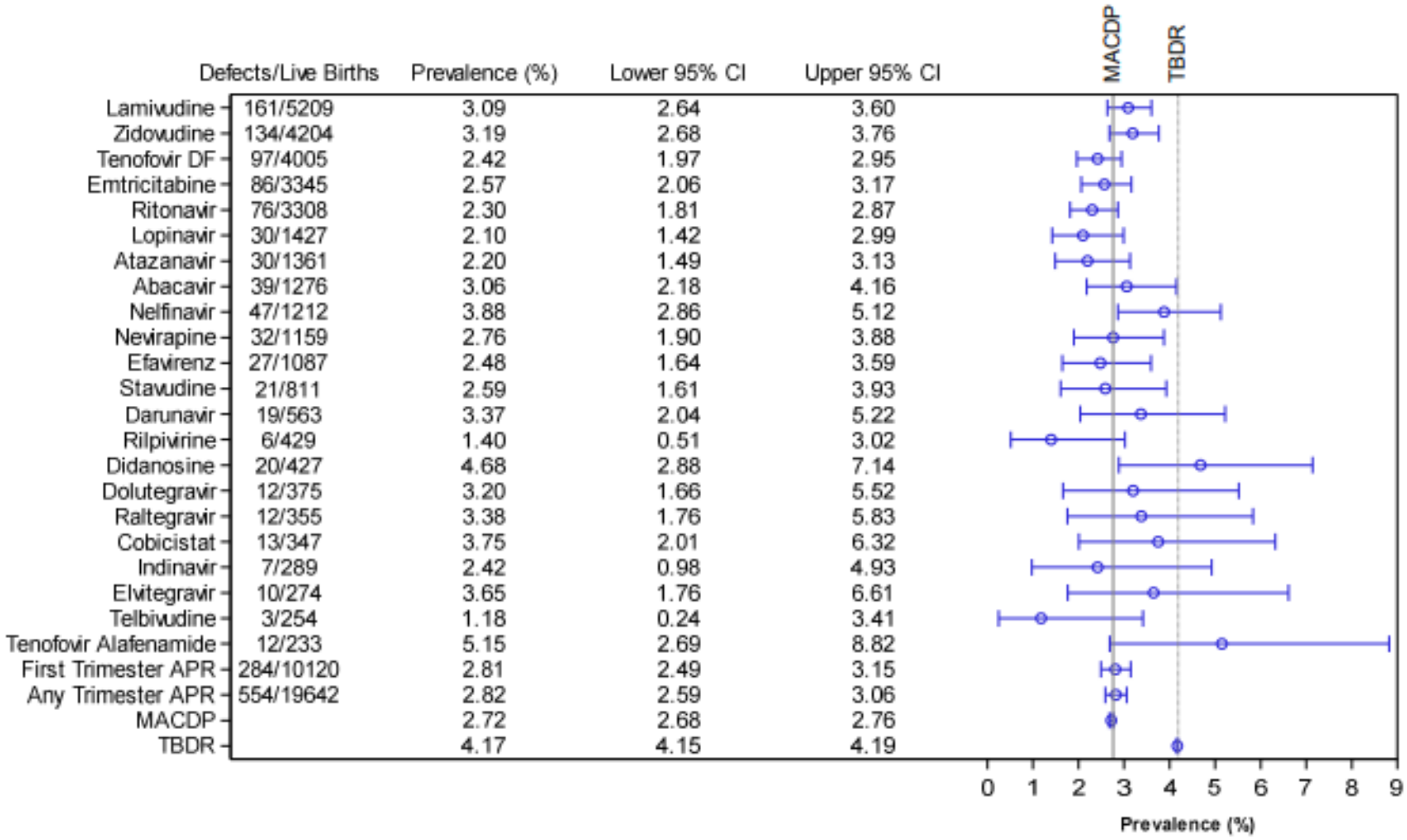
Wilkins, Grace FNP *(Brody School of Medicine at East Carolina University)*

Wright, Rodney MD *(AECOM/ Montefiore Medical Center)*

Yarrington, Christina MD *(Boston Medical Center)*

Zorrilla, Carmen MD and Ibarra, Jessica MD *(Maternal Infant Studies Center, University of Puerto Rico School of Medicine)*

Figure 1: Summary of Birth Defects among First Trimester Exposures, Prospective Registry Cases Closed with Outcome through 31 July 2019



	Defects/Live Births	Prevalence (%)	Lower 95% CI	Upper 95% CI
Lamivudine	161/5209	3.09	2.64	3.60
Zidovudine	134/4204	3.19	2.68	3.76
Tenofovir DF	97/4005	2.42	1.97	2.95
Emtricitabine	86/3345	2.57	2.06	3.17
Ritonavir	76/3308	2.30	1.81	2.87
Lopinavir	30/1427	2.10	1.42	2.99
Atazanavir	30/1361	2.20	1.49	3.13
Abacavir	39/1276	3.06	2.18	4.16
Nelfinavir	47/1212	3.88	2.86	5.12
Nevirapine	32/1159	2.76	1.90	3.88
Efavirenz	27/1087	2.48	1.64	3.59
Stavudine	21/811	2.59	1.61	3.93
Darunavir	19/563	3.37	2.04	5.22
Rilpivirine	6/429	1.40	0.51	3.02
Didanosine	20/427	4.68	2.88	7.14
Dolutegravir	12/375	3.20	1.66	5.52
Raltegravir	12/355	3.38	1.76	5.83
Cobicistat	13/347	3.75	2.01	6.32
Indinavir	7/289	2.42	0.98	4.93
Elvitegravir	10/274	3.65	1.76	6.61
Telbivudine	3/254	1.18	0.24	3.41
Tenofovir Alafenamide	12/233	5.15	2.69	8.82
First Trimester APR	284/10120	2.81	2.49	3.15
Any Trimester APR	554/19642	2.82	2.59	3.06
MACDP		2.72	2.68	2.76
TBDR		4.17	4.15	4.19

MACDP = Metropolitan Atlanta Congenital Defects Program (reference 5); TBDR = Texas Birth Defects Registry (reference 7).
Note: The vertical solid line is the upper 95% confidence interval endpoint for MACDP, 2.76%. The vertical dashed line is the upper 95% confidence interval endpoint for TBDR, 4.19%. Confidence intervals are calculated using the Clopper-Pearson exact binomial method.

Preterm Delivery

Table 2. Unadjusted and Adjusted Odds Ratios (ORs) for Preterm Birth and for Spontaneous Preterm Birth, by Exposure to Combination Antiretroviral (ARV) Regimens During Pregnancy and Other Maternal and Demographic Risk Factors

	Preterm Birth				Spontaneous Preterm Birth			
Characteristic	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
ARV regimen								
Combination, with PI	1.60 (.96–2.67)	.07	1.49 (.83–2.67)	.18	1.41 (.74–2.67)	.30	1.41 (.66–2.99)	.38
Combination, with NNRTI	1.35 (.71–2.58)	.36	1.28 (.62–2.66)	.50	1.39 (.63–3.10)	.41	1.53 (.62–3.81)	.36
Combination, with ≥3 NRTIs	1.13 (.60–2.14)	.70	1.04 (.50–2.14)	.93	0.86 (.37–1.98)	.72	0.88 (.34–2.29)	.80
Monotherapy or dual therapy	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Maternal age <25 y at delivery	0.95 (.74–1.23)	.70			1.04 (.75–1.45)	.80		
Black race	1.40 (1.06–1.86)	.02	1.35 (1.00–1.83)	.05	1.86 (1.26–2.76)	.002	1.79 (1.18–2.71)	.01
Income <$20 000/year	1.57 (1.18–2.09)	.002	1.51 (1.12–2.05)	.01	1.78 (1.21–2.62)	.004	1.77 (1.18–2.66)	.01
Less than high school education	0.95 (.74–1.23)	.72			0.96 (.69–1.34)	.82		
Alcohol use	1.32 (.86–2.04)	.20			1.39 (.80–2.42)	.24		
Cigarette smoking	0.96 (.70–1.33)	.81			0.84 (.56–1.26)	.39		
Illicit drug use	1.32 (.87–2.00)	.20			1.61 (.98–2.64)	.06		
Genital infection	1.21 (.90–1.63)	.20			1.50 (1.04–2.16)	.03		
$CD4^+$ lymphocyte count <200 cells/mm^3	1.79 (1.26–2.55)	.001	1.86 (1.28–2.71)	.001	1.83 (1.17–2.87)	.01	1.88 (1.17–3.01)	.01
HIV RNA load >1000 copies/mL	1.39 (1.03–1.89)	.03			1.55 (1.06–2.27)	.02		

Watts JID 2013

Table 3. Associations of First Trimester Exposures to Combination Antiretroviral (ARV) Regimens Including Protease Inhibitors (PIs), Nonnucleoside Reverse-Transcriptase Inhibitors (NNRTIs), and ≥3 Nucleoside Reverse-Transcriptase Inhibitors (NRTIs) With Preterm Birth and Small for Gestational Age (SGA)

Outcome, First-Trimester Combination ART Regimen	Unadjusted Models		Adjusted Models[a]	
	OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Preterm birth				
Contained PI	1.43 (1.11–1.85)	.006	1.55 (1.16–2.07)	.003
Contained NNRTI	1.26 (.77–2.06)	.37	1.34 (.78–2.30)	.28
Contained ≥3 NRTIs	0.75 (.35–1.60)	.45	0.84 (.37–1.91)	.68
None in first trimester	1.00 (reference)		1.00 (reference)	
Spontaneous preterm birth				
Contained PI	1.40 (1.00–1.95)	.048	1.59 (1.10–2.30)	.014
Contained NNRTI	1.25 (.66–2.36)	.50	1.42 (.72–2.81)	.31
Contained ≥3 NRTIs	0.68 (.24–1.92)	.47	0.66 (.20–2.18)	.49
None in first trimester	1.00 (reference)		1.00 (reference)	
SGA				
Contained PI	0.80 (.53–1.20)	.28	0.79 (.49–1.26)	.32
Contained NNRTI	1.19 (.60–2.37)	.62	1.17 (.54–2.54)	.70
Contained ≥3 NRTIs	1.05 (.41–2.69)	.92	0.99 (.34–2.86)	.99
None in first trimester	1.00 (reference)		1.00 (reference)	

Abbreviations: CI, confidence interval; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; OR, odds ratio; PI, protease inhibitor.

[a] Models for preterm birth and spontaneous preterm birth adjusted for black race, annual income of <$20 000, and maternal $CD4^+$ T-cell count of <200 cells/mm^3 at delivery. Models for SGA adjusted for same covariates as above, as well as for cigarette smoking during pregnancy.

Watts JID 2013

Infant Growth after TDF in-utero

Table 4. Tenofovir disoproxil fumarate use during pregnancy and/or breastfeeding and infant bone/renal markers.

Author – type study; year, location	Number TDF and non-TDF exposed	Finding
Vigano – HIV; 2011, Italy [6]	$N=33$ TDF ART; $N=35$ non-TDF ART	Bone ultrasound z-scores not different (+0.6 TDF ART versus +0.8 non-TDF ART, $P=0.40$) No difference in calcium or phosphorus or bone markers BAP and CTX Urine calcium/creatinine ratio higher in TDF ART (0.08 TDF ART versus 0.05 non-TDF ART, $P=0.039$) Parathyroid hormone decreased with TDF ART (9.9 TDF versus 12.3 non-TDF ART, $P=0.023$) but all values within normal limits
Gibb – HIV; 2012, Uganda/Zimbabwe [7]	$N=111$ TDF ART; $N=62$ non-TDF ART	Grade 1–2 calcium not different: TDF ART 8% versus non-TDF ART 6% ($P=0.60$) Grade 1 phosphorus not different: TDF ART 1% versus non-TDF ART 5% ($P=0.15$) Grade 1–3 alkaline phosphatase not different: TDF ART 20% versus non-TDF ART 20% ($P=0.85$) No bone fractures
Siberry – HIV; 2015, the United States [17]	$N=74$ TDF ART; $N=69$ non-TDF ART	Neonatal BMC with head, adjusted difference 5.3 grams lower BMC with TDF ART versus non-TDF ART exposure ($P=0.013$) BMC without head, not significantly different by type ART ($P=0.15$)
Siberry – HIV; 2016, multicountry Africa [25]	$N=114$ TDF ART; $N=127$ non-TDF ART; $N=118$ ZDV/sdNVP	Neonatal whole-body BMC lower with ART regimens (both TDF ART or non-TDF ART; $P<0.001$) compared with ZDV/sdNVP, but not significantly different TDF ART versus non-TDF ART ($P=0.41$) Lumbar spine BMC not significantly different by type ARV
Jao – HIV; 2016, South Africa [26]	$N=188$ TDF ART < 10 weeks; $N=326$ TDF ART 10–24 weeks; $N=132$ TDF ART ≥ 25 weeks	Fetal femur and humerus length z-score by ultrasound did not vary by duration maternal TDF ART during pregnancy (<10 weeks, 10–25 weeks, or >25 weeks)
Floridia – HIV; 2016, Malawi [29]	$N=136$ TDF ART; $N=40$ non-TDF ART	BAP and CTX not significantly different TDF ART versus non-TDF ART-exposed infants at age 12 months
Mugo – PrEP; 2014, Kenya/Uganda [37]	$N=81$ TDF; $N=47$ TDF/FTC; $N=66$ Placebo	No difference between TDF, TDF/FTC, and placebo for infant creatinine at age 1 and 3 months

Mofenson AIDS 2017

Routine Prenatal Care in HIV

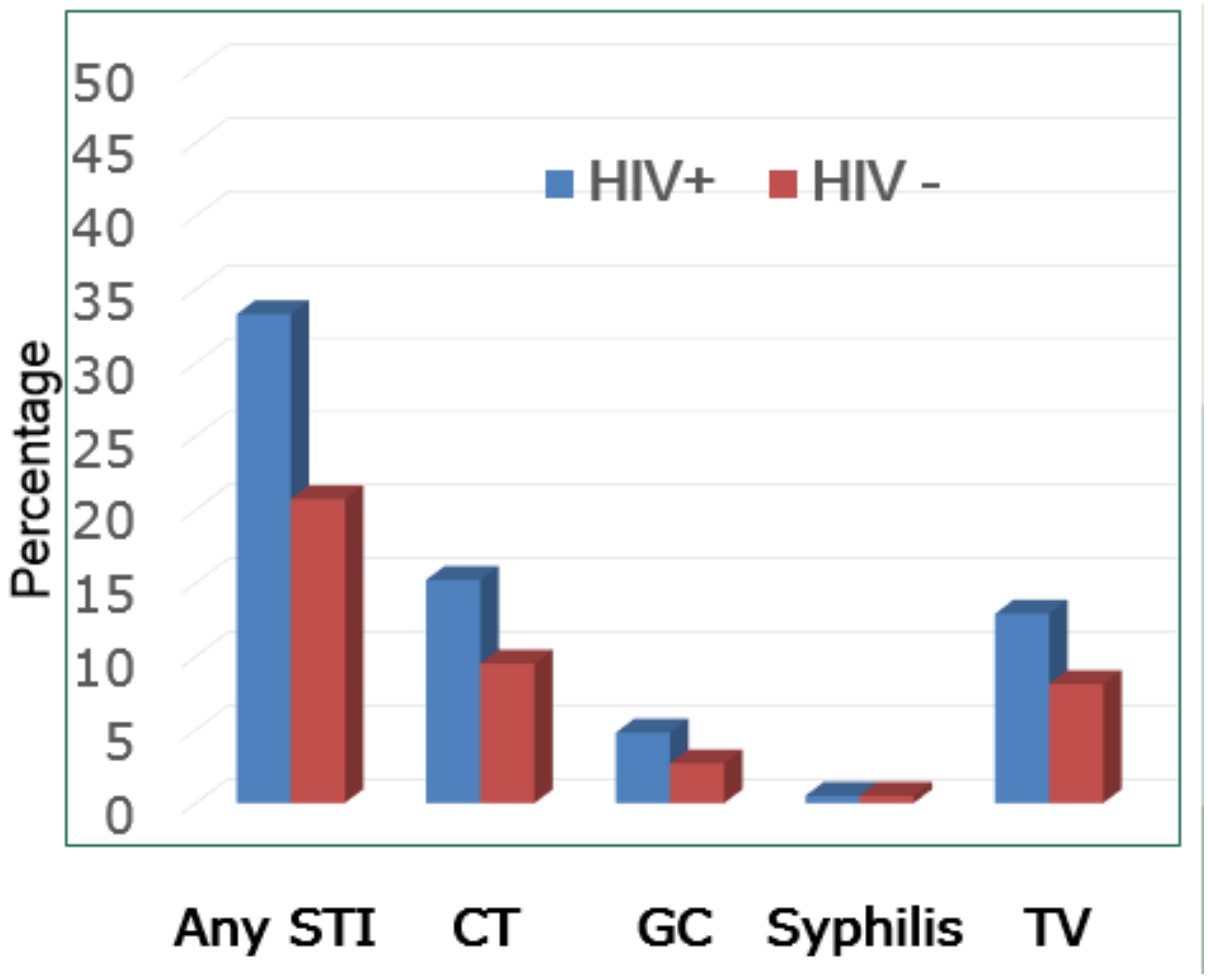
- Laboratory Testing
  - Genotype at baseline visit for newly detected infection or if there is concern for resistance in a treatment experienced patient. (HIV VL must be >500).
  - Follow HIV VL 2-4 weeks after regimen change and monthly until undetectable (<20 copies/mL). Then each trimester and at 36-38 weeks.
  - Follow CBC, BMP and LFTs.
  - Document hepatitis B (HBsAg, HBsAb) and hepatitis C (HCV Ab) status.

- STI Screening
  - CT/GC/Syphilis at first visit and 3rd trimester.
  - Test of cure for CT at 4 weeks and recommend partner therapy.

- Vaccinations
  - Influenza (quadrivalent, killed vaccine)
  - TdaP (after 27 weeks, repeat in every pregnancy due to rapid waning of immunity)
  - HBV (if non immune and indicated)

- Prophylaxis
  - CD4<200: add Bactrim DS 1 daily for PCP prophylaxis
  - CD4<50: continue Bactrim and add azithromycin 1200 mg/week for Mycobacterium Avium Complex (MAC)

Figure 2: STIs Detected During Pregnancy by HIV Status



Routine Prenatal Care in HIV

- Monitor for medication compliance: confirm medication and dosing
- Monitor for side effects: GI symptoms are among the most common adverse events associated.
- Monitor for vaginal and oral candidiasis
- Avoid amniocentesis if possible
  - If necessary, wait until VL is fully suppressed.

Intrapartum Management of Pregnant Women with HIV

Maternal HIV RNA at Time of Delivery Assessed at ≥34 to 36 Weeks Gestation (or 4–6 Weeks Before Delivery) with No Concerns Regarding ART Adherence[a]				
	<50 copies/mL and on ART with No Concerns About Adherence	**≥50 to ≤1,000 copies/mL**	**>1,000 copies/mL**	• **Unknown HIV RNA** • **ART Adherence Concerns** • **Not Receiving ART** • **HIV Diagnosis in Labor**
Intrapartum ART	Women should take their prescribed ART on schedule as much as possible during labor and before scheduled cesarean delivery **(CIII)**. In general, ARV regimens are initiated postpartum for women diagnosed with HIV during labor.			
Intrapartum IV ZDV	Not required **(BII)**.	Not required but may be considered **(CII)**; many experts recommend.	Yes, recommended **(AI)**.[b] IV ZDV: 1-hour loading dose at 2 mg/kg followed by a continuous ZDV infusion of 1 mg/kg for 2 hours (at least 3 hours total) **(AII)**.	
Mode of delivery	Normal vaginal delivery[c] **(AII)**.	Normal vaginal delivery[c] **(AII)**.	Scheduled cesarean delivery at 38 weeks[d] **(AII)**.	Individualized care, see footnote.[d]
Artificial rupture of membranes[e]	Per standard obstetric indications **(BII)**.	Avoid if possible **(BIII)**.	Not applicable, cesarean delivery recommended.	Avoid if possible in women with detectable or unknown viral load who are not receiving a cesarean delivery **(BIII)**.
Induction of labor	Per standard obstetric indications, including use of pitocin. **Women with HIV RNA ≤1,000 copies/mL should NOT be routinely induced at 38 weeks.**		Not applicable, scheduled cesarean delivery recommended.	Avoid if possible **(BIII)**.

Complications and Route of Delivery in a Large Cohort Study of HIV-1–Infected Women—IMPAACT P1025

TABLE 1. Distribution of Maternal Background Characteristics by Mode of Delivery

Characteristics	Total (N = 2297)	Mode of Delivery			*P* Value*
		Vaginal (N = 1055)	Elective Cesarean Section (N = 798)	Nonelective Cesarean Section (N = 444)	
Maternal age at delivery, yrs					
<35	1894 (82%)	865 (82%)	669 (84%)	360 (81%)	0.41
≥35	403 (18%)	190 (18%)	129 (16%)	84 (19%)	
Race/ethnicity					
Hispanic	721 (32%)	297 (28%)	288 (37%)	136 (31%)	<0.001
White non-Hispanic	210 (9%)	103 (10%)	77 (10%)	30 (7%)	
Black non-Hispanic	1300 (57%)	617 (59%)	416 (53%)	267 (60%)	
Other	48 (2%)	30 (3%)	8 (1%)	10 (2%)	
Unknown	18	8	9	1	
HIV characteristics					
Last maternal CD4 (cells/mm^3) during pregnancy					
<200	227 (10%)	79 (8%)	83 (11%)	65 (15%)	<0.001
200–349	419 (19%)	192 (19%)	140 (18%)	87 (20%)	
≥350	1590 (71%)	761 (74%)	551 (71%)	278 (65%)	
Unknown	61	23	24	14	
Last viral load during pregnancy, copies/mL					
>400	370 (16%)	72 (7%)	207 (27%)	91 (21%)	<0.001
≤400	1874 (84%)	966 (93%)	568 (73%)	340 (79%)	
Unknown	53	17	23	13	

46% vaginal delivery, 35% ECS, 19% NECS.

Livingston JAIDS 2016

TABLE 2. Delivery Outcome and Distribution of Maternal Intrapartum/Postpartum Morbidities

Characteristics	Total (N = 2297)	Mode of Delivery			*P* Value*
		Vaginal (N = 1055)	Elective Cesarean Section (N = 798)	Nonelective Cesarean Section (N = 444)	
Planned/actual mode of delivery					
Vaginal	1361 (61%)	998 (98%)	141 (18%)	222 (52%)	<0.001
Cesarean section	858 (39%)	24 (2%)	632 (82%)	202 (48%)	
Unknown	78	33	25	20	
Any intrapartum/postpartum complications					
Yes	442 (19%)	138 (13%)	180 (23%)	124 (28%)	<0.001
No	1855 (81%)	917 (87%)	618 (77%)	320 (72%)	
Surgery plus delivery wound complications					
Yes	327 (14%)	81 (8%)	145 (18%)	101 (23%)	<0.001
No	1970 (86%)	974 (92%)	653 (82%)	343 (77%)	
Infections					
Yes	250 (11%)	76 (7%)	98 (12%)	76 (17%)	<0.001
No	2047 (89%)	979 (93%)	700 (88%)	368 (83%)	
Other complications					
Yes	168 (7%)	57 (5%)	60 (8%)	51 (11%)	<0.001
No	2129 (93%)	998 (95%)	738 (92%)	393 (89%)	
Hemorrhagic events					
Yes	71 (3%)	23 (2%)	24 (3%)	24 (5%)	0.004
No	2226 (97%)	1032 (98%)	774 (97%)	420 (95%)	
Gastrointestinal complications					
Yes	14 (1%)	2 (0%)	9 (1%)	3 (1%)	0.04
No	2283 (99%)	1053 (100%)	789 (99%)	441 (99%)	
Thromboembolic events					
Yes	8 (0%)	2 (0%)	4 (1%)	2 (0%)	0.49
No	2289 (100%)	1053 (100%)	794 (99%)	442 (100%)	

13 cases of MTCT (0.6%) – unable to associate with mode of delivery given small numbers

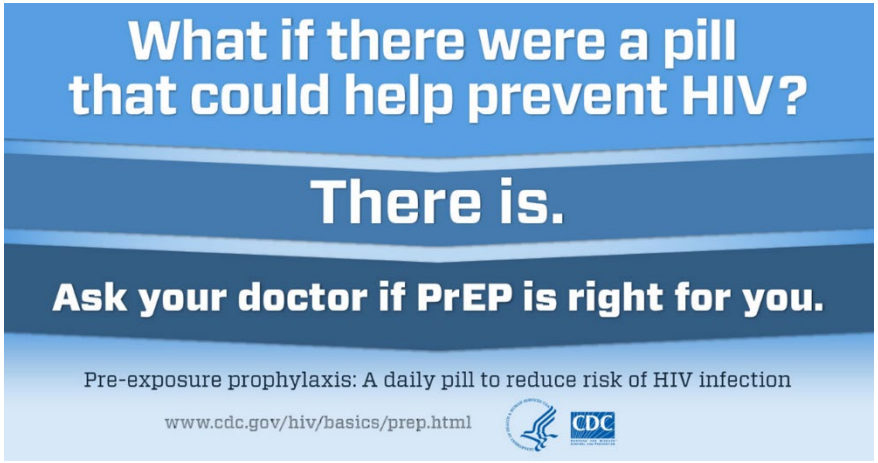
Postpartum Care

- Continue same ART medications.
- AZT BID for HIV-exposed infant x 4-6 weeks.
- No breastfeeding (active area of research).
- Schedule follow up visit with HIV provider for mother and with pediatrician aware of HIV-exposure for baby.
- Contraception
- Importance of care engagement

Pediatric Management of HIV exposed neonates

Level of Perinatal HIV Transmission Risk	Description	Neonatal ARV Management
Low Risk of Perinatal HIV Transmission	Mothers who received ART during pregnancy with viral suppression (defined as a confirmed HIV RNA level <50 copies/mL) near delivery and no concerns related to adherence	ZDV for 4 weeks[a]
High Risk of Perinatal HIV Transmission[a,b]	Mothers who did not receive antepartum or intrapartum ARV drugs Mothers who received only intrapartum ARV drugs Mothers who received antepartum and intrapartum ARV drugs but did not have viral suppression (defined as a confirmed HIV RNA level <50 copies/mL) near delivery Mothers with acute or primary HIV infection during pregnancy or breastfeeding (in which case, the mother **should immediately discontinue breastfeeding**)[c]	Presumptive HIV therapy using either ZDV, 3TC, and NVP (treatment dose) *or* ZDV, 3TC, and RAL administered from birth up to 6 weeks.[d]
Presumed Newborn HIV Exposure	Mothers with unconfirmed HIV status who have at least one positive HIV test at delivery or postpartum *or* Mothers whose newborns have a positive HIV antibody test	ARV management as described above for newborns with a high risk of perinatal HIV transmission Infant ARV drugs should be discontinued immediately if supplemental testing confirms that the mother does not have HIV
Newborn with HIV[e]	Positive newborn HIV virologic test/ NAT	Three-drug ARV regimen using treatment doses

HIV Prevention in Pregnancy



Indications for HIV PrEP:

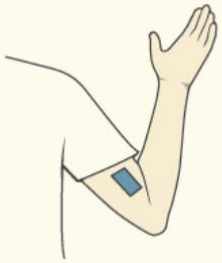
- Partner with HIV infection with viral load detectable or unknown
- Recent STI
- Drug use
- Others who request HIV prevention

NIAID is funding research on 4 types of long-acting HIV prevention.

INTRAVAGINAL RING (IVR)

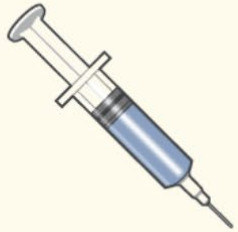
Polymer ring inserted into the vagina releases antiretroviral drug over time.

IMPLANT



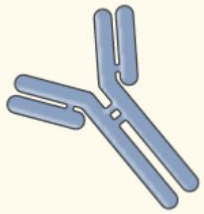
Device implanted in the body releases antiretroviral drug over time.

INJECTABLE



Long-acting antiretroviral drug is injected into the body.

ANTIBODY



Antibody is infused or injected into the body.

NIH National Institute of Allergy and Infectious Diseases: Long-Acting Forms of HIV Prevention

Perinatal HIV Resources

- National Institutes of Health:

  AIDS INFO Perinatal HIV Guidelines

- National Perinatal HIV Consultation Service at UCSF:

  1-888-448-8765

Sign up: Perinatal ReproID HIV Listserv

The CCC Perinatal ReproID HIV Listserv is a forum to connect with providers, discuss difficult perinatal HIV cases, and share tools and protocols. Contact us to join at Marliese.Warren@ucsf.edu.

Future Research

- Safety and efficacy pregnancy data on newer ART
  - Tenofovir alafenamide (TAF)
  - Bictegravir (BIC)
- Pharmacologic studies to inform dosing
- Task Force on Research Specific to Pregnant and Lactating Women (PRGLAC)
- Improving Postpartum Retention in Care
- Breastfeeding Safety in Women with HIV
- Long term pediatric follow up of in-utero ART exposure
- HIV Prevention in Pregnancy (PrEP)
  - Increase access
  - Risk prediction tools validated for women
  - TAF/FTC in cis-gender women

Conclusions

- The role of ART in pregnancy in PMTCT is one of the great success stories of the HIV epidemic to date.
- Observational and prospective clinical trials are needed to identify safety and efficacy outcomes for ART in pregnancy.
  - All analyses must carefully consider confounding.
- Risks and benefits of various ART regimens is an important discussion for all women of reproductive age living with HIV.
- Studies will continue to refine our understanding of ART safety and efficacy for HIV treatment and prevention in pregnancy.
  - ART Registry Data is useful. Anyone can contribute.
- Thoughtful collaboration and frequent communication with colleagues in Obstetrics and Gynecology/Maternal Fetal Medicine and Pediatrics is key.

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