



CROI 2018 Update - Part II

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Disclosures

- **Speaker's Bureau:** Janssen, Gilead, Merck, AbbVie
- **Scientific Advisor:** Gilead, Janssen, AbbVie
- **Grant/Research/Contracted Support:** CDC/HRSA, NWAETC, Pacific AETC, HealthHIV, Project ECHO, National Cancer Institute, Gilead Sciences

Learning Objectives

- Review additional abstracts presented at CROI 2018 in Boston, MA
- List currently recommended ART regimens including DHHS statement on **Bictegravir**
- Discuss recent Pregnancy-related warnings on **Dolutegravir** and **Darunavir/Cobicistat**

Maybe another time...

- How to fix the HIV care cascade (Del Rio, Mugavero, Dombrowski)
- Infectious complications of the Opioid epidemic (Hodder)
- Increased HIV transmission late in pregnancy (Heffron, Thompson)
- M184V in dual 3TC-containing ART switch (Gagliardini, #498)
- ‘Rapidly growing clusters’ HIV transmission, (young Latino MSM)
- Hepatitis C co-infection!!!
 - Recognition of sexual transmission and re-infection
 - Swiss HCVfree study shows Treatment as Prevention in HCV works!
 - Salvage Rx for GLE/PIB relapsers (GLE/PIB+SOF+Riba)
- TDF in HBV-infected pregnant women (Jourdain, #131, ITAP study)
- Limited HIV Vaccine progress (one moving to human trials)
- Glimmer of hope in Cure research: 4 months after BNaB (PGT121)+TLR7 agonist GS-6290 provides ‘functional cure’ in monkeys

HIV Transmission in Pregnancy

An HIV- woman presents to your clinic. She and her HIV+ male partner want to discuss conception options. Which do you suggest?

- A. If he is able to get HIV VL undetectable, there is no risk of HIV transmission
- B. Sperm washing services are covered by Medical and performed by most OB-GYN offices
- C. PrEP should be started 2-3 weeks before conception and continued through the end of pregnancy
- D. PrEP can be used around times of ovulation to decrease chances of infection

Partners Studies: Increased Risk of Female HIV Acquisition in Late Pregnancy and Postpartum

- **N = 2751** HIV-negative women in relationship with HIV-positive ART-naive men followed until first evidence of HIV infection linked to male study partners
 - 78 incident HIV infections occurred during follow-up; 22.4% became pregnant
- **In adjusted model, HIV acquisition risk per sex act was increased 3-fold in late pregnancy and 4-fold postpartum**

RR of HIV Acquisition by Reproductive Stage	Base Model*		Adjusted Model†	
	RR (95% CI)	P Value	RR (95% CI)	P Value
Not pregnant or postpartum	1.00	--	1.00	--
Early pregnancy through postpartum	4.97 (2.95-8.38)	< .001	2.76 (1.58-4.81)	< .001
▪ Early pregnancy (0-13 wks gestation)	3.20 (1.24-8.25)	.02	2.07 (0.78-5.49)	.14
▪ Late pregnancy (14 wks to delivery/loss)	5.54 (2.62-11.69)	< .001	2.82 (1.29-6.15)	.01
▪ Postpartum (delivery to 6 mos or less for losses)	7.80 (3.04-20.02)	< .001	3.97 (1.50-10.51)	.01

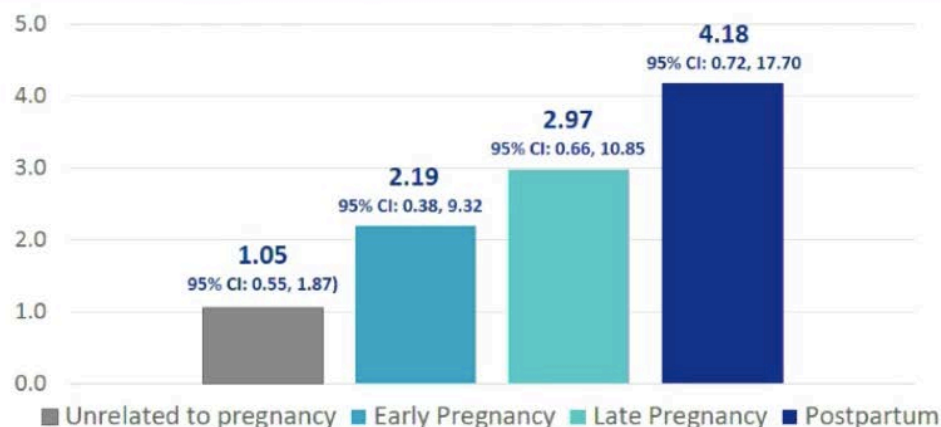
*Adjusted for condom use, reproductive stage. †Adjusted for condom use, reproductive stage, female age, active PrEP use, HIV-1 RNA of male partner.

1. Thomson KA, et al. CROI 2018. Abstract 45.
2. Thomson KA, et al. J Infect Dis. 2018;[Epub ahead of print].

Partners Studies: Increased Risk of Female HIV Acquisition in Late Pregnancy and Postpartum

- Results adjusted for decrease in sexual frequency and condom use as pregnancy progressed
- Increased risk of acquisition per sex act
 - 3-fold increase in late pregnancy
 - 4-fold increase in Post-Partum period.

HIV infectivity per 1,000 sex acts



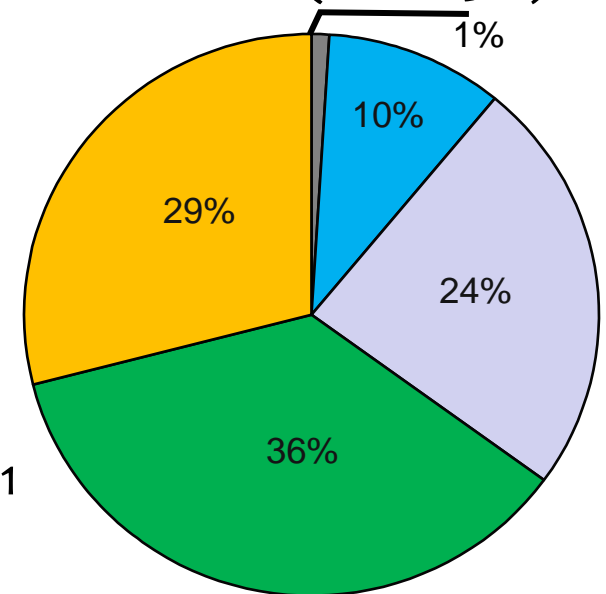
Calculated using a reference case of a 25-year old woman not pregnant, not using PrEP, with a partner with viral load of 10,000 copies/ml

1. Thomson KA, et al. CROI 2018. Abstract 45.
2. Thomson KA, et al. J Infect Dis. 2018;[Epub ahead of print].

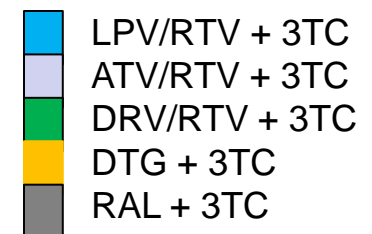
Anti-Retroviral Therapy

Impact of M184V on Virologic Efficacy of Switch to 3TC-Based Dual ART

- Retrospective observational study comparing efficacy of 3TC-based dual ART for pts with/without M184V history in Antiretroviral Resistance Cohort Analysis database (N = 436)
 - Inclusion criteria: HIV RNA \leq 50 copies/mL, switching to dual therapy (3TC + either PI/RTV or INSTI), \geq 1 prior genotype to determine M184V
 - Primary endpoint: time to virologic failure in M184V-positive vs M184V-negative pts
 - **VF**: VL $>$ 50/ml in 2 consecutive or $>$ 200/ml x 1
 - **Blips**: VL 51-199 x 1

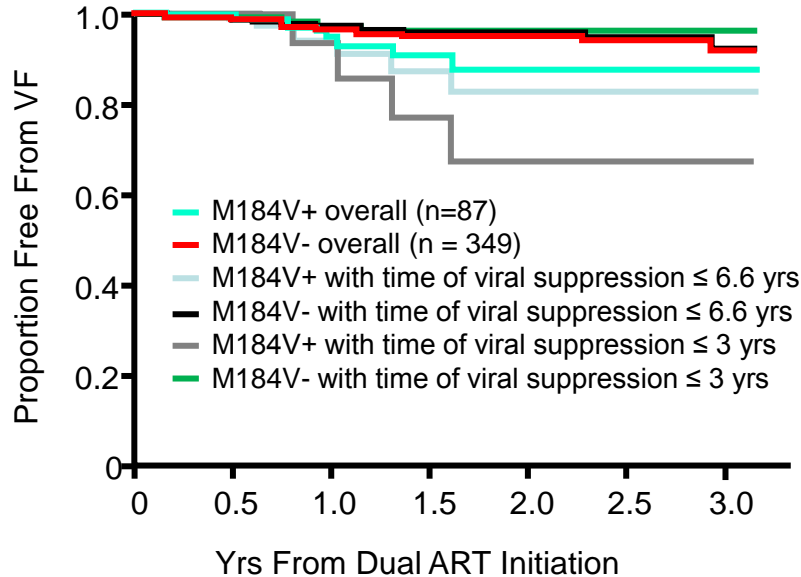


Dual Therapy Initiated



M184V & Switch to 3TC-Based Dual ART: More Blips But No Greater Risk of Virologic Failure

Estimated Probability of Remaining VF-Free on Dual Therapy*†



- No difference in 3-yr probability of remaining free from VF without vs with M184V (91.9% vs 87.8%, $P = .323$)
- Significantly higher 3-yr probability of remaining free from viral blip‡ without vs with M184V (90.1% vs. 79.8% log-rank $P = .016$)
- Multivariate analysis: M184V was only predictor of viral blip
- Longer time of viral suppression reduced risk of VF and viral blip (>6 yrs vs. >3 yrs)

*VF: 2 HIV-1 RNA findings > 50 c/mL or 1 finding \geq 200 c/mL.

†No VF in 21 pts on DTG + 3TC over median f/u of 10 mos.

‡Viral blip: single HIV-1 RNA finding 51-199 c/mL, not confirmed.

Bictegravir/F/TAF studies → DHHS recommendation

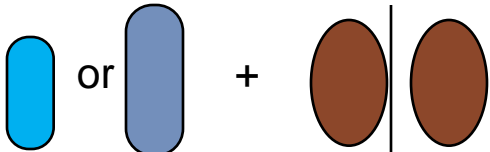
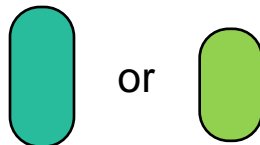
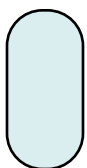
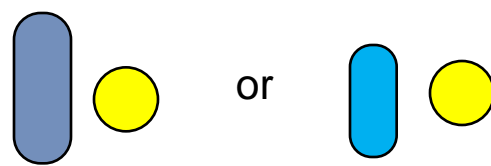

- **Study 380-1844:** Switch From Suppressive DTG/ABC/3TC to BIC/FTC/TAF (N = 563):
 - Non-inferior viral suppression (93.6 vs 95%, P = 0.59)
 - No treatment-emergent resistance in any patient at 48 weeks
 - No change in proteinuria, BMD, lipids, tiny change in GFR (+1.0 vs -1.8 ml/min)
- **Study 380-1961:** Women only; Switch from suppressive E/C/F/TAF (53%), E/C/F/TDF (42%) or ATZ/r+FTC/TDF (5%) to B/F/TAF (N = 470):
 - Open-label, randomized phase III trial; outcome: suppression at wk 48
 - Non-inferior viral suppression (96 vs 95%, P = NS)
 - No treatment-emergent resistance; no D/C for adverse event
- **Previously Presented:**
 - **1489 - Rx naïve:** B/F/TAF vs. ABC/3TC/DTG (N = 629)
 - **1490 - Rx naïve:** B/F/TAF vs. DTG+F/TAF (N = 645)
 - **1878 - Switch:** ABC/3TC or FTC/TDF + ATZ/r or DRV/r (N = 577)

Bictegravir/F/TAF studies → DHHS recommendation

- **3/27/18 - DHHS Statement on Bictegravir:** *“DHHS Classifies a Fixed-Dose Combination Product of Bictegravir/Tenofovir Alafenamide/Emtricitabine as One of the Recommended Initial Regimens for Most People with HIV (A1)”*
 - Not recommended if CrCl < 30 ml/min or severe liver impairment
 - Not approved for persons under 18 yrs
 - Insufficient safety information on use in pregnant women
- **Other Considerations:**
 - DDI’s with Rifamycins, anti-convulsants, and St. John’s Wort
 - Contraindicated with Dofetilide
 - Oral absorption may be reduced with divalent cations (Ca, Fe, Al, Mg)
- Treatment-emergent mutations have not yet been reported
- Bictegravir not yet studied in INSTI failure or INSTI resistance

DHHS Antiretroviral Therapy Guidelines: March 2018

Recommended Regimens for Most Patients

Class	Brand	Therapy	Pill Burden
INSTI-Based	Isentress + Truvada/Descovy	Raltegravir + Tenofovir (DF/AF)/Emtricitabine	
	Stribild/Genvoya	Elvitegravir/Cobicistat/Tenofovir (DF/AF)/Emtricitabine*	
	Triumeq	Dolutegravir/Abacavir/Lamvudine	
	Tivicay + Truvada/Descovy	Dolutegravir + Tenofovir-Emtricitabine OR Abacavir-Lamivudine	
	Biktarvy	Bictegravir/Emtricitabine/TAF	

- * only of eGFR > 70 mL/min

Pharmacokinetics of B/F/TAF (BID) Plus Rifampin

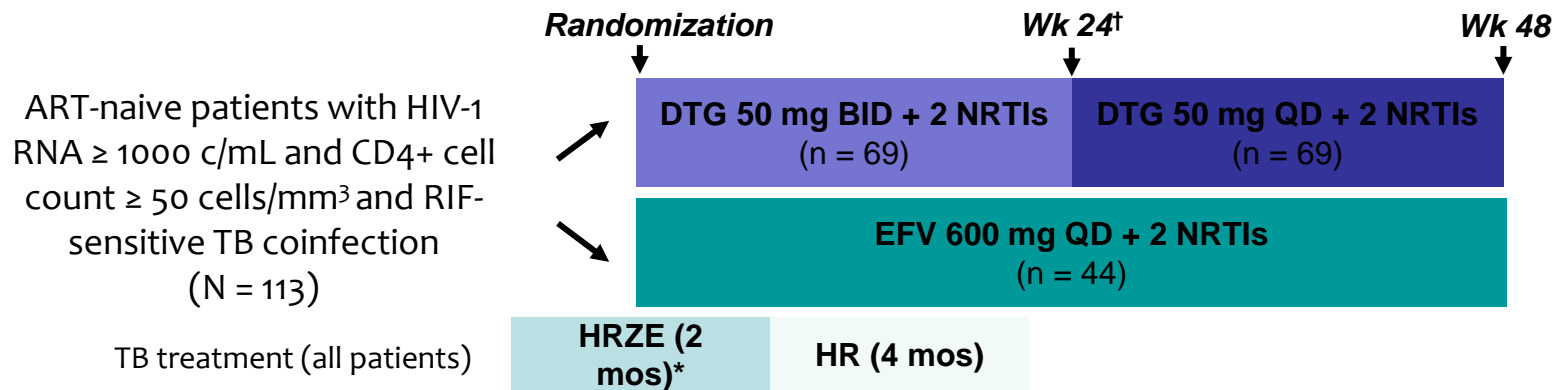
- Open-label, parallel-design, multiple-dose, single-center phase I study in which BIC pharmacokinetics were assessed in healthy volunteers who received BIC/FTC/TAF* QD or BIC/FTC/TAF* BID + RIF 600 mg QD for 28 days (N = 52)

Mean BIC PK (% CV)	Cohort 1 BIC/FTC/TAF QD (n = 26)	Cohort 2 BIC/FTC/TAF BID + RIF QD (n = 26)	GLSM Ratio (90% CI)
AUC ₀₋₂₄ , ng*h/mL	115,200 (21)	45,600 (23)	39.5 (35.7-43.7)
C _{max} , ng/mL	8530 (16)	4560 (19)	53.2 (49.1-57.6)
C _{trough} , ng/mL	3070 (28)	608 (30)	19.7 (17.2-22.7)

- **Coadministration of BIC/FTC/TAF BID + RIF resulted in ~ 80% reduction in BIC C_{trough} and ~ 60% reduction in daily BIC exposure**
- **This combination is not recommended**

INSPIRING: DTG BID + 2 NRTIs For ART-Naive Patients Receiving Rifampin-Based TB Therapy

- Interim analysis of open-label, randomized, noncomparative, active-controlled phase IIIb study
 - RIF decreases plasma DTG concentrations; DTG BID may restore concentrations to those noted for DTG QD in patients not receiving RIF
 - Primary endpoint: Wk 48 HIV-1 RNA < 50 c/mL; patients from South Africa, Brazil, Peru, Mexico, Russia, Argentina, and Thailand



*TB treatment containing RIF could be started up to 8 wks before randomization and no later than screening (28 to 14 days prior to randomization). †DTG dose switch to occur 2 wks after TB treatment completed.

INSPIRING: Efficacy and PK Outcomes

Virologic Outcome at Wk 24, n (%)	DTG + 2 NRTIs (n = 69)	EFV + 2 NRTIs (n = 44)
HIV-1 RNA < 50 copies/mL	56 (81)	39 (89)
HIV-1 RNA ≥ 50 copies/mL	7 (10)	3 (7)
No virologic data	6 (9)	2 (5)

Wk	n	DTG Concentration (Geometric Mean), ng/mL (90% CI, %CV)
DTG 50 mg BID + RIF (TB Treatment Phase)		
8	41	852 (208-2340, 118)
24	22	942 (19-3380, 276)
DTG 50 mg QD (Post-TB Treatment Phase)		
36	16	1143 (80-4370, 151)
48	12	591 (19-3310, 359)

- DTG 50 mg BID with Rifampin showed similar concentrations to DTG 50 mg QD without Rifampin and to previously measured PK in phase 2/3 trials
- DTG 50 BID with Rifampin demonstrated high efficacy rates through wk 24 (81%, 95% CI 72-90%)

HCV Transmission in MSM

I test my HIV+ MSM patients for HCV:

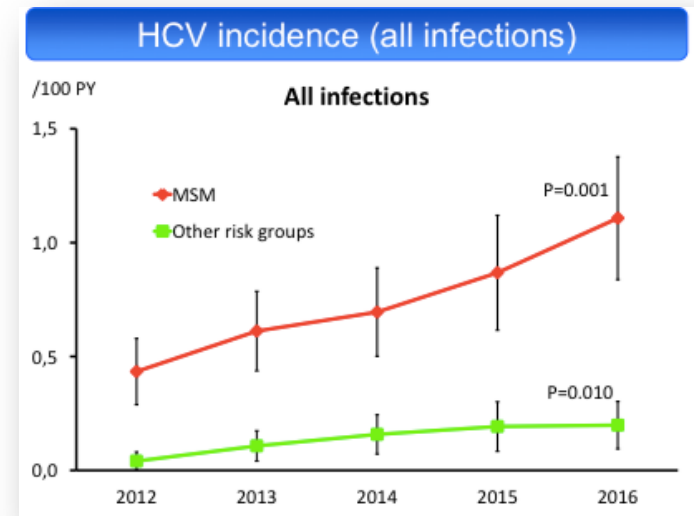
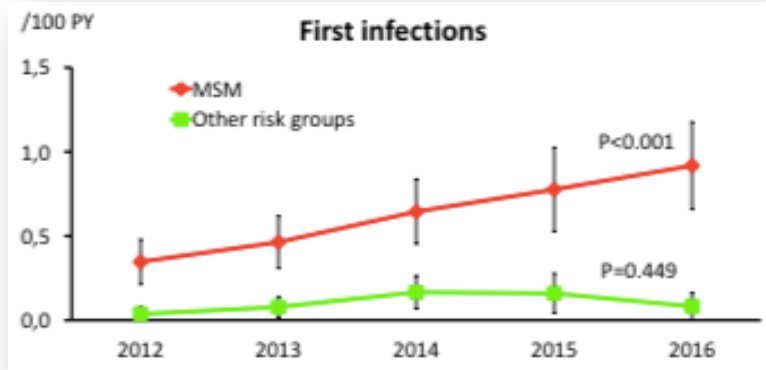
- A. Once on entry into care
- B. Periodically based on risk behaviors (IVDU)
- C. Annually only if IVDU
- D. Annually for all HIV+ patients, regardless of IVDU

Low Rates of HCV Clearance in HIV+ MSM

- **PROBE-C:** Observational European Cohort of Acute HCV in HIV+ patients.
- 2007-2016 465 acute HCV cases
 - 98% male, median age 41
 - 98.9% MSM, 1.1% IDU
 - Median CD4+ count 574 cells/ul, 91% had suppressed HIV
- Spontaneous clearance of HCV only 10%!

PrEP and HCV incidence

- **Cotte, L et al** - Incidence of acute HCV similar between HIV+ MSM and HIV- MSM on PrEP (1.03/100 p-y vs. 1.24/100 p-y)
- **Cotte, L et al** - Dat'AIDS cohort of French HIV+ MSM showing steady increases in HCV incidence



- **Mikati, T et al** - NYC cohorts of PEP (N = 758) and PrEP recipients (N = 381) showed low Prevalence of HCV infection (0.4% and 0% respectively)

HCV Re-infection in GECCO Cohort

- Real-world DAA Rx derived from 9 German centers
- N = 2,074, started 2/2014
- 41 reinfections over 2,239 p-y of follow-up (1.97%)

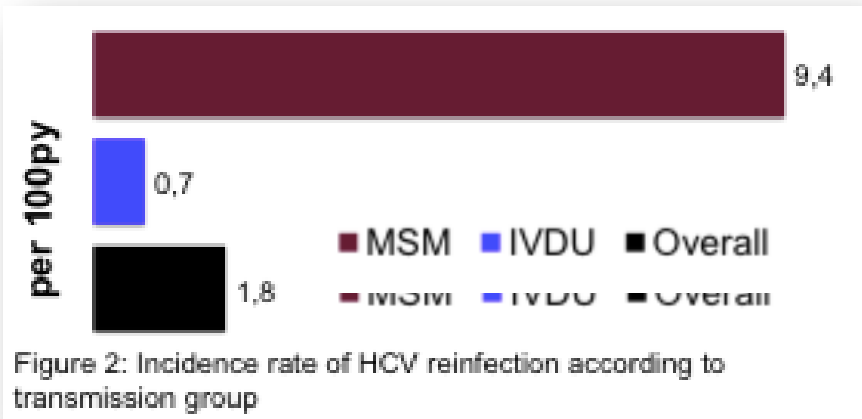


Figure 2: Incidence rate of HCV reinfection according to transmission group

Median Age [years (SD)]	51 (+/-11.3)
Male [n (%)]	1346 (65)
Mode of HCV transmission	
- IVDU [n (%)]	764 (37)
- MSM [n (%)]	256 (12)
- Other [n (%)]	1054 (61)
HIV coinfection [n (%)]	482 (23)
HCV genotype	
- GT 1 [n (%)]	1,3664 (66)
- GT 2 [n (%)]	83 (4)
- GT 3 [n (%)]	491 (24)
- GT 4 [n (%)]	129 (6)

	Reinfection, n=41
Median Age [years (SD)]	47 (+/-8.5)
Male [n (%)]	41 (100)
Mode of HCV transmission	
- IVDU [n (%)]	5 (12)
- MSM [n (%)]	26 (63)
- MSM + IVDU [n (%)]	10 (24)
HIV coinfection [n (%)]	34 (83)
Median time to reinfection [weeks (IQR)]	63 (16-180)

Table 2: Characteristics at reinfection

Recent Updates/Warnings

When starting women of childbearing age on ART, I typically:

- A. Stick with one or two 'go to' regimens
- B. Have deep discussions re: plans for childbearing and if answer is 'No' I ensure patient is on contraception before prescribing ART
- C. Look up regimens in the DHHS Perinatal Guidelines
- D. Don't know what to choose!

Dolutegravir In Pregnancy

The screenshot shows the AIDSinfo website interface. At the top, it says "U.S. Department of Health and Human Services" and "Contact Us | En Español". The AIDSinfo logo is on the left. A navigation bar includes "Home", "Guidelines", "Understanding HIV/AIDS", "Drugs", "Clinical Trials", and "Apps". A search bar is on the right. A white notification pop-up is centered on the screen with the title "Recommendations Regarding Dolutegravir" and a close button (X). The pop-up text reads: "On Wednesday, May 30, 2018 the HHS Antiretroviral Guideline Panels issued these recommendations regarding the use of dolutegravir in adults and adolescents with HIV who are pregnant or of child-bearing potential." Below the text is a green "OK" button. In the background, the website content is partially visible, including a sidebar with "Guideline Adolesce" and a main content area with a heading "Dolutegravir" and a paragraph: "Recommendations Regarding Use of Dolutegravir in Adults and Adolescents with HIV who are Pregnant or Of Child Bearing Potential, a joint statement from the HHS Antiretroviral Guideline Panels, was released on May 30, 2018." Below this, there is a section for "Bictegravir" with a bullet point: "On Tuesday, March 27, 2018 the Panel issued this statement on bictegravir." and a section for "People-First Language".

Dolutegravir In Pregnancy

Home

Guidelines

Understanding HIV/AIDS

Drugs

Clinical Trials

Apps

HIV/AIDS News

Home > HIV/AIDS News > Recommendations Regarding the Use of Dolutegravir in Adults and Adolescents with HIV who are Pregnant or of Child-Bearing Potential

Recommendations Regarding the Use of Dolutegravir in Adults and Adolescents with HIV who are Pregnant or of Child-Bearing Potential

Date: May 30, 2018

Source: *AIDSinfo*

A National Institutes of Health (NIH)-funded observational surveillance study of birth outcomes among pregnant women on antiretroviral therapy (ART) in Botswana identified neural tube defects (NTDs) in four infants born to 426 women **who initiated a dolutegravir (DTG)-based regimen prior to pregnancy, and who were still receiving it at the time of conception.**¹ This study is ongoing, and more data from approximately 600 additional births among pregnant women who have been using a DTG-based regimen from conception are expected in the next 9 months. Importantly, the same study presented data on women who **initiated ART during the first trimester of pregnancy**, and no NTDs were identified in the infants of the 116 women who initiated a DTG-based regimen in the first trimester or in 396 women who initiated an efavirenz (EFV)-based regimen.² In the upcoming months, data from this study and other investigations will provide more information about the safety of DTG for infants exposed *in utero*.

The Department of Health and Human Services (HHS) Antiretroviral Guidelines Panels* are issuing these recommendations to elaborate on our previous statement of May 18, 2018³ and to support the related Food and Drug Administration (FDA) Drug Safety Communication.⁴

For treatment of adults and adolescents with HIV who are pregnant or of child-bearing potential, we recommend the following:

- For individuals not known to be pregnant, documentation of a negative pregnancy test is recommended prior to initiating DTG.
- Those who are currently receiving DTG as a component of their ART or who wish to be started on DTG should be counseled about the potential risk of NTDs when DTG is taken near the time of conception. NTDs occur within the first 28 days after conception or 6 weeks from the last menstrual period.
- Those who are pregnant, taking DTG, and within 8 weeks from last menstrual period should discuss the risks and benefits of their current regimens with their health care providers. If there are other good options to replace DTG, then switching to a non-DTG ART regimen is recommended (see Table 2).
- Those who are pregnant and 8 weeks or greater from last menstrual period may initiate or continue DTG-based regimens. Discontinuing DTG-based regimens is unlikely to confer any benefits after the neural tube has formed, and medication changes during pregnancy could increase the risk of viremia and transmission of HIV to the infant.

Dolutegravir In Pregnancy - the Data

- NIH-funded observational study of birth outcomes in woman receiving ART in Botswana
- Initial report IAS 2017 (Paris, FR)
 - In Women initiating ART in 1st trimester, Neural Tube defects (NTD's) seen in:
 - 0/116 women on DTG-based regimen
 - 0/396 women on EFV-based regimen
- Recent data:
 - Women on ART prior to pregnancy
 - 4/426 women on DTG-based regimen had children with NTD's
- Ongoing data on 600 women on DTG in next 9 mos.

Zash, R. Jacobson D., et. al. DTG/TDF/FTC started in pregnancy is as safe as EFV/TDF/FTC in nationwide birth outcomes surveillance in Botswana. 9th IAS 2017 Paris, France

www.aidsinfo.nih.gov

Dolutegravir In Pregnancy - Recs

- **5/30/18 DHHS Recommendations:**
 - Negative Pregnancy test prior to DTG initiation
 - OK to use if can ensure reliable contraception
 - If on DTG, counsel on risk of Neural Tube Defect
 - If pregnant and on DTG within 8 wks of LMP, switch:
 - RAL, DRV/r (BID), ATZ/r, EFV, RPV
 - If pregnant and on DTG after 8 wks of LMP, may continue
 - Strongly encouraged to use Antiretroviral Pregnancy Registry (www.apregistry.com)

Zash, R. Jacobson D., et. al. DTG/TDF/FTC started in pregnancy is as safe as EFV/TDF/FTC in nationwide birth outcomes surveillance in Botswana. 9th IAS 2017 Paris, France

www.aidsinfo.nih.gov

Dolutegravir in Pregnancy

I acknowledge that it is difficult to walk the fine line between transparency and sharing timely information about new studies, and the concern about provoking anxiety amongst patients who may already struggle with adherence. I am trying to approach my patient discussions with an overall non-alarming framing that this is just 1 study that is ongoing, in a study population and setting that may not have generalizable results to our setting and population, and keeping in mind that prior studies and systematic reviews have not found adverse effects of Dolutegravir in pregnancy. Hopefully as this study is ongoing, more light will be shed in the coming months regarding this issue

Monica Hahn - UCSF Women's Primary Care Practice

In my clinic, women with HIV who become pregnant:

- A. Are transferred to the local Academic Medical Center for 'High Risk OB' care
- B. Stay in my care and are co-managed by me and a trusted OB-GYN provider familiar with HIV
- C. Continue comprehensive care with me (or a colleague within my organization)
- D. Not sure, have not had one yet!

Prezcobix in Pregnancy

- 6/4/18 FDA updated Prezcobix label stating that it is not recommended for use in pregnant women due to lower exposures of DRV and cobinavir in pregnancy

Package Insert

- Pregnancy: PREZCOBIX is not recommended in pregnant women due to substantially lower exposures of darunavir and cobicistat during pregnancy. (8.1, 12.3)
- The exposure to total and unbound darunavir boosted with cobicistat after intake of PREZCOBIX as part of an antiretroviral regimen was substantially lower during the second and third trimesters of pregnancy compared with 6-12 weeks postpartum (see Table 3 and Figure 1).

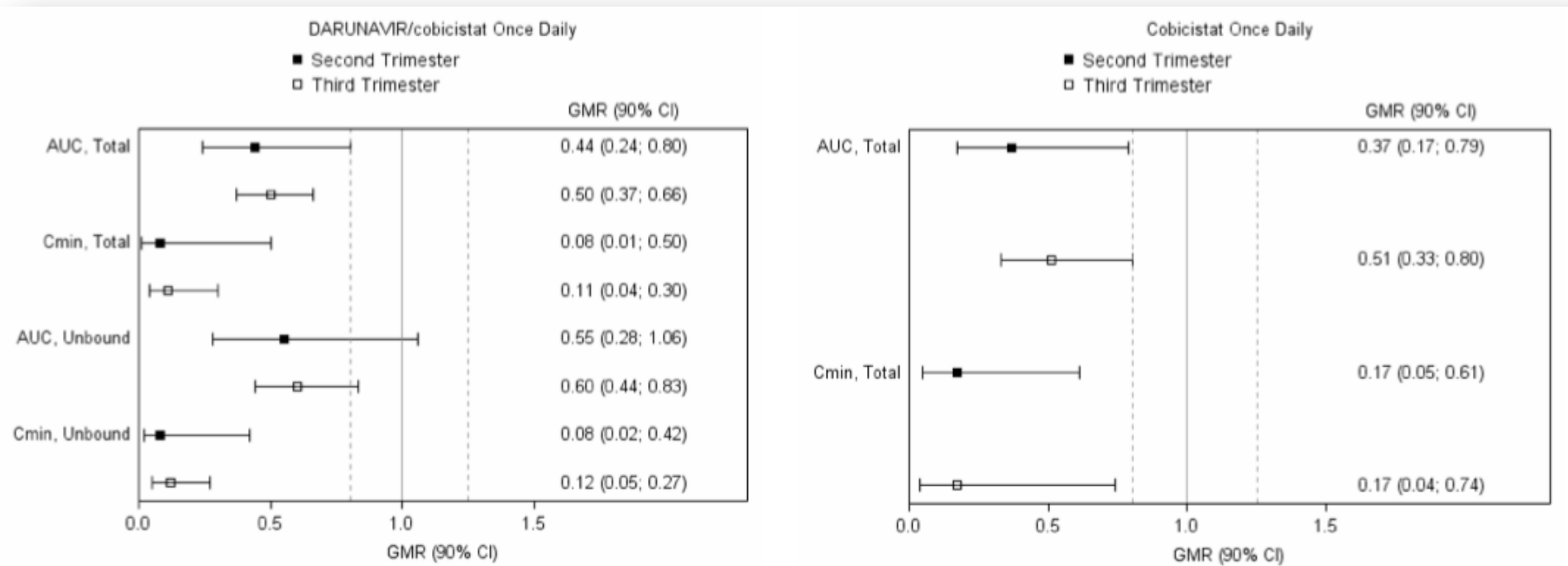
Table 3: Pharmacokinetic Results of Total Darunavir after Administration of PREZCOBIX Once Daily as Part of an Antiretroviral Regimen, During the 2nd Trimester of Pregnancy, the 3rd Trimester of Pregnancy, and Postpartum

Pharmacokinetics of total darunavir (mean ± SD)	2 nd Trimester of pregnancy N=7	3 rd Trimester of pregnancy N=6	Postpartum (6-12 weeks) N=6
C _{max} , ng/mL	4340 ± 1616	4910 ± 970	7918 ± 2199
AUC _{24h} , ng.h/mL	47293 ± 19058	47991 ± 9879	99613 ± 34862
C _{min} , ng/mL	168 ± 149	184 ± 99	1538 ± 1344

- Prezcobix Package insert

Prezcobix in Pregnancy

- Figure 1: Pharmacokinetic Results (Within-Subject Comparison) of Total and Unbound Darunavir and Total Cobicistat After Administration of PREZCOBIX at 800/150 mg Once Daily as Part of an Antiretroviral Regimen, During the 2nd and 3rd Trimester of Pregnancy Compared to Postpartum



- Prezcobix Package insert



More Info

- **HIVLN - August 9 - Monica Hahn - “HIV and Safer Conception”**
- World Health Organization (WHO):
http://www.who.int/medicines/publications/drugalerts/Statement_on_DTG_18May_2018final.pdf?ua=1
- Prezcofix Package Insert: <http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/PREZCOBIX-pi.pdf>
- www.aidsinfo.nih.gov - Perinatal Guidelines
- National Clinical Consultation Center
 - Perinatal HIV/AIDS Hotline: (888) 448-8765

Summary

- Increased HIV acquisition observed in 3rd trimester and after birth
- ART options continue to evolve with new INSTI's and combinations (2-drugs)
- Sexual transmission of HCV is occurring
- Two recent antiretroviral warnings