BREACH
BELGIAN RESEARCH AIDS&HIV CONSORTIUM

Pregnancy and HIV : what's new?

Breach Symposium, November 30th 2021

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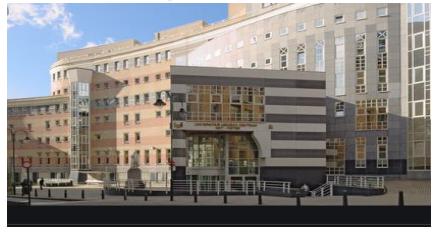

Infectious Diseases Department
and
AIDS Reference Centre

ULB UNIVERSITÉ LIBRE DE BRUXELLES

World Health Organization

- 1,3 million WLWH become pregnant each year (WHO 2020)

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Version 11.0
October 2021

English

Treatment of Pregnant Women Living with HIV or Women Considering Pregnancy

Scenarios for pregnant women or women who wish to conceive

1. Women planning to be pregnant or becoming pregnant while already on ART	- Maintain ART: The main goal of ART during pregnancy is maintaining treatment efficacy, both for the women's benefit and HIV transmission risk. - ART may be switched temporarily for the duration of pregnancy to the preferred combinations recommended for ART naïve pregnant women, see table 1 - The decision on switching ART should be individualized taking into account the person's history of treatment, adherence and tolerability, and weighed against potential risk coming from ART exposure or suboptimal pharmacokinetics in pregnancy - If the purpose for switching is insufficient data about safety and efficacy in pregnancy, it should be explained to the pregnant woman and her decision/ willingness to switch current regimen taken into account: • Lower serum concentration was observed in persons on therapies boosted with COBI, DRV/r qd and RPV • There is insufficient data in pregnancy for BIC, EVG, DOR, RAL qd, and dual regimens - Pregnant women should be monitored monthly or bimonthly (depending on adherence and length of virological suppression) and as close as possible to the predicted delivery date. HIV-VL should be tested every two months of pregnancy and including 36 weeks of gestation
2. Women becoming pregnant while treatment-naïve	Starting ART as soon as possible is highly recommended, see table 1
3. Women whose follow-up starts late in the second or in the third trimester	Start ART immediately (see table 1) and consider RAL or DTG as the preferred choice to obtain rapid HIV-VL decline and to ensure the HIV-VL is undetectable by the time of delivery
4. Women whose HIV-VL is not undetectable at third trimester	Perform resistance testing and consider changing to or adding INSTI (RAL or DTG) if not on this class to obtain rapid HIV-VL decline
5. Women whose HIV-VL is > 50 copies/mL at week 34-36 of pregnancy	Elective cesarean section to be planned at week 38, see labour and breastfeeding
6. Women diagnosed with HIV in labour	See labour and breastfeeding
7. Labour	**1) Women whose HIV-VL is > 50 copies/mL at week 34-36:** • Elective cesarean section to be planned at week 38 • iv ZDV: During labour and delivery: 2 mg/kg loading dose followed by continuous iv infusion of 1 mg/kg/hour until delivery - Scheduled cesarean delivery: start iv ZDV 3 hours before surgery - Unscheduled cesarean delivery: consider administering loading dose then proceed to delivery **2) Women diagnosed with HIV during labour:** • If possible, perform caesarean section • iv ZDV: During labour and delivery: 2 mg/kg loading dose followed by continuous iv infusion of 1 mg/kg/hour until delivery. Consider administering loading dose then proceed to delivery PEP should be given to all newborns born to mothers living with HIV according to local guidelines. For antiretroviral therapy in children with HIV, See page 140
8. Breastfeeding	• The topic of feeding intentions should be discussed with a pregnant woman as early as possible in pregnancy, together with providing education and support to the mother • **We advise against breastfeeding**, as in high-income settings the optimal

Tsempano update (World AIDS 2020)
A small non significant increase in neural tube defect for women taking DTG around conception
0.19% (95% CI 0.09 to 0.4) vs 0.11% (95% CI 0.07 to 0.17) with other ART.

RAL 400 mg bid
RAL 1200 mg QD
Pharmacokinetics is currently under investigation in the PANNA study
Prospective data: no neural tube defet among 456 women with periconception intake

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Table 1. Antiretroviral regimen for ART-naïve pregnant women

ART-naïve pregnant women should initiate treatment as soon as possible. The decision of ART regimen should be discussed with the person and individualized taking into account tolerability, possible adherence issues, as well weighed against potential risk coming from ART exposure or suboptimal pharmacokinetics in pregnancy.

Pregnant women starting ART should be monitored monthly or bimonthly (depending on adherence and length of virological suppression) and as close as possible to the predicted delivery date. HIV-VL should be tested every two months of pregnancy and including 36 weeks of gestation

Regimen	Main requirements	Additional guidance (see footnotes)
Recommended regimens		
2 NRTIs + INSTI (PREFERRED)		
ABC/3TC + DTG or ABC/3TC/DTG	DTG to be discussed with women considering to become pregnant or if to be used in first 6 weeks of pregnancy HLA-B*57:01 negative HBsAg negative	I (ABC: HLA-B*57:01, may delay starting ART) II (DTG: neural tube defects risk during periconception)
TDF/XTC or TAF/FTC + DTG	DTG to be discussed with women considering to become pregnant or if to be used in first 6 weeks of pregnancy. TAF/FTC not recommended in first 14 weeks of pregnancy	II (DTG: neural tube defects risk during periconception) III (Tenofovir salts) IV (TAF & pregnancy)
TDF/XTC or TAF/FTC + RAL 400 mg bid	TAF/FTC not recommended in first 14 weeks of pregnancy	III (Tenofovir salts) IV (TAF & pregnancy) V (RAL in pregnancy, bid dosing)
2 NRTIs + PI/r		
TDF/XTC or TAF/FTC + DRV/r 600 mg/100 mg bid	With food TAF/FTC not recommended in first 14 weeks of pregnancy	III (Tenofovir salts) IV (TAF & pregnancy) VI (DRV dosing) VII (COBI boosting)
Alternative regimens		
2 NRTIs + INSTI		
ABC/3TC + RAL 400 mg bid	HBsAg negative HLA-B*57:01 negative	I (ABC: HLA-B*57:01, may delay starting ART) V (RAL in pregnancy, bid dosing)
2 NRTIs + NNRTI		
ABC/3TC + EFV	HLA-B*57:01 negative HBsAg negative HIV-VL < 100,000 copies/mL At bedtime or 2 hours before dinner	I (ABC: HLA-B*57:01, may delay starting ART) VIII (EFV HIV-2 & group O)
TDF/XTC or TAF/FTC + EFV or TDF/FTC/EFV	At bedtime or 2 hours before dinner TAF/FTC not recommended in first 14 weeks of pregnancy	III (Tenofovir salts) IV (TAF & pregnancy) VIII (EFV HIV-2 & group O)
TDF/XTC or TAF/FTC + RPV or TDF/FTC/RPV or TAF/FTC/RPV	CD4 count > 200 cells/µL HIV-VL < 100,000 copies/mL Not on gastric pH increasing agents With food TAF/FTC not recommended in first 14 weeks of pregnancy	II (Tenofovir salts) IV (TAF & pregnancy) IX (RPV exposure during 2nd and 3rd trimester, HIV-2) X (Interactions)
2 NRTIs + PI/r		
ABC/3TC + DRV/r 600 mg/100 mg bid	HLA-B*57:01 negative HBsAg negative With food	I (ABC: HLA-B*57:01, may delay starting ART) VI (DRV dosing) VII (COBI boosting)

Additional guidance

I ABC contraindicated if HLA-B*57:01 positive. Even if HLA-B*57:01 negative, counselling on HSR risk still mandatory. If testing for HLA-B*57:01 results in delay of ART initiation, consider other recommended backbone

TAF instead of TDF has been studied in RCT in pregnant women starting from 14-28 weeks (IMPAACT2010/VESTED study)

DRV/r 600 mg bid

Dolutegravir versus efavirenz in women starting HIV therapy in late pregnancy (DolPHIN-2): an open-label, randomised controlled trial

Kenneth Kintu, Thokozile R Malaba, Jesca Nakibuka, Christiana Papamichael, Angela Colbers, Kelly Byrne, Kay Seden, Eva Maria Hodel, Tao Chen, Adelline Twimukye, Josaphat Byamugisha, Helen Reynolds, Victoria Watson, David Burger, Duolao Wang, Catriona Waitt, Miriam Taegtmeyer, Catherine Orrell, Mohammed Lamorde, Landon Myer, Saye Khoo, for the DolPHIN-2 Study Group

55 days

- Uganda and South Africa
- RCT open labelled
- 268 pregnant woman
- Start DTG vs EFV after 28 weeks of pregnancy

- In non pregnant adults

time to CV <50 cp/ml

  - DTG 28 days
  - EFV 84 days

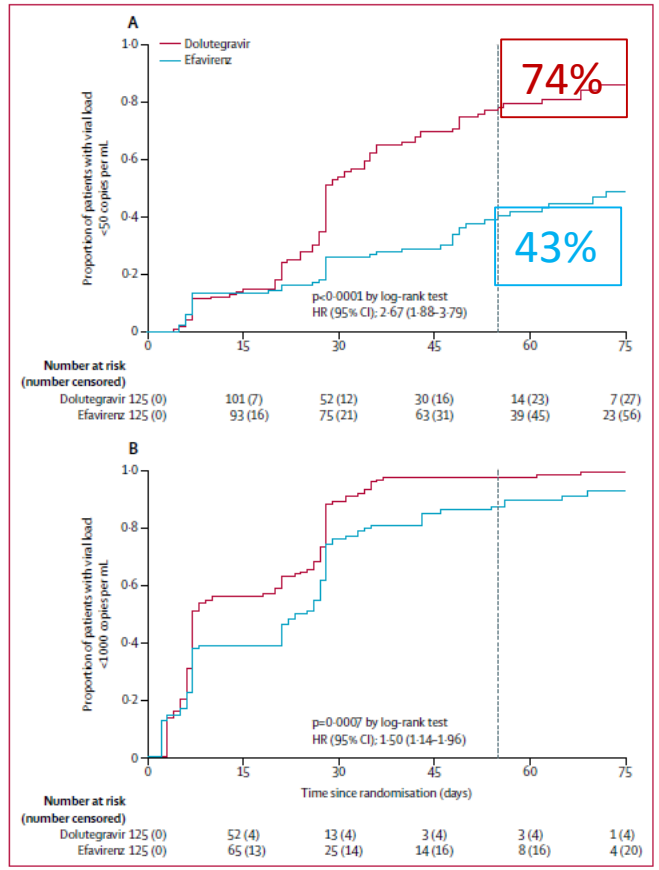


Figure 2: **Proportion of patients with viral load <50 copies per mL and <1000 copies per mL following randomisation**
Kaplan-Meier plots of time from randomisation to an HIV viral load of (A) <50 copies per mL and (B) <1000 copies per mL. The dashed vertical line in each plot represents the median time from randomisation to giving birth (55 days) in all patients.

April 2021

Efficacy and safety of dolutegravir with emtricitabine and tenofovir alafenamide fumarate or tenofovir disoproxil fumarate, and efavirenz, emtricitabine, and tenofovir disoproxil fumarate HIV antiretroviral therapy regimens started in pregnancy (IMPAACT 2010/VESTED): a multicentre, open-label, randomised, controlled, phase 3 trial

Shahin Lockman, Sean S Brummel*, Lauren Ziemba, Lynda Stranix-Chibanda, Katie McCarthy, Anne Coletti, Patrick Jean-Philippe, Ben Johnston, Chelsea Krotje, Lee Fairlie, Risa M Hoffman, Paul E Sax, Sikhulile Moyo, Nahida Chakhtoura, Jeffrey SA Stringer, Gaerolwe Masheto, Violet Korutaro, Haseena Cassim, Blandina T Mmbaga, Esau João, Sherika Hanley, Lynette Purdue, Lewis B Holmes, Jeremiah D Momper, Roger L Shapiro, Navdeep K Thoofer, James F Rooney, Lisa M Frenkel, K Rivet Amico, Lameck Chinula†, Judith Currier†, on behalf of the IMPAACT 2010/VESTED Study Team and Investigators‡*

- Multicentric (Botswana, South Africa, Tanzania, Uganda, Zimbabwe, (87%); Brazil (9%); Thailand, India (4%) and USA (1%))
- Open label, RCT phase 3 trial
- Virological efficacy and safety of 3 ART regimens

TDF/FTC **DTG**
TAF/ FTC **DTG**
TDF/ FTC **EFV**

- Inclusion: Pregnant (W**14-28** at inclusion) WLWH ART naïve (exception: previous PEP or treatment only in previous pregnancy accepted or already treatd for less than 14 days)

Dolutegravir containing regimens **met the superiority criteria**

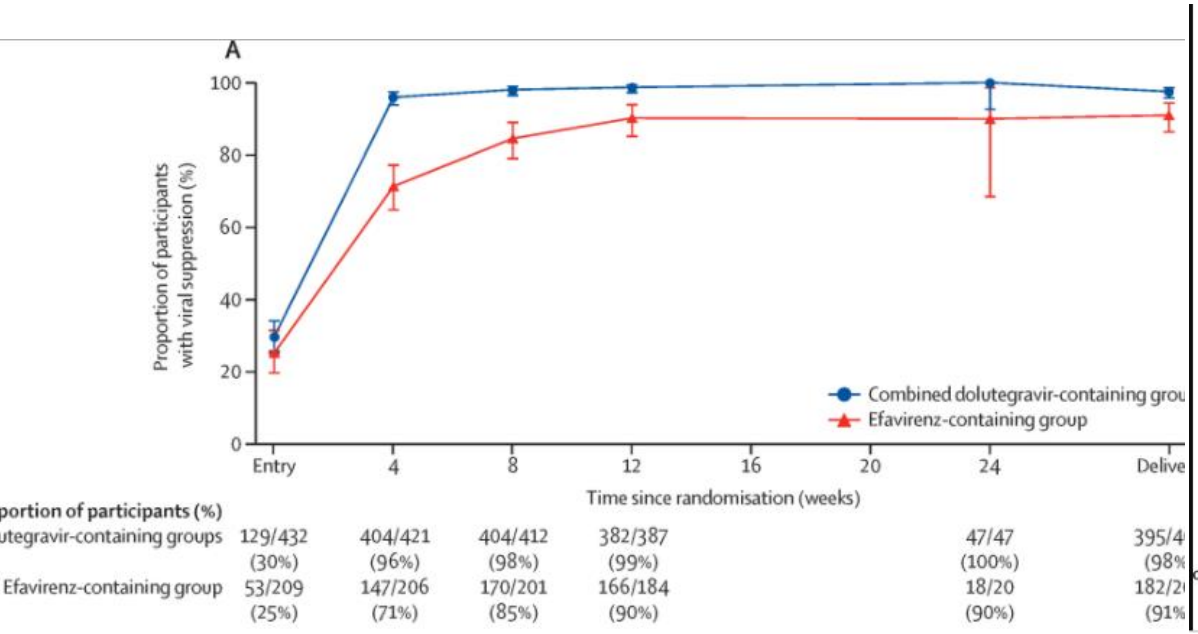
<200 cp/ml at delivery: **98%** vs **91%** EFV regimen

(estimated difference 6,5 (95%CI:2-10,7),p=0,0052)

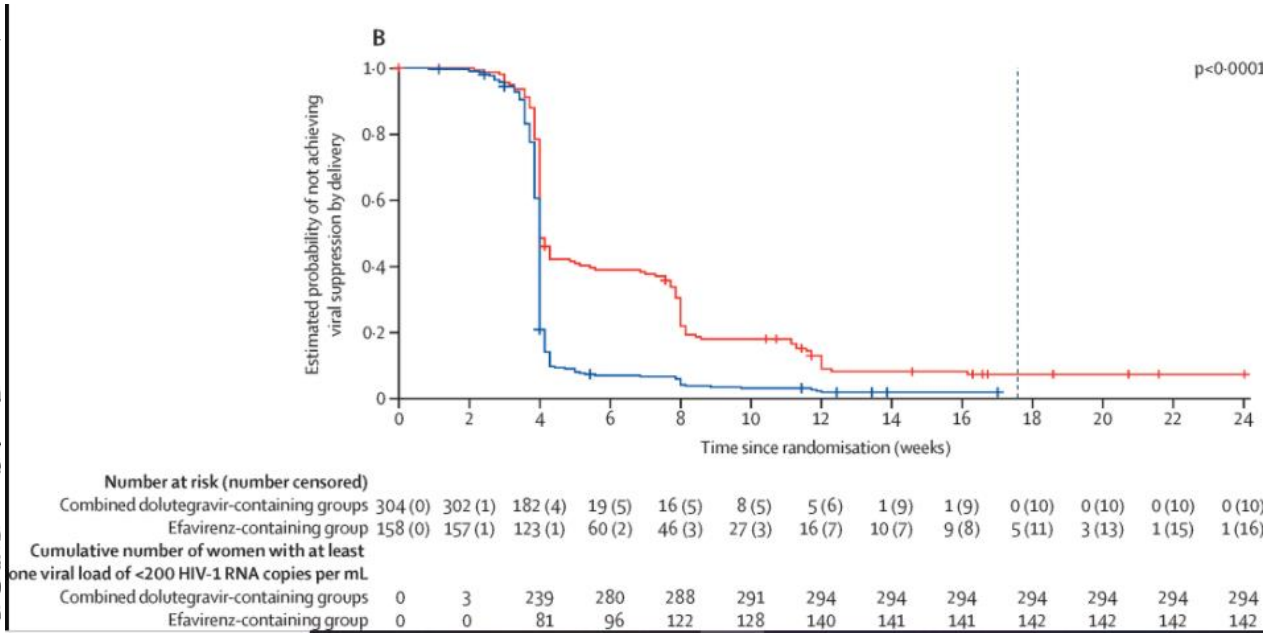
<50 cp/ml at delivery: **95%** vs **80%** EFV regimen

(estimated difference 15,5 (95%CI:9,5-24),p<0,0001)

Shorter time to viral suppression



portion of participants (%)							
utegravir-containing groups	129/432 (30%)	404/421 (96%)	404/412 (98%)	382/387 (99%)	47/47 (100%)	395/4 (98%
Efavirenz-containing group	53/209 (25%)	147/206 (71%)	170/201 (85%)	166/184 (90%)	18/20 (90%)	182/2 (91%



Number at risk (number censored)													
Combined dolutegravir-containing groups	304 (0)	302 (1)	182 (4)	19 (5)	16 (5)	8 (5)	5 (6)	1 (9)	1 (9)	0 (10)	0 (10)	0 (10)	0 (10)
Efavirenz-containing group	158 (0)	157 (1)	123 (1)	60 (2)	46 (3)	27 (3)	16 (7)	10 (7)	9 (8)	5 (11)	3 (13)	1 (15)	1 (16)
Cumulative number of women with at least one viral load of <200 HIV-1 RNA copies per mL													
Combined dolutegravir-containing groups	0	3	239	280	288	291	294	294	294	294	294	294	294
Efavirenz-containing group	0	0	81	96	122	128	140	141	141	142	142	142	142

The IMPAACT trial

Lockman S et al. The Lancet. April 2021

Composite adverse pregnancy outcome

- Spontaneous abortion <20 weeks
- Stillbirth ≥ 20 weeks
- Preterm <37 sem
- Small gestational age (<10th percentile)

?

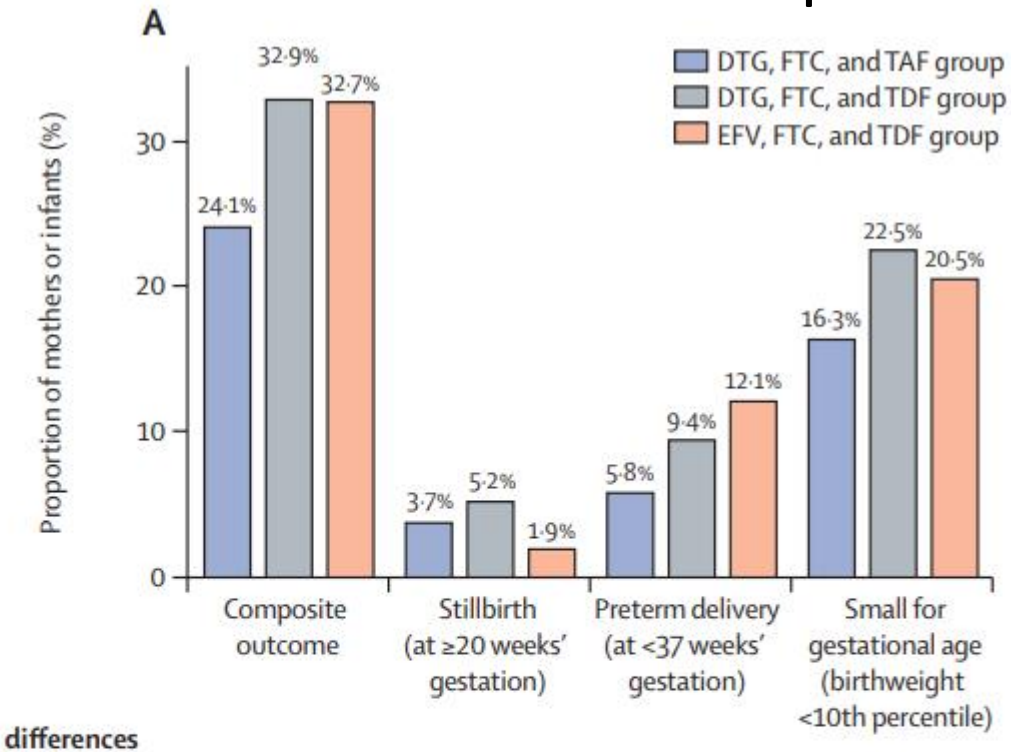
-Linked with weight gain that was the higher with TAF at T2 and T3 but still less than the expected WG 0,42 kg/week

Inadequate weight gain in pregnancy is associated with preterm birth and small gestational age

The IMPAACT trial

Lockman S et al. The Lancet. April 2021

Lockman S et al. The Lancet. April 2021



Group differences (95% CI)				
DTG, FTC, and TAF group *vs* DTG, FTC, and TDF group	−8·8% (−17·3% to −0·3%)	−1·5% (−5·4% to 2·4%)	−3·6% (−8·8% to 1·5%)	−6·2% (−13·9% to 1·5%)
DTG, FTC, and TDF group *vs* EFV, FTC, and TDF group	0·2% (−8·8% to 9·1%)	3·3% (−0·2% to 6·8%)	−2·7% (−8·7% to 3·3%)	2·0% (−6·0% to 10·0%)
DTG, FTC, and TAF group *vs* EFV, FTC, and TDF group	−8·6% (−17·1% to −0·1%)	1·8% (−1·3% to 4·9%)	−6·3% (−11·8% to −0·9%)	−4·2% (−11·7% to 3·4%)

C

The IMPACT STUDY

Lockman S et al. The Lancet. April 2021

- Similar rate of AE event between regimens
- Higher rate of infant death in EFV based regimen

Dolutegravir compared to EFV

Higher and more rapid virological efficacy

Better tolerability

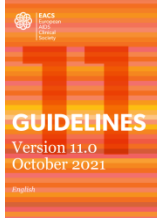
Previously acquired EFV resistance? 9-20% in SSAfrica

	Dolutegravir, emtricitabine, and tenofovir alafenamide fumarate group (n=208)	Dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group (n=202)	Efavirenz, emtricitabine, and tenofovir disoproxil fumarate group (n=207)
Grade 3 or higher adverse events			
Any	29 (14%)	33 (16%)	43 (21%)
Infection	3 (1%)	10 (5%)	9 (4%)
Nervous system disorder*	3 (1%)	0	7 (3%)
Respiratory tract disorder	11 (5%)	6 (3%)	10 (5%)
Hypoglycaemia	4 (2%)	4 (2%)	4 (2%)
Elevated creatinine	2 (1%)	5 (3%)	4 (2%)
Elevated bilirubin	1 (<1%)	1 (<1%)	0
Other infant outcomes			
Median gestational age at birth, weeks	39·7 (38·6–40·7)	39·9 (38·7–40·7)	39·6 (38·4–40·4)
Median birthweight, g	3160 (2850–3500)	3065 (2800–3440)	3000 (2705–3325)
Low birthweight (<2500 g)	13 (6%)	19 (10%)	24 (12%)
Very low birthweight (<1500 g)	0	1 (1%)	2 (1%)
Birthweight >4 kg	8 (4%)	3 (2%)	4 (2%)
Died by age 28 days†	2 (1%)	3 (2%)	10 (5%)
Born <37 weeks	1/2 (50%)	0	3/10 (30%)
Small for gestational age	2/2 (100%)	2/3 (67%)	3/10 (30%)
Mean creatinine clearance at birth mL/min‡	52·5 (30·9)	53·3 (68·8)	49·6 (26·1)
Mean creatinine concentrations at birth, mg/dL	0·62 (1·72)	0·56 (0·31)	0·50 (0·24)

Data are n (%), median (IQR), mean (SD), or n/N (%). Some infants might have had more than one grade 3 or higher adverse event. Additional safety outcome measures from birth to age 28 days are provided in the appendix (p 25). *Two infants had hypoxic-ischaemic encephalopathy and one had a seizure in the dolutegravir, emtricitabine, and tenofovir alafenamide fumarate group; and one infant had bulging fontanelle, one had hydrocephalus and intraventricular haemorrhage, and five had hypoxic-ischaemic encephalopathy in the efavirenz, emtricitabine, and tenofovir disoproxil fumarate group. †Causes of death in the dolutegravir, emtricitabine, and tenofovir alafenamide fumarate group were hypoxic-ischaemic encephalopathy (n=1) and birth asphyxia (n=1); in the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group were birth asphyxia (n=1), probable pneumonia (n=1), and unknown (n=1); and in the efavirenz, emtricitabine, and tenofovir disoproxil fumarate group were hypoxic-ischaemic encephalopathy (n=3), severe prematurity (n=1), neonatal sepsis (n=3), neonatal respiratory distress syndrome (n=1), fetal distress due to prolonged labour (n=1), and unknown (n=1). ‡Calculated by the Schwartz formula.

Table 4: **Infant outcomes and grade 3 or higher adverse events from birth to age 28 days**

EACS guidelines



Women planning to be pregnant

- If ART regimen is temporarily switched because of planned pregnancy

decision should be DISCUSSED and INDIVIDUALISED to each woman according to

  - preference, tolerability, compliance and adherence issues
  - Potential subexposure due to pharmacokinetics

Risk of lower exposure if

- COBICISTAT
- DRV/r QD
- RPV

Insufficient data in pregnancy for

- Elvitegravir
- Biktegravir
- Doravirine
- RAL qd regimens
- Dual regimen

WLWH becoming pregnant on a stable regimen with HIVRNA < 50 cp/ml

Open Forum Infectious Diseases

MAJOR ARTICLE

2019

A Multicenter Analysis of Elvitegravir Use During Pregnancy on HIV Viral Suppression and Perinatal Outcomes

Martina L. Badell,[1] Anandi N. Sheth,[2] Florence Momplaisir,[3] Lisa Rahangdale,[4] JoNell Potter,[5] Padmashree C. Woodham,[6] Gweneth B. Lazenby,[7] William R. Short,[8] Scott E. Gillespie,[9] Nevert Baldreldin,[10] Emily S. Miller,[10] Gregg Alleyne,[11] Lunthita M. Duthely,[5] Stephanie M. Allen,[12] Judy Levison,[12] and Rana Chakraborty[13] on behalf of the HOPES (HIV and OB Pregnancy Education Study) Group

88% of WLWH under EVG from pre-pregnancy up to delivery had CV <40 cp/ml at time of delivery

J Antimicrob Chemother 2020; **75**: 1324–1331
doi:10.1093/jac/dkaa017 Advance Access publication 11 March 2020

Journal of Antimicrobial Chemotherapy

Rilpivirine in HIV-1-positive women initiating pregnancy: to switch or not to switch?

Pierre Frange [1,2]*, Roland Tubiana[3,4], Jeanne Sibiude[5,6], Ana Canestri[7], Cédric Arvieux[8], Cécile Brunet-Cartier[9], Laurent Cotte[10], Jacques Reynes[11], Laurent Mandelbrot[5,6], Josiane Warszawski[12–14] and Jérôme Le Chenadec[12] on behalf of the ANRS EPF CO1/CO11 Study Group†

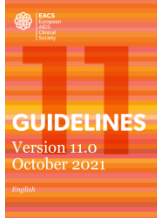
FPCS

247 WLWH under rilpivirine regimens with cv<50 cp/ml before pregnancy

74,5% were switched to non rilpivirine ART according to guidelines…and to several pills regimens instead of once daily

Switching was associated with rebound in 20% (median 160 cp/ml but range 59-223.648); all but one resuppressed at delivery

compared to 0% in non switching women.



EACS guidelines

Pregnant women

- If naïve: start ART triple therapy as soon as possible
- If third trimester: include INSTI (RAL bid or Dolutegravir)
- Monitor women ***every month or 2 months*** depending on adherence and previous sustained undetectable VL or not
- Control VL ***every 2 months*** and at week 36 of gestation
- If ***CV>50 cp/ml*** at W34-36, (during labour)
  - plan Cesarian section on W38: **(cut-off?)**
  - IV ZDV during labour and delivery
  - PEP in children ***"according to local guidelines"***

Threshold of HIV VL Week 36 for prevention measures

	Programmed Cesarian section at 38 weeks		IV ZDV per partum	
	recommended	considered	recommended	considered
EACS Oct 2021	>50 cp/ml		>50 cp/ml	
DHHS Dec 2020	>1000 cp/ml		>1000 cp/ml	50-1000 cp/ml
BHIVA 2020	> 400 cp/ml	50-399 cp/ml	>1000 cp/ml	50-1000 cp/ml

EACS: ART in children

! Also Weight based!

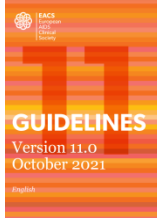


Table 1. Preferred and Alternative First Line Options in Children and Adolescents Living with HIV

	Backbone		3rd Agent (in alphabetical o	
Age	Preferred	Alternative	Preferred	Alterna
0 - 4 weeks	ZDV[i] + 3TC	-	LPV/r[ii, iii] NVP[iii] RAL[iii]	-
4 weeks - 3 years	ABC[iv] + 3TC[ix]	ZDV[i] + 3TC[ix] TDF[vii] + 3TC	DTG[viii]	LPV/r NVP RAL
3 - 6 years	ABC[iv] + 3TC[ix]	TDF + XTC[ix] ZDV + XTC[ix]	DTG	DRV/r EFV LPV/r NVP RAL
6 - 12 years	ABC[iv] + 3TC[ix] TAF[x] + XTC[ix]	TDF + XTC[ix]	DTG	DRV/r EFV EVG/c RAL
> 12 years	ABC[iv] + 3TC[ix] TAF[x] + XTC[ix]	TDF + XTC[ix]	BIC[xi] DTG	DRV/b EFV[xii] RAL[xii] RPV[xii]

Notes:

i In view of potential long-term toxicity, any child on ZDV should be switched to ABC or TAF (preferred) or TDF (alternative) once increase in age and/or weight makes licensed formulations available

ii LPV/r should not be administered to neonates before a postmenstrual age of 42 weeks and a postnatal age of at least 14 days although it may be considered if there is a risk of transmitted NVP resistance and INSTI in appropriate formulations are unavailable. In these circumstances the neonate should be monitored closely for LPV/r related toxicity

iii If starting a non-DTG 3rd agent in the neonatal period it is acceptable to continue this option. However, when over 4 weeks and 3 kg, a switch to DTG is recommended if and when an appropriate formulation is available

iv ABC should NOT be prescribed to HLA-B*57:01 positive individuals (where screening is available). ABC is not licensed under 3 months of age but dosing data for younger children are available from the WHO and DHHS

v At HIV-VL > 100,000 copies/mL ABC + 3TC should not be combined with EFV as 3rd agent

vi If using NVP as a 3rd agent in children aged 2 weeks to 3 years, consider using 3 NRTI backbone (ABC + ZDV + 3TC) until VL consistently < 50 copies/mL

vii TDF is only licensed from 2 years of age

viii DTG is licensed from 4 weeks and 3 kg

ix XTC indicates circumstances when FTC or 3TC may be used interchangeably

x TAF is only licensed in Europe for treatment of HIV in combination with FTC from 12 years of age and 35 kg in TAF/FTC and from 6 years of age and 25 kg in TAF/FTC/EVG/c

xi BIC is a preferred first line option in adult PLWH. At time of writing it is not licensed under 18 years of age but may be considered in those aged 12-18 years following discussion at MDT/PVC

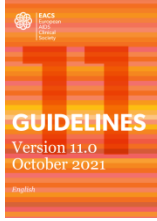
xii Due to predicted poor adherence in adolescence, PI/b are favoured as alternative first line 3rd agent options due their high barrier to resistance

Table 2. Antiretroviral Formulations Useful for Paediatric and Adolescent Dosing and Administration

NRTI	
ABC	tablet (300 mg) solution (20 mg/mL)
FTC	capsule (200 mg) solution (10 mg/mL)
3TC	tablet (300, 150 mg) solution (10 mg/mL)
TDF	tablet (245, 204, 163, 123 mg) granules (33 mg/g)
ZDV	capsule (250 mg, 100 mg) solution (10 mg/mL) iv infusion: 10 mg/mL (20 mL/vial)
TAF/FTC	tablet (25/200 mg and 10/200 mg)
TDF/FTC	tablet (300/200 mg)
ABC/3TC	tablet (600/300 mg)
ZDV/3TC	tablet (300/150 mg)
NNRTI	
EFV	tablet (600 mg) capsule (200, 100, 50 mg)
NVP	tablet (200 mg) prolonged release tablet (400, 100 mg) suspension (10 mg/mL)
RPV	tablet (25 mg)
TDF/FTC/EFV	tablet (300/200/600 mg)
TAF/FTC/RPV	tablet (25/200/25 mg)
TDF/FTC/RPV	tablet (300/200/25 mg)
PI	
DRV	tablet (800, 600, 400, 150, 75 mg) solution (100 mg/mL)
DRV/c	tablet (800/150 mg)
LPV/r	tablet (200/50 mg and 100/25 mg) solution (80/20 mg/mL)
RTV	tablet (100 mg) powder for oral suspension (100 mg sachet)
TAF/FTC/DRV/c	tablet (10/200/800/150 mg)
INSTI	
DTG	tablet (50, 25, 10 mg) dispersible tablets (5 mg)
RAL	tablet (600 mg, 400 mg) chewable tablets (100, 25 mg) granules for oral suspension (100 mg)
ABC/3TC/DTG	tablet (600/300/50 mg)
TAF/FTC/BIC	tablet (25/200/50 mg)
TAF/FTC/EVG/c	tablet (10/200/150/150 mg)
TDF/FTC/EVG/c	tablet (300/200/150/150 mg)

Switch Strategies for virologically supressed children and adolescents

- The general indications for switching when virologically suppressed are as for adult PLWH, see page 16 but with some additional considerations for children and adolescents relating to increasing age and weight, licensing, formulation availability, vulnerability to toxicity and predicted adherence issues in adolescence
- As children age and grow on suppressive ART, consideration should be given to simplification to robust once daily low pill burden regimens with optimal toxicity profiles and efficacy data. For example, in children aged less than 3 years commenced on liquid LPV/r, consider switching to once daily regimens when pill swallowing achieved or dispersible DTG is available
- If "preferred" options become available for a child as they get older then a switch to this option can be considered. However, if they are fully virological-



EACS

Breastfeeding

- Should be discussed as soon as possible in pregnancy ***(or even before?)***
- **Against breastfeeding**
- If the woman choose to breastfeed
  - No evidence supporting PreP for the child
  - Input/FU by a multidisciplinary team (adult HIV specialist, pediatrician, gynecologist)
  - Monthly FU
  - Increased VL FU for both mother and child including after cessation
  - if mother VL> 50 immediate cessation
  - If mastitis, child mouth or gut infection: advice by the multidisciplinary team
- TDM in milk

PEP for the infant

No HIV transmission among Swiss infants born to mothers with undetectable viral load and who did not receive neonatal PEP

24 February 2020. Related: Conference reports, HIV prevention and transmission.

Polly Clayden, HIV i-Base

Swiss data suggests that neonatal post-exposure prophylaxis (PEP) might be unnecessary in HIV-exposed infants if maternal viral load is fully suppressed in the third trimester. [1] These findings were shown at EACS 2019.

Since January 2016 the Swiss Federal Office of Public Health (FOPH) guidelines no

Since 2016
84/96 didn't receive ZDV PEP because VL <50 cp/ml at the end of pregnancy

longer recommend PEP for infants born to HIV positive women with plasma viral load <50 copies/mL in the third trimester (two viral load results at least 4 weeks apart including at or after 36 weeks).

The study was performed to investigate the implementation and safety of these national recommendations in Switzerland.

The investigators evaluated data from the Swiss Mother and Child HIV Cohort Study and the linked Swiss HIV Cohort Study database.

The evaluation included infants born between 2010 and 2018 and for whom information on maternal viral load in the third trimester was available. It compared the frequency of neonatal PEP in infants born before and after the introduction of the recommendations. Infant HIV status was assessed by PCR at 6 months of age.

Maternal viral load in third trimester was <50 copies/mL for 363/383 (94.8%) infants born during the study period.

Of these, 264/267 (98.9%) infants born before the 2016 guideline change received PEP versus 12/96 (12.5%) born afterwards (p<0.001).

PEP was given to all 20 infants with detectable maternal viral load in the third trimester. This included 5 infants born 2016 and after.

Safety of ARV on fetus

The EFV story

- Teratogenic in animals: CNS abnormalities
- In humans, numerous studies could not show an association
- Several studies with prospective screening including up to 1 year of life did detect CNS defects
- WHO recommended EFV as first line therapy because of favorable balance between benefits and risks

SMARTT Pediatric HIV/AIDS Cohort Study in USA: up to 4 years

Safety of in-utero antiretroviral exposure: neurologic outcomes in children who are HIV-exposed but uninfected

Claudia S. Crowell[a], Paige L. Williams[b], Cenk Yildirim[b], Russell B. Van Dyke[c], Renee Smith[d], Ellen G. Chadwick[e], George R. Seage III[b], Alexandria Diperna[f], Rohan Hazra[g], for the Pediatric HIV/AIDS Cohort Study

- Neurological (microcephaly, febrile seizure or other CNSAb) or ophtalmological Ab :

6,2% (vs 0,3-2% in similar previous study)

AIDS 2020, **34**:1377–1387

- Diagnostic at 2 years
  - In utero EFV (n=3653) was associated with 50% increased risk of abnormalities
  - DTG (n=782) signal but not significant because not enough cases

Safety of ARV on fetus

« The INSTI story » ?

- Signal in Tsempano study that did waine when folic acid was given
- Recommended as first line including in pregnant WLWH

OPEN

Citation: Cell Death and Disease (2017) 8, e2852; doi:10.1038/cddis.2017.237
Official journal of the Cell Death Differentiation Association
www.nature.com/cddis

HIV integrase inhibitor, Elvitegravir, impairs RAG functions and inhibits V(D)J recombination

Mayilaadumveettil Nishana[1,2], Namrata M Nilavar[1,2], Rupa Kumari[1], Monica Pandey[1] and Sathees C Raghavan*,[1]

- Integrase inhibitors target HIV integrase, an HIV enzyme responsible for integration of viral cDNA into host genome.
- RAG complex, comprising of RAG1 and RAG2, is essential for the generation of antigen receptor diversity and its absence leads to immunodeficiency diseases.
- RAG1, a critical enzyme involved in V(D)J recombination exhibits structural similarity to HIV integrase and shares a common active site with HIV integrase.
- Treatment with Elvitegravir resulted in significant reduction of mature B lymphocytes in 70% of mice studied.

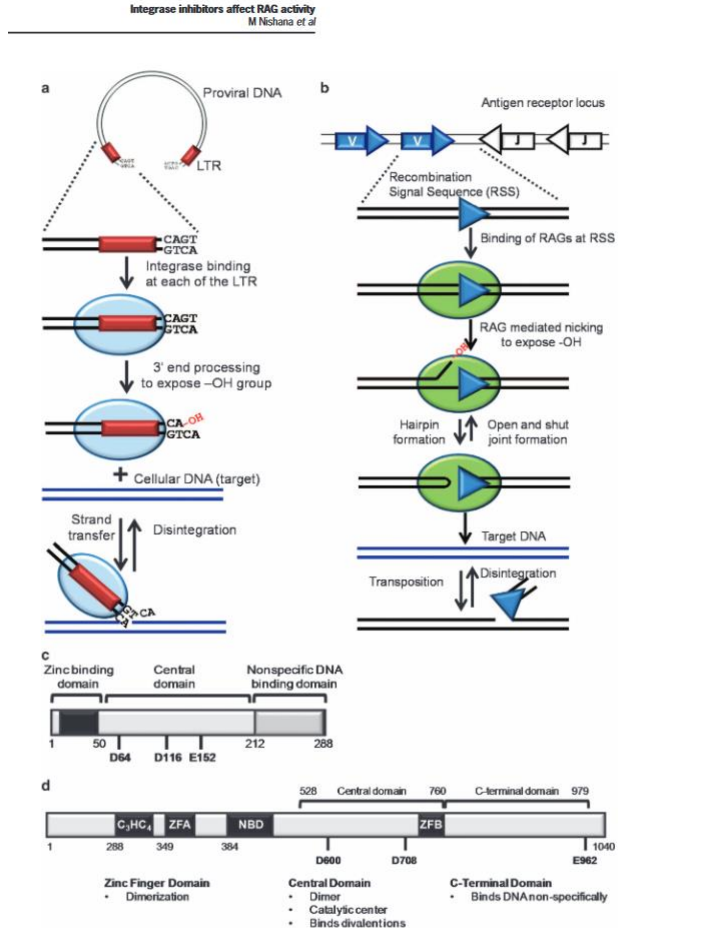


Figure 1 Similarities between HIV1 integrase and RAG1. (a) HIV integrase (blue oval) binds to the long terminal repeats/LTR (maroon box) near the ends of viral cDNA. It nicks the LTRs at a conserved 'CA', leaving a free 3′-OH group that can attack the cellular (target) DNA by a process called 'strand transfer'. This process is reversible and is termed 'disintegration'. (b) RAG complex (green oval) binds to RSS (white/blue triangles) and induces a nick 5′ to it. The 3′-OH group so created, attacks the opposite strand leading to formation of a hairpin at the coding end and a blunt signal end. The signal end can attack target DNA non-specifically by a process termed 'transposition'. Both hairpin formation and transposition are reversible leading to 'open-and-shut joint formation' and 'disintegration', respectively. (c) Schematic representation of domains of HIV1 integrase. The zinc binding domain with its C_2H_2 motif (black box), catalytic core domain with DDE motif and the nonspecific DNA binding domain at C-terminal is shown. (d) Schematic representation of RAG1 domains. The zinc binding domains, central domain and C-terminal domain are shown. C_3HC_4 and Zinc Finger A (ZFA) forms the N-terminal dimerisation domain. Nonamer binding domain (NBD), Zinc finger B (ZFB) and the triad of catalytic amino acids, DDE is also marked. The functions of each domain conserved among RAG1 and HIV1 integrase are listed

Conclusion

- INSTI and DTG in particular are recommended as first line therapy in naive WLWH that starts treatment during pregnancy
- Switch to « safer » drug in previously suppressed and stable women might lead to viral rebound and the benefit should be put in balance with the risks
- Close monitoring of pregnant women is needed
- We should continue to pay attention to safety of drug used in pregnant women
- We need a longer term FU of HIV-exposed but non infected children to detect potential AE of drug exposure