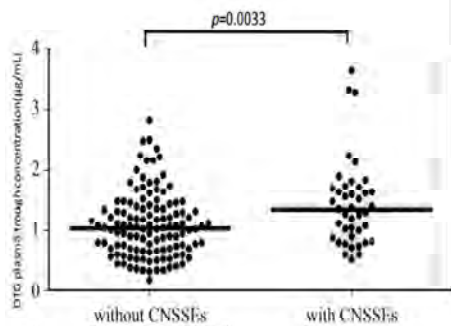


Knowledge gaps on clinical use of dolutegravir

Higher DTG plasma concentration in NP-AE



SINGLE 48 wk : insomnia 15% in DTG vs 1

ENCORE : EFV 400 mg vs 600 mg

2% vs 6% of EFV discontinuation due

Lancet 2014

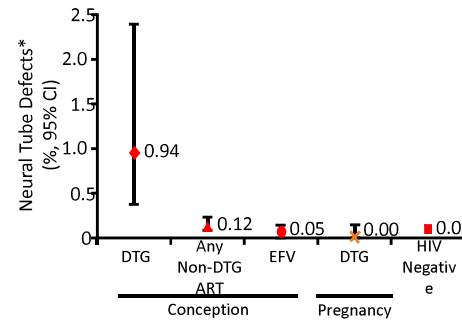
N=107 Japanese NP-AEs after the use of DTG were observed in 32%, Insomnia 13%,

Yagura H BMC Infect Dis 2017; 17: 622



Knowledge gaps on clinical use of dolutegravir: DTG Exposure at Conception and During Pregnancy

- Tsepamo: ongoing birth outcomes surveillance study among Botswanan women \pm HIV infection^[1,2]



*In 89,064 births as of May 1, 2018.

1. Zash R, et al. N Engl J Med. 2018.

2. Zash R, et al. AIDS 2018. Session TUSY15. 3. Orrell C, et al. AIDS 2018. Abstract THAB0307LB.

- At latest analysis on **July 15, 2018**^[2]
 - NTD prevalence with DTG exposure **at conception**: 4/596 (0.67%; 95% CI: 0.26% to 1.7%)
 - NTD prevalence with DTG started **during pregnancy**: 1/3104 (0.03%; 95% CI: 0.01% to 0.18%)
- Next formal analysis to occur after **March 31, 2019**^[2]
- Median time to virologic suppression approximately halved with DTG vs EFV, each with 2 NRTIs, when initiated during the **third trimester**^[3]



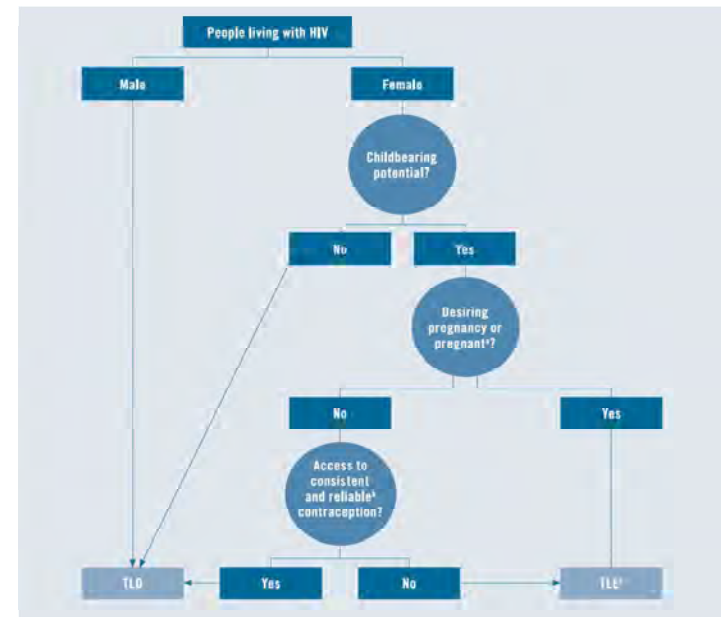
2018 Guidance on the Use of DTG in Women

■ DTG may be used ■ Use DTG or another option ■ Do not use DTG

Currently Receiving DTG?	Pregnancy Status	Recommendation on DTG		
		DHHS	BHIVA	WHO
No	Early pregnancy*	■	■	■
	Late pregnancy†	■	■	■
	Childbearing potential, no contraception	■	■	■
	Childbearing potential, effective contraception	■	■	■
Yes	Early pregnancy*	■	■	■
	Late pregnancy†	■	■	■
	Childbearing potential, no contraception	■	■	■
	Childbearing potential, effective contraception	■	■	■

*DHHS: ≥ 8 wks from last menstrual period; BHIVA and WHO: second and third trimesters.

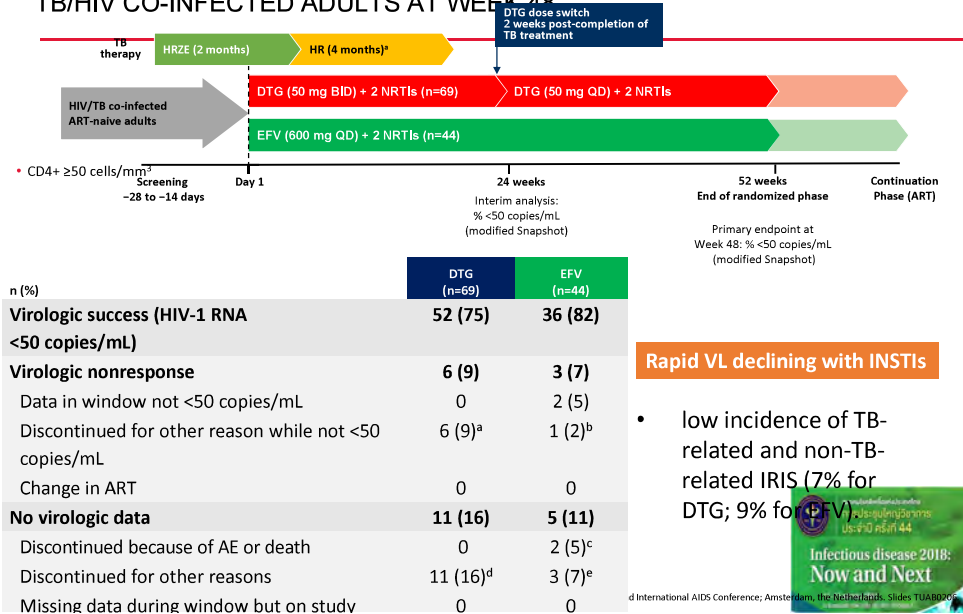
Adapted from Doherty M, et al. AIDS 2018. Session TUSY15.



WHO guideline 2018



INSPIRING: SAFETY AND EFFICACY OF DOLUTEGRAVIR-BASED ART IN TB/HIV CO-INFECTED ADULTS AT WEEK 48



Challenging issues in anti HCV in NLEM : HCV genotype

HCV prevalence and genotype distribution



Hajarizadeh B, Grebe J, Dore GJ. Nat Rev Gastroenterol Hepatol 2013

MSM_HIV + 464 cases,
14 % HCV + (2.65%)
New HCV =29 cases (2014-2018):
81% GT1a ,27.6%
HIV/HBV/HCV

GT3 47%, GT1 34%, GT6 17%

Avihingsanon A. J Gastroenterol Hepatol. 2014 Sep;29(9):17



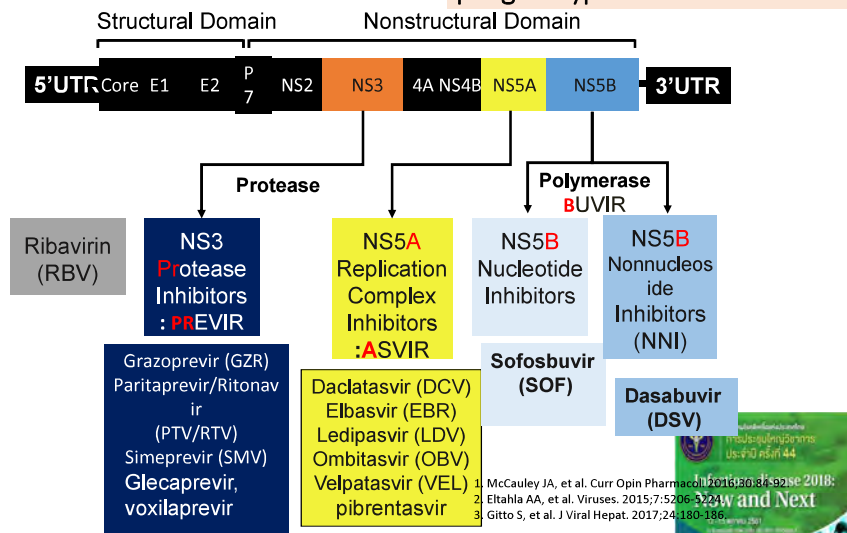
Challenging issues in anti HCV in NLEM :

HCV GT3 : Peg IFN +Sofosbuvir,
Non HCV GT3 :sofosbuvir/ledipasvir

GT3 47%, GT1 34%, GT6 17%

Avihingsanon A. J Gastroenterol Hepatol. 2014 Sep;29(9):17

Sofosbuvir/velpatasvir :
pangenotype



HIV/HCV Drug-Drug Interactions

ARV(s)	GLE/PI B	GZR/EB R	SOF/LD V	SOF/VEL	SOF/VE LVOX	SOF + DCV
ATV + (RTV or COBI) + EFV	X	X	✓*	✓*	X	Decrease DCV dose (30 mg)
DRV + (RTV or COBI)	X	X	✓*	✓*	✓*	✓
LPV + RTV	X	X	✓*	✓*	X	✓
EFV	X	X	✓*	X	X	Increase DCV dose (90mg)
RPV	✓	✓	✓*	✓	✓	✓
DTG	✓	✓	✓*	✓	✓	✓
RAL	✓	✓	✓	✓	✓	✓
EVG/COBI/FTC/TDF	✓*	X	X	✓*	✓*	Decrease DCV dose
EVG/COBI/FTC/AF	✓†	X	✓	✓	✓†	Decrease DCV dose
3TC/ABC	monitor for tenofovir toxicity if used with TDF. *No clinically significant drug interaction per prescribing information; AASLD/IDSA and DHHS guideline recommend monitoring liver enzymes.					
TAF						



EFV :
velpatasvir
AUC₀₋₂₄ 43%
, C_{min} 100
47%
, C_{max} 100
37%



Challenging issues in antiHBV in NLEM

- **Lamivudine**
 - HBV resistance 20% per year
- **Tenofovir disoproxil fumarate**
 - TDF related nephrotoxicity and Bone
 - Rarely HBV resistance
- **Entecavir**
 - 50 % HBV drug resistance if 3TC exposure
- **Role of other agents**
- **Tenofovir alafenamide**



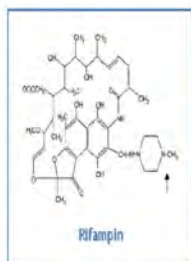
TAF vs TDF in HBV mono : similarly efficacy but less renal and bone toxicity

	N (%) of patients with HBV DNA < 29 IU/ml			N (%) of patients with normalized ALT by AASLD normal range		
	48 wks	96 wks	144 wks ^a	48 wks	96 wks	144 wks ^a
Pooled analysis						
TAF	630 (74)	680 (70)	91	304 (46)	438 (52)	65
TDF	325 (75)	345 (80)	88	149 (35)	176 (41)	65
Study 108						
TAF	268 (94)	257 (90)		137 (50)	139 (50)	
TDF	130 (83)	127 (91)		44 (32)	55 (40)	
Study 110						
TAF	371 (65)	423 (73)		257 (45)	299 (52)	
TDF	195 (67)	218 (75)		105 (36)	121 (42)	

[Pharmacotherapy](#). 2018 Oct;38(10):1051-1057



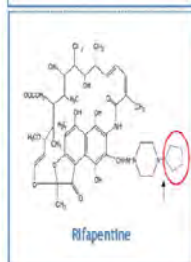
Challenging issues in TB drug (rifapentine) in NLEM



- Binds to β subunit of bacterial RNA polymerase for the inhibition of bacterial transcription
- Bactericidal against both replicating & non-replicating *M. tuberculosis*

	Rifapentine	Rifampin
MIC	0.06 µg/mL	0.25 µg/mL
Intra / Extracellular ratio	24	5
t _{1/2}	13h	3h

Shortening TB treatment
A 5349 : 17 wk vs 24 wk
TRUNCATE study



- More lipophilic → ↑ intracellular penetration
- Longer half life (x5)
- More potent (x5)
- Longer PAE (137h RPT + INH) Chan et al AAC 2004
- Cross resistance
- Same DDI

Latent TB treatment

- INH900 mg/RPT 900 mg weekly x12
- INH300/RPT 450-600 mg daily x4 wks (BRIEF/A5279)

