

# Managing TB in the Context of First Line ART Failure

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# 28-year-old female

## **Presenting complaints (February 2017):**

- Fever, weight loss, malaise
- Abdominal fullness

## **Past medical history**

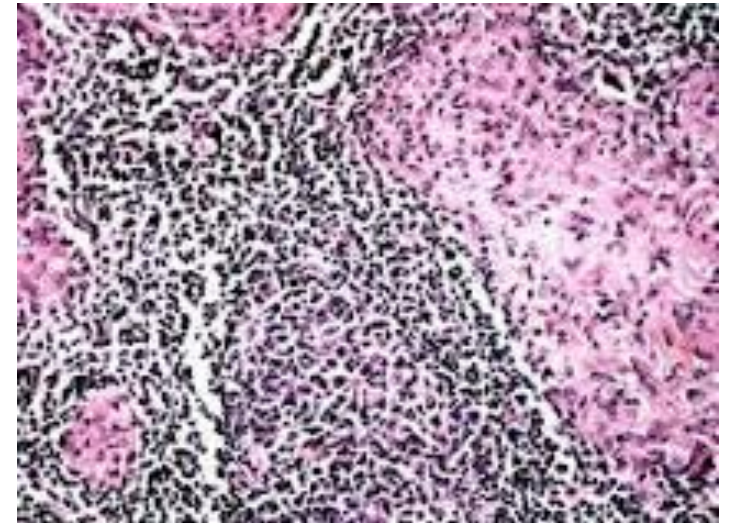
- TB lymphadenitis on biopsy of left neck lymph-node (June 2015)
  - completed 6/12 treatment
- HIV positive: on TDF/FTC/EFV for several years

## **Investigations**

- U/S abdomen: multiple abdominal lymph-nodes
- Laparoscopic lymph-node biopsy

# Lymph-node biopsy Feb 2017: Histology

- Nodal tissue with **necrotising and non-necrotising granulomas**.
- Granulomas comprise of palisading **epithelioid histiocytes** with central areas of **caseous necrosis**
- **Stains for Acid fast bacilli and fungi are negative.**
- Comment:
- Although stains for acid fast bacilli are negative, a tuberculous aetiology is favoured.



Histology favours TB: Is it still necessary to get microbiology: GxP, Culture and Susceptibility?

1. Yes
2. No



# Histology favours TB: Why is necessary to get microbiology: GXP, Culture and Susceptibility?

1. Detect MTB
2. Detect MOTT
3. Drug susceptibility of organism
4. All of the above
5. I don't think its necessary



# Lymph-node biopsy Feb 2017: TB work-up

- Direct prep: Acid fast bacilli - not observed
- Gene expert for MTB complex: Not detected
- Mycobacterial culture: Positive, confirmed to be MTB complex
- MTB HAIN TB-PCR Sensitivity Both Rifampicin and INH Sensitive

# Progress Feb-Dec 2017

Date	CD4	Viral load	VL log
1/2/2017	249	106414	5,03

- Complained of intermittent nausea and vomiting and dizziness from ART \*\*\*
- Adherence to ARVs was emphasized and patient discharged on first line treatment and anti-TB-therapy
- Inconsistent follow up- misses appointments.
  
- Returned to care - Dec 2017
- Confused, dull mental state and obtunded.
- One week history of nausea and vomiting.
- HIV monitoring (Nov 2017): CD4 178 (16.91%), VL 98451 CPM (4.993)

# CT findings

- Significant leptomeningeal enhancement involving the right sylvian fissure with mass effect effacing the proximal sylvian fissure at the suprasellar cistern. The enhancement also includes the adjacent cortical tissue without any significant perifocal edema.

- **COMMENT**

Tuberculous granulomatous meningo-encephalitis involving the right sylvian fissure.



# Lumbar puncture

- Cell count: Polymorphs: 0, **Lymphocytes: 280**, Erythrocytes: 10
- Protein: **1.935 g/L**
- CSF glucose: **2.0 mmol/L**, Blood glucose: 6.2 mmol/L
- FTA: neg
- GXP negative
- AFB smear negative
- TB culture negative

## In summary (Dec 2017):

- HIV positive failing first line treatment for several years.
- Recent (Feb 2017) histologic and microbiologically confirmed susceptible TB lymphadenitis - on ATT for about 10 months – **questionable adherence**
- Current presentation consistent with TBM

# Management: December 2017

- Recommended on rifafour and continued FDC
- She developed a hemiplegia in hospital \*\*\*
- Further problem: Abnormal LFT

Date	Bili/ conj B µmol/L	ALT IU/L N= <40	AST IU/L N= 15-40	ALP IU/L N= 40-150	GGT IU/L N= <64
30/12/2017	N	73	59	87	137
05/1/2018	N	104	70	85	164
09/1/2018	-	120	63	-	-
13/1/2018	-	148	115	-	-

# What is the next step in management?

1. Continue therapy, monitor adherence, check ALT in 1 week
2. Stop all therapy and check ALT in 1 week
3. Stop rifabutin only
4. Stop TDF/FTC/EFV only
5. start liver friendly TB Rx: moxifloxacin, ethambutol and amikacin.



# Patient continued Rifafour and FDC

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13/1/2018	-	148	115	-	-
19/1/2018	N	64	23	-	-
12/2/2018	N	44	31	82	166

# Tolerating standard TB treatment. How do we deal with failing ART?

- ~~1. TDF/FTC/EFV, continue rifampin~~
- ~~2. Double dose ATV/r (600/200) + AZT + 3TC, continue rifampin~~
- ~~3. ATV/r (300/100) + AZT + 3TC, rifampin based TB treatment~~
4. Double dose LPV/r (800/200) bid + AZT + 3TC, continue rifampin
5. DTG/TDF/3TC and continue rifampin
6. Call a friend



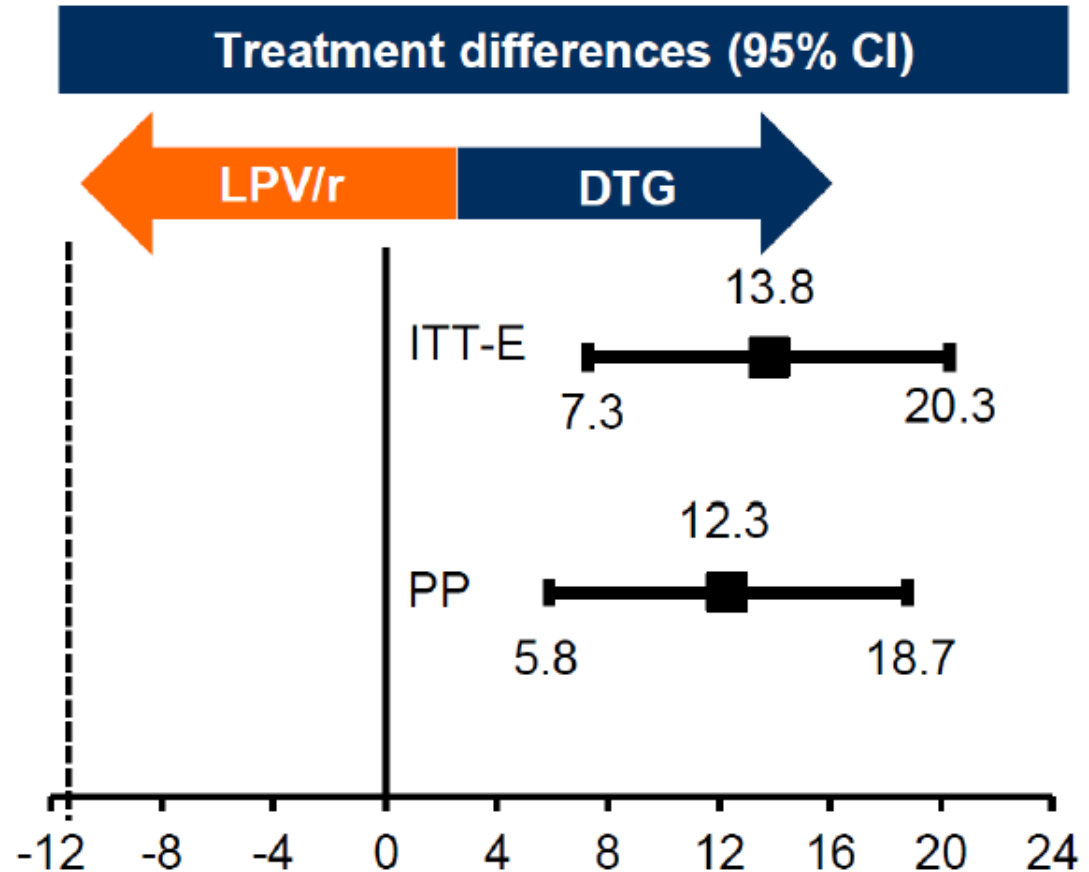
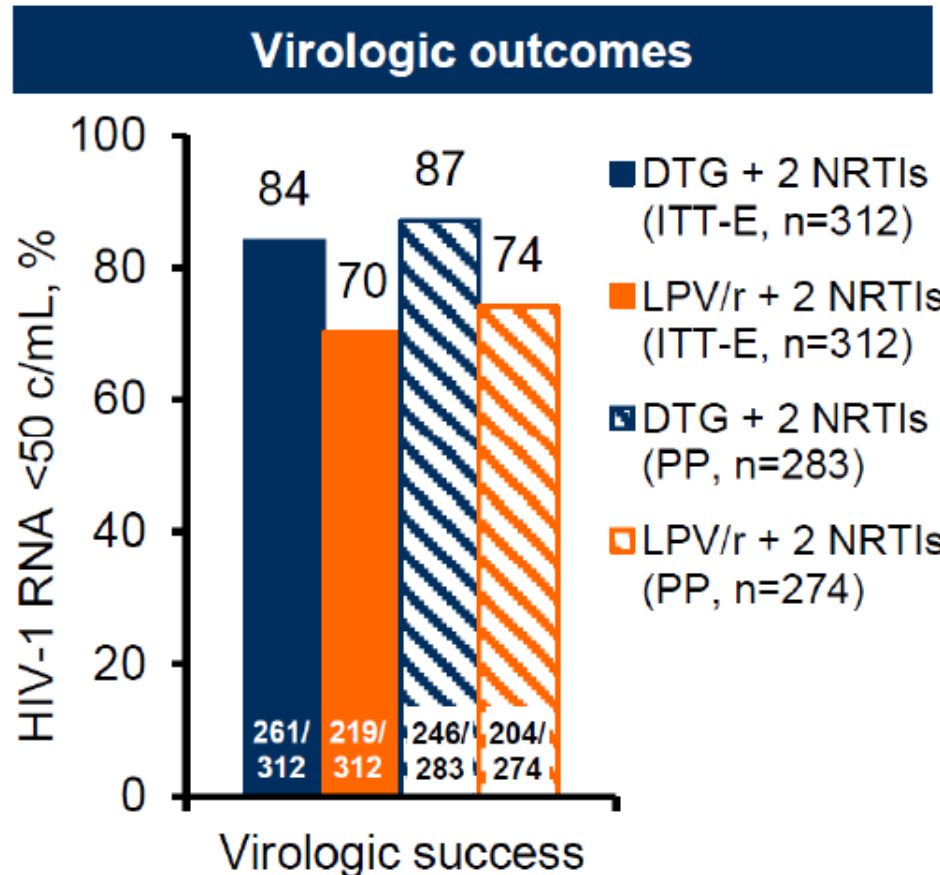
# Dolutegravir versus ritonavir-boosted lopinavir both with dual nucleoside reverse transcriptase inhibitor therapy in adults with HIV-1 infection in whom first-line therapy has failed (DAWNING): an open-label, non-inferiority, phase 3b trial

*Michael Aboud, Richard Kaplan, Johannes Lombaard, Fujie Zhang, José A Hidalgo, Elmira Mamedova, Marcelo H Losso, Ploenchan Chetchotisakd, Carlos Brites, Jörg Sievers, Danna Brown, Judy Hopking, Mark Underwood, Maria Claudia Nascimento, Yogesh Punekar, Martin Gartland, Kimberly Smith*

- Evaluated safety & efficacy of DTG + 2 NRTIs vs LPV/r + 2 NRTIs in participants failing first-line therapy with NNRTI + 2 NRTIs
- **Key eligibility criteria:** HIV-1 RNA  $\geq 400$  c/mL after  $\geq 6$  mths first-line Rx, investigator-selected NRTIs had to include at least one fully active NRTI based on resistance testing

# Dawning: Virologic outcomes at 48 weeks

In the intention-to-treat exposed (ITT-E) analysis, proportion of participants with HIV-1 RNA <50 c/mL at Week 48 was significantly higher in the DTG + 2 NRTIs group (84%) compared with the LPV/r + 2 NRTIs group (70%; treatment difference [95% CI], 13.8% [7.3%-20.3%];  $P < 0.001$  for superiority)



# Dawning: Adverse Effects

	DTG + 2 NRTIs (n=314) <sup>a</sup>	LPV/r + 2 NRTIs (n=310)
Any AE, n (%)	223 (71)	244 (79)
Most common AEs (≥5% in either group)		
Diarrhea	28 (9)	105 (34)
Upper respiratory tract infection	45 (14)	43 (14)
Headache	25 (8)	17 (5)
Nausea	10 (3)	30 (10)
Lower respiratory tract infection	13 (4)	14 (5)
Anemia	11 (4)	15 (5)
Vomiting	5 (2)	21 (7)
Any neuropsychiatric AE	19 (6)	17 (5)
Drug-related AEs	50 (16)	119 (38)
All drug-related grade 2-4 AEs	11 (4)	44 (14)
Diarrhea	1 (<1)	23 (7)
Nausea	0	6 (2)
Serious AEs or deaths <sup>b</sup>	20 (6)	20 (6)
Drug-related serious AEs	3 (<1)	2 (<1)
AEs leading to withdrawal	8 (3)	18 (6)

# Dawning Conclusion

- DTG has superior efficacy at 48 weeks
- lower rates of virologic non-response at 48 weeks
- Favorable safety profile

Important study to guide second-line treatment decisions in resource-limited settings

Patient is failing first line treatment. Do you think a genotype would help in deciding the next ART regimen?

1. Yes
2. No



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# Genotype: Stanford resistance score

- NRTI: M184V

NRTI	ABC	AZT	FTC	3TC	TDF
M184V	15	-10	60	60	-10

- NNRTI: K103N, V106M

NNRTI	EFV	ETR	NVP	RPV
K103N	60	0	60	0
V106M	60	0	60	0
Total	120	0	120	0

Resistance score: low level 15-29, intermediate 30-59, high level 60+ <https://hivdb.stanford.edu/hivdb/by-mutations/>

# 12<sup>th</sup> Feb 2018

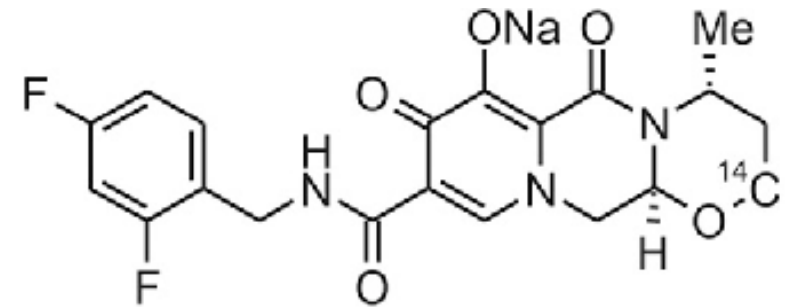
- Rifafour week 6
- Still on failing ART-TDF/FTC/EFV
- Hb 12.0, Platelets, 264, WCC 1.93, Abs neutrophil count 0.64, Abs L/C 0.92
- U&E: 139/3.6/100/32/3.1/65 (>89)
- LFT: TP 85, Alb 38, Total bili 2, Alk Phos 82, GGT 166, ALT, 44, AST 31
- CRP 3.9

Considering the genotype the following regimens are reasonable

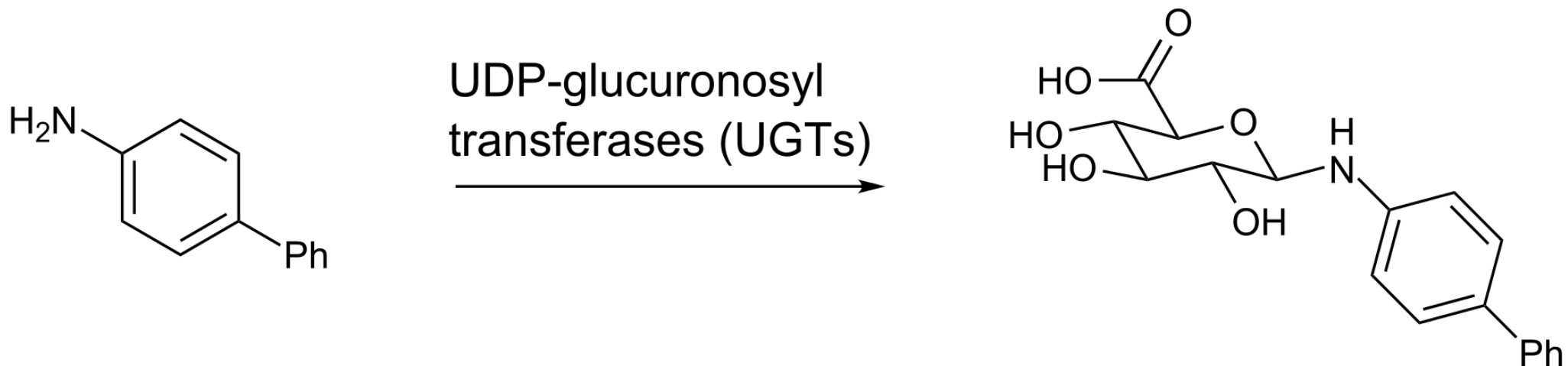
1. Double dose LPV/r (800/200) bid + TDF + 3TC, continue rifabutin
2. DTG + TDF +3TC and continue rifabutin

# Metabolism of DTG

- Dolutegravir is metabolized in the liver
- Primarily metabolized by UGT1A1
- Some by CYP450 3A4
- Does not inhibit or induce CYP450 enzymes

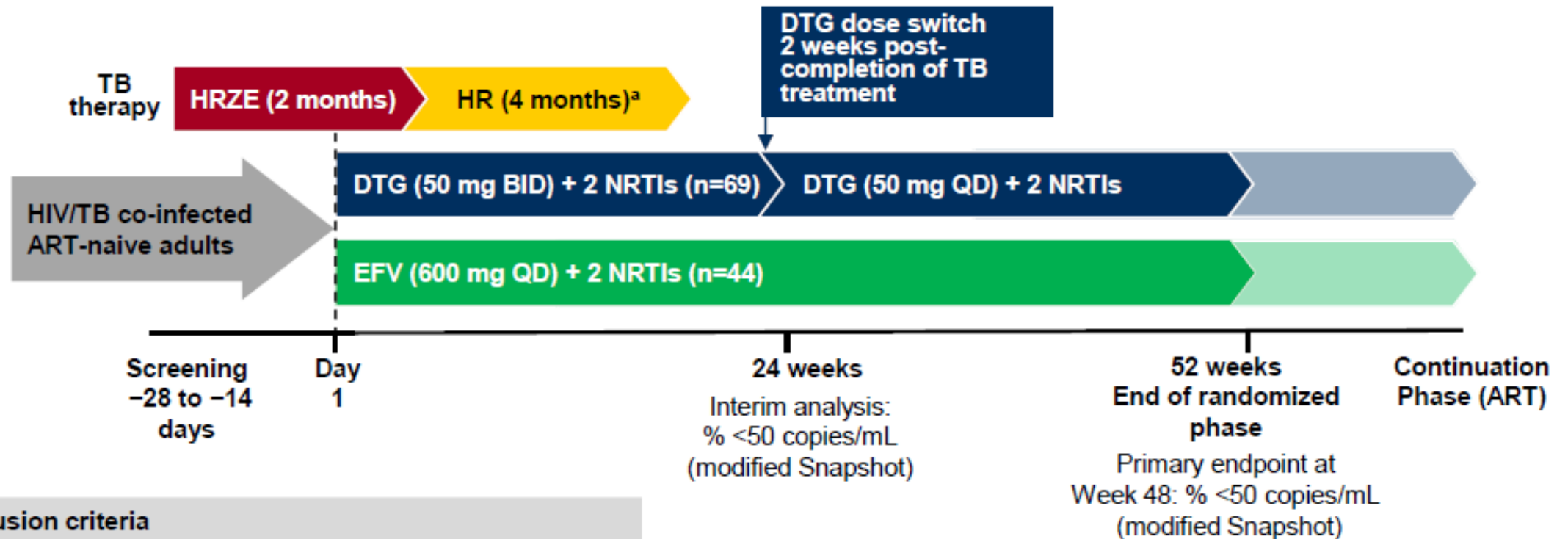


IG 1 Structure of [<sup>14</sup>C]dolutegravir (sodium salt)



# INSPIRING: Study Design

Phase IIIb, randomized, multicenter, open-label, non-comparative, active-controlled, parallel-group study



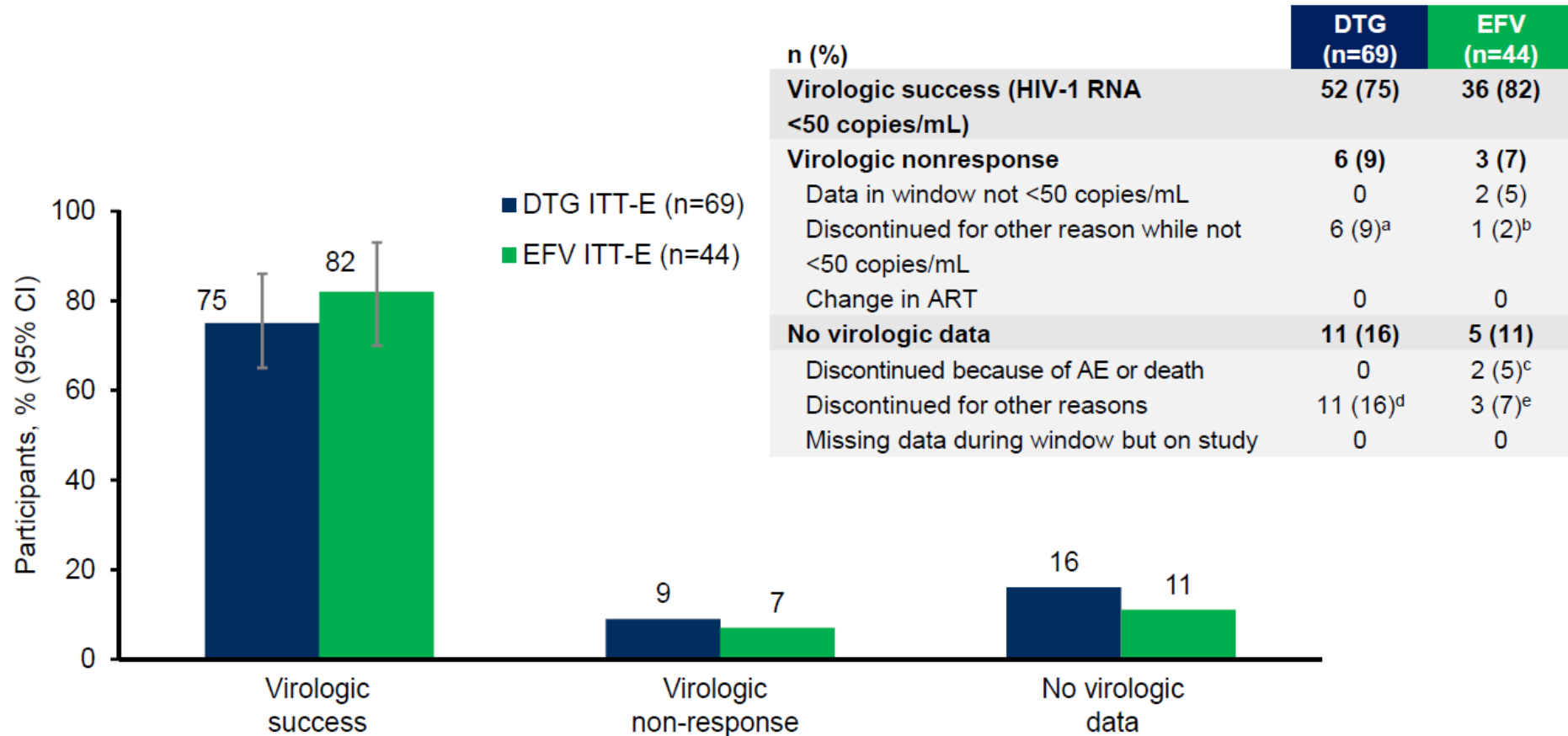
## Inclusion criteria

- HIV-1 RNA  $\geq 1000$  copies/mL and CD4+  $\geq 50$  cells/mm<sup>3</sup>
- Pulmonary, pleural, or lymph node tuberculosis with RIF-sensitive MTB confirmed by culture or GeneXpert
- RIF-containing TB treatment started up to a maximum of 8 weeks before randomization and no later than the screening date

## DTG:EFV 3:2 randomization stratified by

- Screening plasma HIV-1 RNA  $\leq 100,000$  or  $> 100,000$  copies/mL
- Screening CD4+  $\leq 100$  or  $> 100$  cells/mm<sup>3</sup>

# INSPIRING: Virologic Outcome at 48 weeks



<sup>a</sup>DTG: discontinued for other reasons while not <50 copies/mL: 3 lost to follow-up; 2 withdrawal of consent; 1 pregnancy.

<sup>b</sup>EFV: discontinued for other reasons while not <50 copies/mL: 1 lost to follow-up.

<sup>c</sup>EFV: discontinued due to AE: 1 EFV hypersensitivity; 1 increased gamma-glutamyltransferase.

<sup>d</sup>DTG: No virologic data/Discontinued for other reasons: 7 lost to follow-up; 2 pregnancies; 1 physician decision; 1 withdrawal of consent.

<sup>e</sup>EFV: No virologic data/Discontinued for other reasons: 2 lost to follow-up; 1 withdrawal of consent (patient relocated).

# TB Treatment Outcomes

n (%)

**Treatment Success**

Treatment failure

Died

Not evaluated / Lost to follow-up

**DTG  
(n=69)**

**EFV  
(n=44)**

**61 (88)**

**40 (91)**

0

1 (2)

0

0

8 (12)

3 (7)

# ARV options with TB therapy

- **Rifampicin**- containing TB therapy:
  - EFV
  - Double dosed lopinavir/ritonavir
  - Dolutegravir 50 mg **BD**
- **Rifabutin** (150 mg daily) containing TB therapy:
  - With all PIs (lopinavir, atazanavir, darunavir)
- NRTIs are not affected by TB treatment

# Final Treatment

- ART regimen switched to TDF/FTC/DTG **BD** in Feb 2018  
(week 6 of ATT)
- TB treatment planned to stop in January 2019  
(about one year of ATT)

# Follow up on 21<sup>st</sup> August 2018

## Month 8 of TB treatment

- Patient is well. Complete recovery from hemiplegia
- Hb 11.1, WCC 6.16, neutrophil count 4.53
- Albumen 37, total bilirubin 8, ALK Phosphate 70, GGT 26, ALT 10, AST 18
- CD4 count 272 (25%), VL BLD
- Plan: to complete one year ATT and continue TDF/3TC/once daily DTG

# Take home messages

Managing TB in the context of HIV is complicated in **patients failing first line treatment.**

- Double dose LPV/r (800/200) BD with rifafour – poorly tolerated
- Double dose DTG with rifafour – better tolerated but need genotype
- ATV/r with rifabutin and individual co-drugs – higher pill burden
  
- ID adult hotline: 0800111740 (sms 0636825333)

