HIV Neuropsychiatry

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Overall and CNS safety of HIV integrase inhibitors

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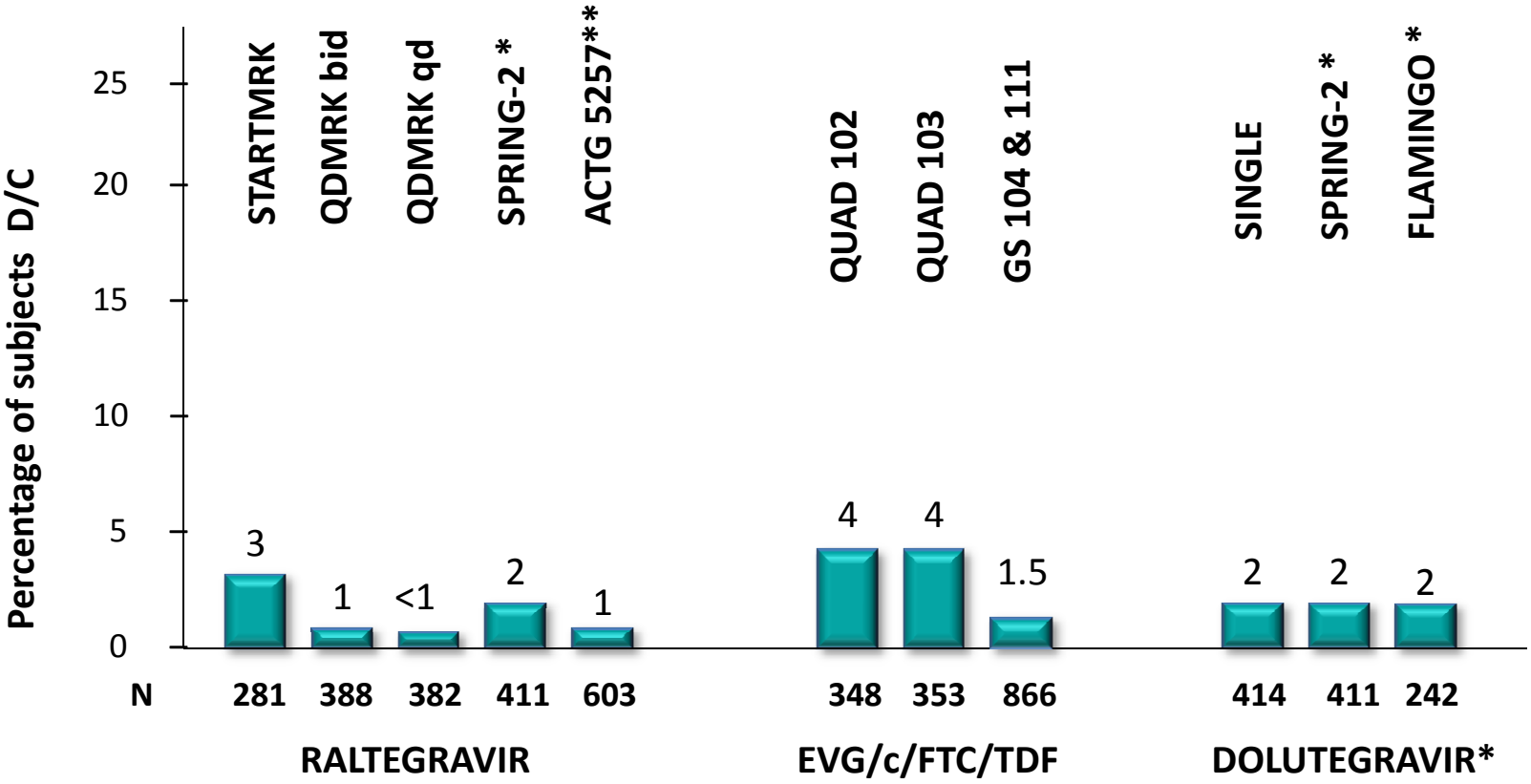
Flow.

- ✓ INI toxicity in RCT.
- ✓ INI psychiatric toxicity in RCT.
- ✓ Observational data in real life settings.
- ✓ Data on PK: any potential relationship with toxicity?.
- ✓ INI toxicity warning data in INI SPCs (EMA).

INI drug D/C in phase III RCT, naives, 48 weeks

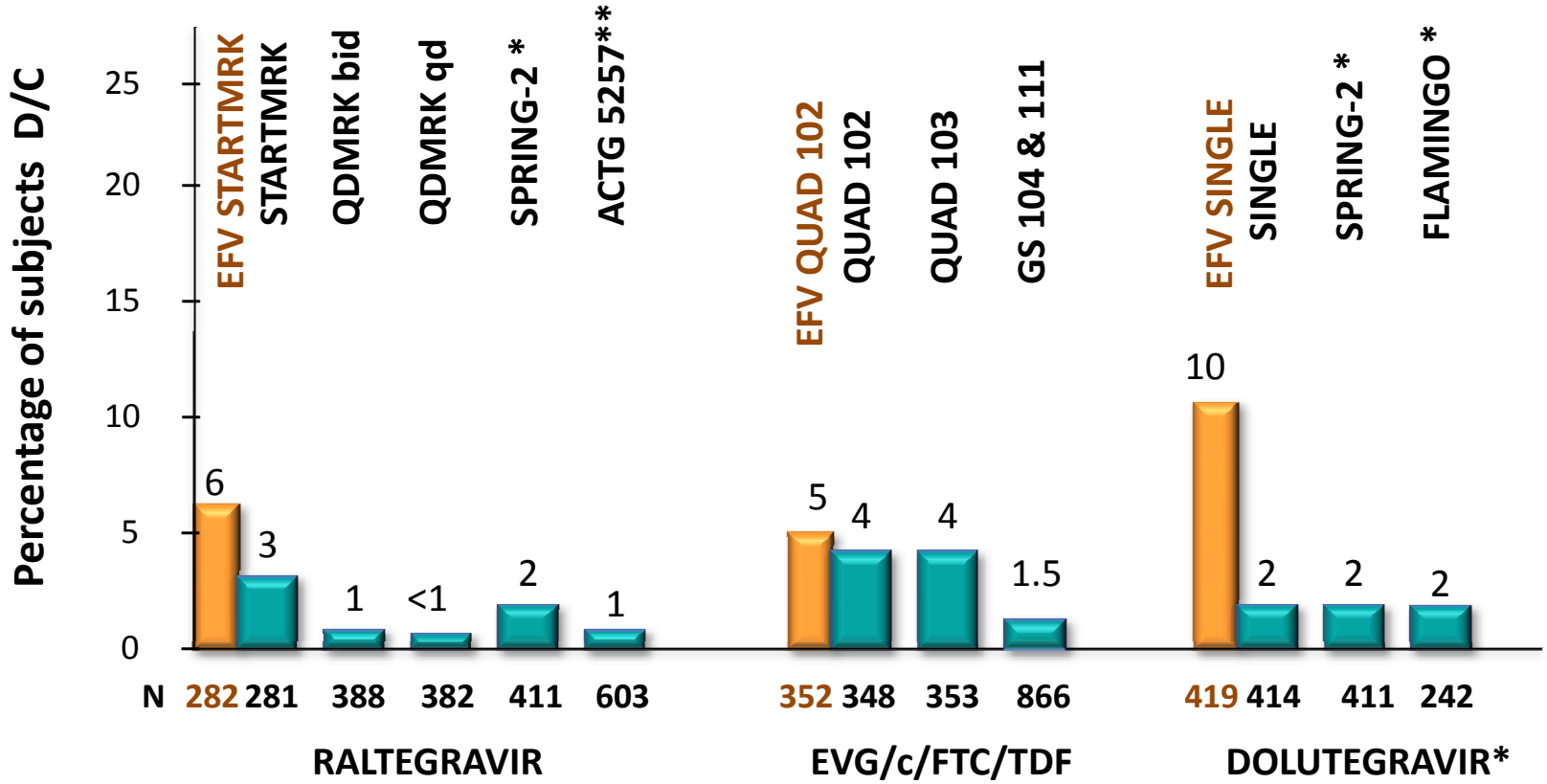
No organ-specific toxicity. D/C due to psych AEs: 0 - <1%.



* *Backbone*: TDF/FTC or ABC/3TC. ** 96 weeks

INI drug D/C in phase III RCT, naives, 48 weeks

Comparison vs EFV/FTC/TDF, double-blind.



* *Backbone*: TDF/FTC or ABC/3TC. ** 96 weeks

Shortcomings with Psych AEs analysis in RCT.

Short-term (<96 weeks) AEs are to be investigated in blinded RCT, but…

No uniformity criteria in the reports!.

- Can report only those **occurring in ≥2%, ≥5% or ≥10%.**
- Can report **all** (any), or only those of **G2-4**, or **moderate to severe**.
- Can report only those "**more common**".
- Some **psych AEs** are only reported when specifically targetted (eg, when compared with EFV).
- The investigator decides whether an AE is **drug-related or not**. No control.

STARTMRK 48 w– CNS Adverse Events

Accumulated Up to Week 8 and 48 (predefined endpoint)

	RAL*	EFV*	p-value
CNS Adverse Events, week 8	10%	18%	0.015
CNS AEs, week 48	14%	23%	p=0.004

- **CNS terms compared at Week 8**
  - Depression
  - Major depression
  - Nightmare
  - Abnormal dreams
  - Suicide attempt or ideation
  - Nervous system disorder
  - Psychotic disorder
  - Acute psychosis
  - Confusional state
  - Delirium
  - Depressed level of consciousness
  - Hallucination

*In combination with TDF/FTC

2008 ICAAC-IDSA Abstract H-896a

JL Lennox. Lancet 2009.

SPRING 2. Select Summary of AEs

	DTG 50 mg QD n=411 n (%)	RAL 400 mg BID n=411 n (%)
Grade 2-4 Drug-Related Events	**24 (6)**	**27 (7)**
Grade 3	**2***	**5****
Grade 4	**2****	**0**
Serious Adverse Events	**29 (7)**	**31 (8)**
Drug related	**3**	**5**
	Arrhythmia, hypersensitivity, hepatitis	**Convulsion (2), Aphasia, hypersensitivity/hepatitis#, diarrhea**
AEs Leading to Withdrawal	**10 (2)**	**7 (2)**
Events with >1 subject		
Acute Hepatitis C	**2 (<1)**	**0**
ALT or AST increased	**3 (<1)**	**2 (<1)**
Death	**1 (<1) Homicide**	**1 (<1) Suicide**
Nausea	**1 (<1)**	**1 (<1)**

* Grade 3: headache, dizziness, feeling abnormal, arrhythmia
** Grade 4: Drug hypersensitivity with associated ALT/AST/ALP/BilT/LFT, hepatitis
*** Grade 3: nausea, abdominal pain, aphasia, drug eruption, fatigue, ALT increased, CPK increased, lipase increased, decreased appetite
#One subject with cytolytic hepatitis, hypersensitivity, influenza, lymphadenitis viral

SPRING 2. Common AEs (≥5%)

Adverse Event (any grade)	DTG 50 mg QD n=411 n (%)	RAL 400 mg BID n=411 n (%)
Any Event	**339 (82)**	**340 (83)**
Nausea	59 (14)	53 (13)
Headache	51 (12)	48 (12)
Nasopharyngitis	46 (11)	48 (12)
Diarrhea	47 (11)	47 (11)
Upper respiratory tract infection	26 (6)	26 (6)
Dizziness	23 (6)	23 (6)
Pyrexia	20 (5)	22 (5)
Fatigue	20 (5)	18 (4)
Insomnia	21 (5)	17 (4)
Bronchitis	19 (5)	16 (4)
Depression	21 (5)	14 (3)
Pharyngitis	20 (5)	13 (3)
Influenza	14 (3)	21 (5)
Anxiety	14 (3)	20 (5)
Syphilis	10 (2)	19 (5)

F Raffi. Lancet 2013; 381: 735–43

SAILING Study. Adverse Events, 48 weeks

Double-blind study.	DTG 50 mg QD (N=357)	RAL 400 mg BID (N=362)
Discontinuations due to safety events	9 (3%)	14 (4%)
Most commonly reported (≥10%) AEs in either arm		
Diarrhea	71 (20%)	64 (18%)
Upper respiratory tract infection	38 (11%)	29 (8%)
Drug-related (≥2% in either arm)	**73 (20%)**	**85 (23%)**
Diarrhea	29 (8%)	21 (6%)
Nausea	13 (4%)	16 (4%)
Vomiting	8 (2%)	11 (3%)
Headache	7 (2%)	7 (2%)
Fatigue	4 (1%)	10 (3%)
Rash	5 (1%)	6 (2%)
Insomnia	0	6 (2%)
Abdominal pain upper	6 (2%)	0
Drug-related Grade 2-4	**28 (8%)**	**32 (9%)**
Drug-related Grade 4	**1 (<1%)**	**1 (<1%)**
Serious – any event	**33 (9%)**	**42 (12%)**
Serious drug-related – any event	**2 (<1%)[a]**	**4 (1%)[b]**
Fatal AEs	**0**	**3 (<1%)[c]**

[a] DTG: 1 hepatotoxicity, 1 myositis and acute renal failure

[b] RAL: 1 oral mucosal blistering and rash pruritic, 1 pancreatitis, 1 hepatitis, **1 suicidal ideation**

[c] 1 adenocarcinoma, 1 acute hepatic and renal failure, 1 cervical carcinoma

Cahn et al. IAS 2013; Kuala Lumpur, Malaysia. Abstract WELBB03.

Pre-defined Adverse Events: Neuro-psychiatric AEs of Interest (any grade)

48 weeks

≥2%

System Organ Class Preferred Term	DTG 50mg +ABC/3TC QD (N=414) (%)	Atripla QD (N=419) (%)	Difference in Percentage (95% CI)	Fisher's Exact P-value
Any Event	**169 (41)**	**260 (62)**		
Nervous system disorders	**91 (22)**	**196 (47)**	**-24.8 (-31.0, -18.6)**	**<0.001**
Dizziness	37 (9)	148 (35)	-26.4 (-31.7, -21.0)	<0.001
Headache	55 (13)	56 (13)	-0.1 (-4.7, 4.5)	1.000
Somnolence	9 (2)	23 (5)	-3.3 (-5.9, -0.7)	
Psychiatric disorders	**120 (29)**	**158 (38)**	**-8.7 (-15.1, -2.3)**	**0.008**
Insomnia	64 (15)	43 (10)	5.2 (0.7, 9.7)	0.029
Abnormal dreams	30 (7)	72 (17)	-9.9 (-14.3, -5.5)	<0.001
Nightmare	9 (2)	17 (4)	-1.9 (-4.2, 0.5)	
Sleep disorder	6 (1)	11 (3)	-1.2 (-3.1, 0.7)	
Depression	23 (6)	26 (6)	-0.6 (-3.8, 2.5)	
Depressed mood	3 (<1)	7 (2)	-0.9 (-2.4, 0.5)	
Anxiety	14 (3)	27 (6)	-3.1 (-6.0, -0.1)	

Only AEs of interest occurring in at least 2% of subjects in either group are presented. P-value only derived if more than 10% of subjects in either group experience this AE.

Walmsley S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b.

DTG/ABC/3TC vs EFV/FTC/TDF, 48 weeks. SINGLE Study.

Table 1. Selected Adverse Events and Laboratory Abnormalities That Developed during Treatment.*

	Event	Dolutegravir and Abacavir–Lamivudine (N = 414)	Efavirenz–Tenofovir DF–Emtricitabine (N = 419)
		no. of participants (%)	
*	Adverse event leading to discontinuation of study drug†	10 (2)	42 (10)
*	Psychiatric disorder	2 (<1)	15 (4)
*	Nervous system disorder	0	13 (3)
	Skin and subcutaneous-tissue disorder	2 (<1)	8 (2)
	Gastrointestinal disorder	0	8 (2)
	General disorder or administration-site condition	0	7 (2)
	Adverse event of grade 2–4		
	Bronchitis	8 (2)	11 (3)
	Diarrhea	21 (5)	17 (4)
	Nausea	7 (2)	13 (3)
	Insomnia	17 (4)	16 (4)
	Anxiety	9 (2)	12 (3)
	Depression	7 (2)	14 (3)
	Headache	12 (3)	13 (3)
*	Dizziness	2 (<1)	21 (5)
	Rash	3 (1)	19 (5)

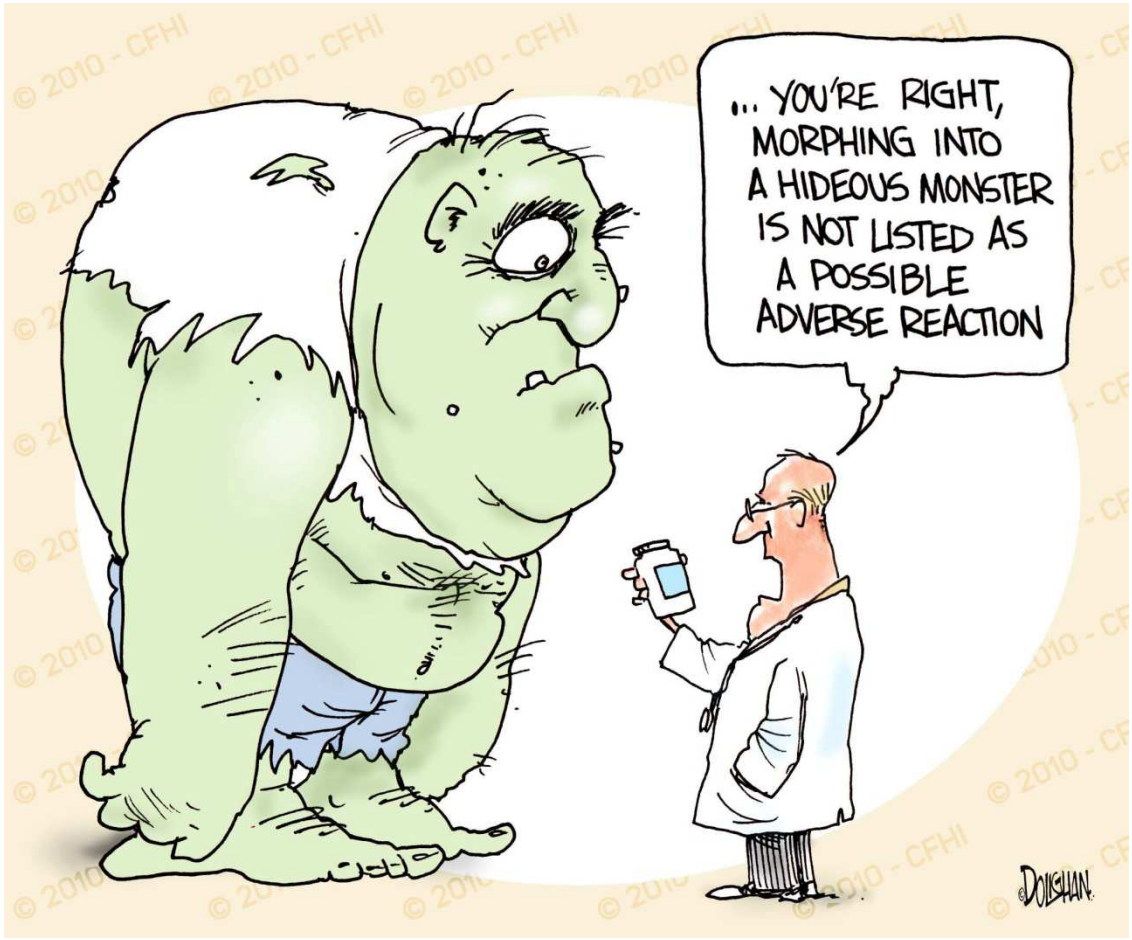
SL Walmsley. N Engl J Med 2013;369:1807-18.

Summary of AEs Leading to Discontinuation. 96 weeks. SINGLE

Parameter	DTG + ABC/3TC QD (n=414)	EFV/TDF/FTC QD (n=419)
Body system (at least 2% in either arm)		
Psychiatric disorders	4 (<1%)	23 (5%)
Nervous system disorders	1 (<1%)	17 (4%)
Skin and subcutaneous tissue disorders	2 (<1%)	9 (2%)
General disorders and administration site conditions	0	10 (2%)
Gastrointestinal disorders	0	8 (2%)

Walmsley et al. CROI 2014; Boston, MA. Poster 543.

- Every time a new ARV drug is launched, unexpected AEs not seen in RCT are soon reported.
- Sometimes they are true & useful, sometimes not.



te Onset Insomnia Associated with the Initiation
of Ra A Report of Two Cases and Literature Review

Exacerbation of depression associated with starting raltegravir: a report of four cases

Severe insomnia related to high conce f raltegravir

C Eiden. AIDS 2011, 25:725–726; J Gray. AIDS Patient Care STDs 2009;23:689-690; M Harris. AIDS 2008;22:1890-92.

Dolutegravir discontinuation – real life

	Discontinuations		D/C AEs
Todd (Belfast)[1]	6/68	9%	9%
Waqas (Dublin)[2]	1/61	1.6%	1.6%
Van den Be		16%	14.5%
Kirby (Brigh		14%	12.5%
Simons (St			5%
Shaw (Mar		14.6%	8.4%
Negedu (St		2.2%	2.2%
Cunningham (Cardiff)		10%	??
Zucman (France) [5]	6/105	6%	6%
Le Baut (France) [6]	26/279	10.8%	9.3%

Unknown uncontrolled factors could be influencing these retrospective analyses:

- Prescription bias
- Withdrawal bias (patient, physician or both)
- Other

- **Mainly due to neuropsych and GI AEs**

1. BHIVA 2015, Abstract P8
2. EACS 2015, Abstract PE8/36
3. CROI 2016, Abstract 948
4. BHIVA 2016, Abstracts P26, P9, P20, P28, P36
5. AFRAVIH 2016. PJ160
6. 36ème RICAI, Paris.

TUPEB256

Adverse drug reactions associated with integrase strand transfer inhibitors (INSTI) in clinical practice: Post-marketing experience with raltegravir, elvitegravir-cobicistat and dolutegravir.

K.J. Lepik[1,2], A. Nohpal[1], B. Yip[1], K.J. Toy[2], L. Akagi[1,2], J.S.G. Montaner[1], S. Guillemi[1], R. Hogg[1], R. Barrios[1]

1. B.C. Centre for Excellence in HIV/AIDS, Vancouver Canada; 2. St. Paul's Hospital Ambulatory Pharmacy, Vancouver Canada

Retrospective, observational.

N=1467

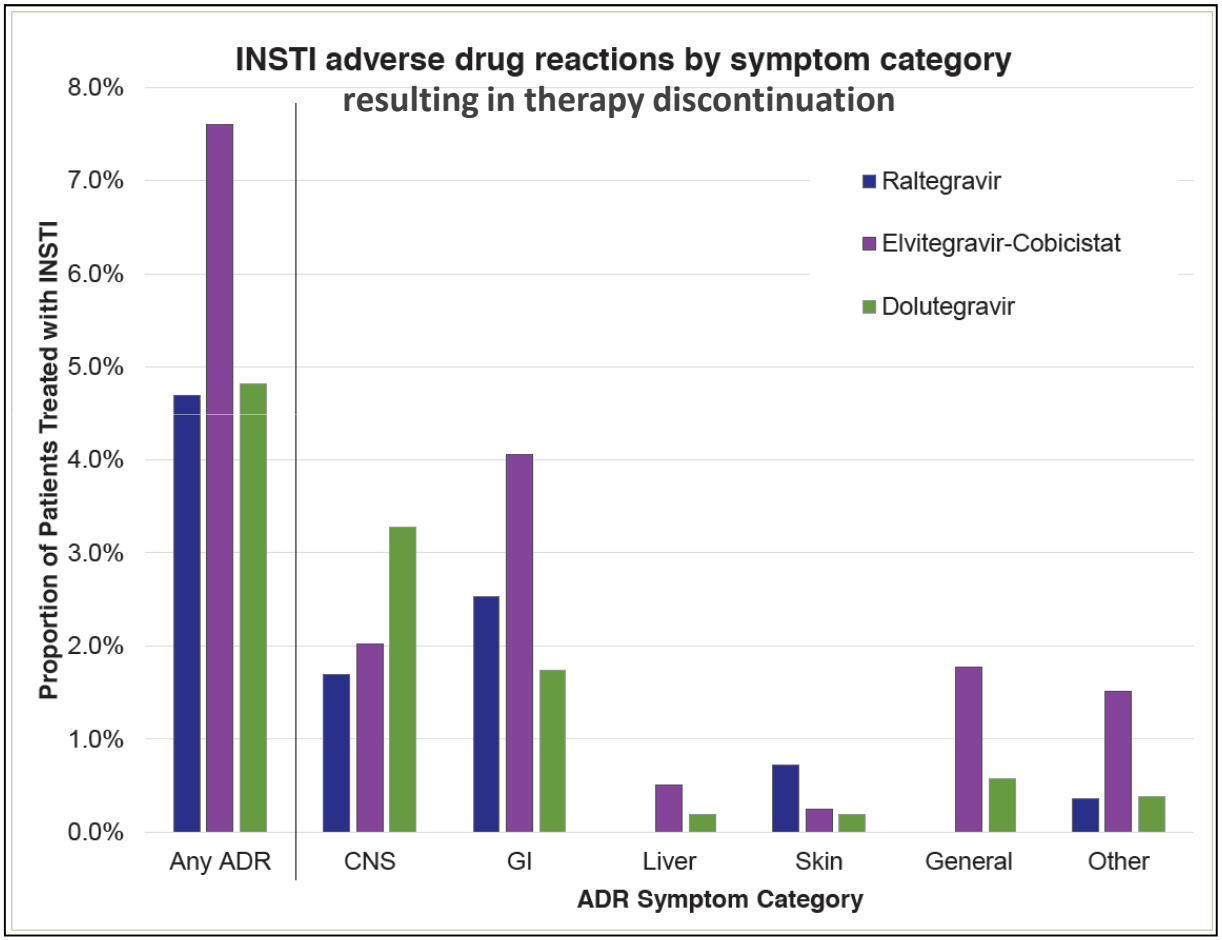
RAL 553, **EVG/c**, 395, **DTG** 519.

Adjusted ADR rate/100 p/y (95%CI):

RAL: 1.6 (0.6-4.1)
EVG/c: 4.5 (1.7-12-1)
DTG: 2.9 (1.1-8.0)

Adjusted relative rates ADR (95%CI):

RAL (ref): 1
EVG/c: 2.9 (2.8, 3.0)
DTG: 1.9 (1.8, 2.0)



- Gastrointestinal tract: Nausea, diarrhea, gastrointestinal discomfort.
- Central nervous system: Sleep disturbance, nightmares, headache.
- General: fatigue/ malaise (more common with elvitegravir-cobicistat.

- No serious ADRs (grade IV severity or leading to hospitalization) were reported.

IAS 2015. Vancouver; CA.

Any relationship between DTG toxicity & PK levels?

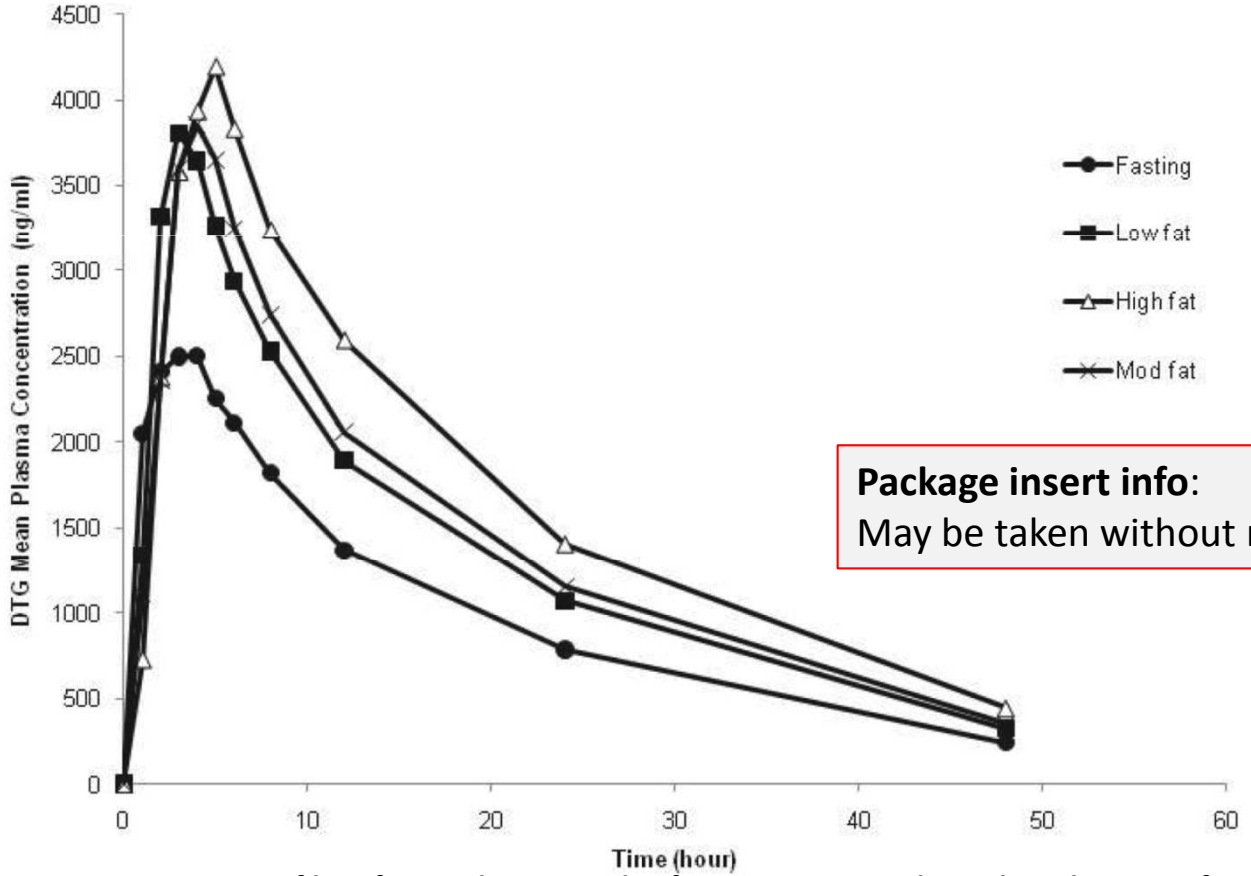
We noted **no association between DTG exposure and** virological response, **common adverse events**.

SPRING-2 Study (DTG vs RAL). F Raffi. Lancet 2013; 381: 735–43

- ✓ Influence of food on DTG PK
- ✓ Data in children (IMPAACT)(CROI 2016 and Ped Infect Dis)
- ✓ Data in phase II studies with different doses
- ✓ Data in salvage with double DTG dose

Food increases DTG exposure

The **AUC_{0-} increased by 33%, 41%, and 66%** when administered **with low-, moderate-, or high-fat meals**, respectively, compared with fasting.
This increase in DTG exposure is **not anticipated to impact clinical safety**, and therefore can be taken w or w/ food and w/ regard to fat content.



Package insert info:
May be taken without regard to meals

Mean concentration-time profiles of DTG administered in fasting state or with meals with various fat contents

I Song. AAAC 2012; 56:1627–1629

SPRING-1 Phase II Study. AEs (by System Organ Class)

Reported in >1 Subject, 48 weeks

	N=205	DTG 10mg (N=53)	DTG 25mg (N=51)	DTG 50mg (N=51)	DTG Subtotal (N=155)	EFV 600mg (N=50)
Grade 2-4 Drug Related (all)		5 (9%)	4 (8%)	4 (8%)	13 (8%)	10 (20%)
Gastrointestinal		1 (2%)	1 (2%)	1 (2%)	3 (2%)	2 (4%)
Psychiatric disorders		0	0	0	0	3 (6%)
Metabolic disorders		0	3 (6%)	1 (2%)	4 (3%)	0
Skin disorders		0	0	0	0	2 (4%)
Infections		2 (4%)	0	0	2 (1%)	0
General disorders		1 (2%)	0	1 (2%)	2 (1%)	1 (2%)
Serious Adverse Events (all)		3 (6%)	1 (2%)	4 (8%)	8 (5%)	4 (8%)
AEs Leading to WD/IP Discontinuation		0	1 (2%)	1 (2%)	2(1%)	4 (8%)

- **No SAEs judged related to DTG**
- **One SAE judged related to EFV (suicide attempt)**
- **No clear dose-response relationship in DTG AEs**
- **Events leading to withdrawal:**
  - **DTG (n=2): dyspepsia and Burkitt's lymphoma**
  - **EFV (n=4): abnormal dreams, suicide attempt, drug intolerance, drug hypersensitivity**

J van Lunzen. Lancet Infect Dis 2012;12: 111–18

Outcome at Week 24: <50 c/mL by TLOVR

VIKING Study.

Outcome	DTG 50 mg QD Cohort I (N=27)	DTG 50 mg BID Cohort II (N=24)
Responders	**11 (41%)**	**18 (75%)**
Non-responders	**16 (59%)**	**6 (25%)**
Virological Failure:		
Any	13 (48%)	5 (21%)
Never suppressed through Week 24	11 (41%)	4 (17%)
Rebound from <50c/mL	2 (7%)	1 (4%)
Non-Virological Failure:		
Any	3 (11%)	1 (4%)
Adverse event	1 (4%)	
Death	1 (4%)	
Non-permitted change in ART	1 (4%)*	1 (4%)**

No D/C Due to AEs with DTG 100 mg/day. No serious drug related AEs.

VIKING 3 Week 24-48. Safety
DTG 50 mg BID + OBR in salvage

- Open, single-arm. N= 183 subjects.

- **No new safety signals since Week 24 analysis**
  - Most common drug related AEs were nausea (6%) and diarrhea (5%)
  - **Insomnia 3% (only CNS symptom reported), none drug-related**.
  - **Few AEs leading to withdrawal**, n=5 (3%), **none psychiatric** *.
  - No new drug related SAE's since Week 24.

* hepatitis (3), rash, pruritus, paresthesia (1), and cholelithiasis (1).

Castagna et al. *J Infect Dis*. 2014;210:354–62.

Vavro et al. EUDRW 2014; Barcelona, Spain. Abstract O_10.

IMPAACT 1093: Dolutegravir in 6-12 Year Old HIV Infected Children: 48-Week Results

Andrew A. Wiznia[1], Carmelita Alvero[2], Terry Fenton[2], Kathleen George[3], Ellen Townley[4], Rohan Hazra[5], Bobbie Graham[6], Annie Buchanan[7], Cindy Vavro[7], Rolando Viani[8], and the P1093 Team

[1]Jacobi Medical Center, Albert Einstein College of Medicine, Bronx, NY, [2]Harvard School of Public Health, MA, [3]Family Health International, Durham, North Carolina, [4]NIAID, MD, [5]NICHD, MD, [6]Frontier Sciences Research Foundation Inc, NY, [7]ViiV Healthcare, NC, [8]University of California San Diego, CA

- Phase I/II multicenter open-label study.
- **n=23 children & adolescents** (age 12-18) with ARV-failure but naive to INI (≈SAILING). 48 week data.
- **Dose**: 50 mg/d if ≥40 kg; 35 mg if 30-40 kg (≈1 mg/kg/d).

- **PK data similar to adults**: GM AUC_{0-24} 46 µg/h/mL (target 37-67) and C_{24} 0.90 µg/mL (target 0.77-2.26).

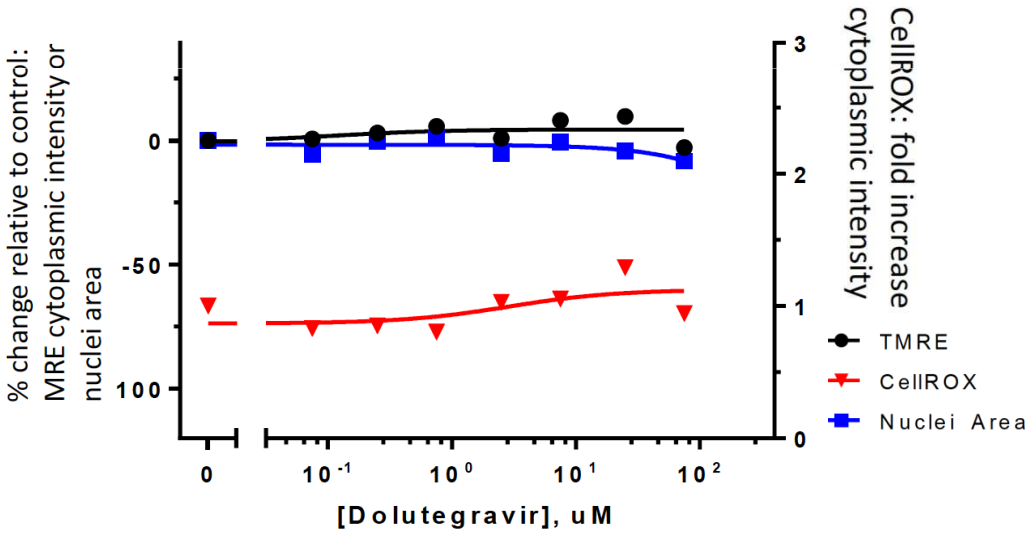
- **DTG was well tolerated**.
- Diarrea in 8(35%), decreased appetite in 7(30%), abdominal pain in 5(21%), dizziness in 4(17%), nausea in 3(13%). **No psych AEs**.
- None of the clinical AEs were considered related to DTG and **are common among adolescents with intercurrent illnesses**.

AA Wiznia. CROI 2016, #816. RM Viani. Ped Infect Dis J 2015;34:1207-1213.

Could DTG be neurotoxic?

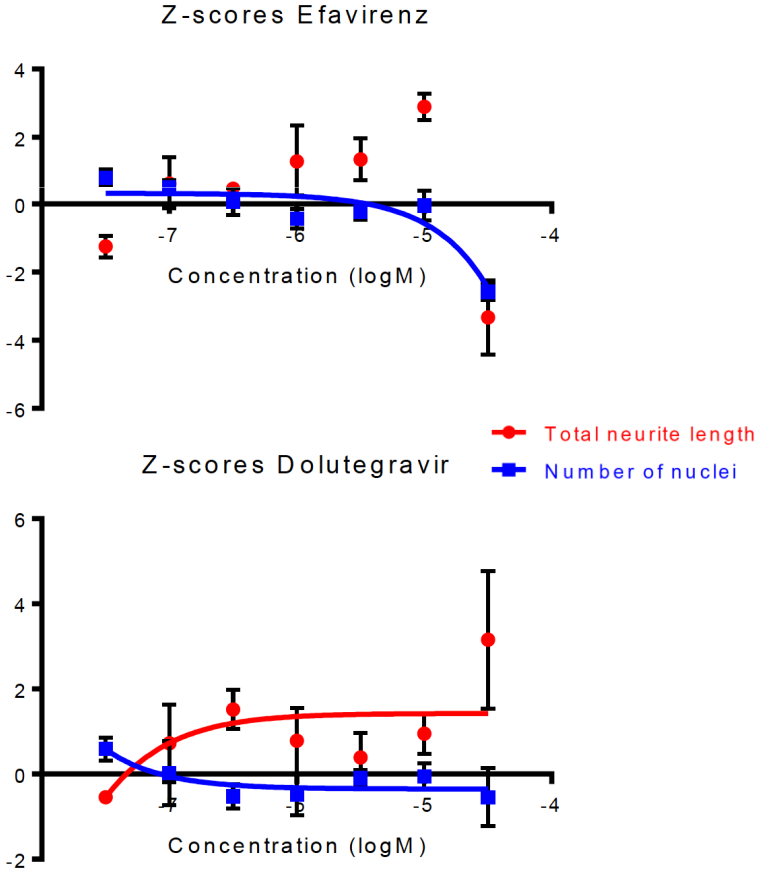
In a **non-validated *in vitro* live cell assay**, most ARV (NNRTIs the worse) drugs show a direct effect on neuronal mitochondrial function, morphology, and/or health. **DTG is one of the safest drugs** but **has a potential impact in neurite outgrowth length and branch**.

No Effect on Mitochondrial Function or Cell Health



iCell neurons were loaded with the mitochondrial membrane potentiometric dye TMRE and reactive oxygen species sensor CellROX deep red

No effect on neurite Outgrowth

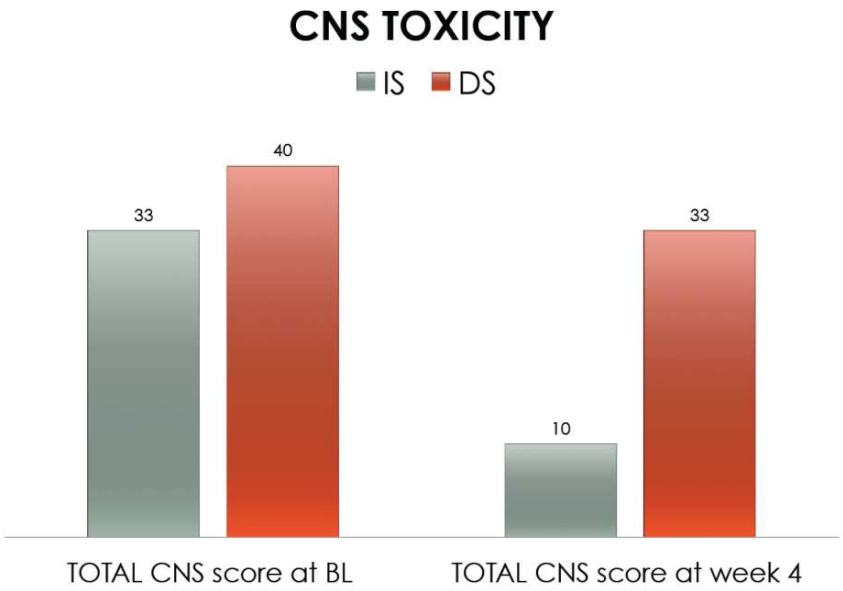


S Hinckley. CROI 2016. Boston, MA. #395.

Switching EFV to DTG for CNS toxicity.

SSAT056 Interim analysis results.

- Multicenter, open-label pilot study.
- **40 subjects** receiving **EFV** for ≥12 weeks with virological suppression.
- Randomized to IS or DS (at 4 weeks); all followed for 16 weeks.
- **Primary endpoint:** rate of CNS toxicity (CNS score) at 4 weeks in the IS vs DS arms, measured by a questionnaire based on EFV SPC, and graded according to ACTG AEs scale.



Significant improvement in:

- CNS score at week 4 in the IS arm vs DS arm ($p<0.001$).
- Combined (both arms) total CNS score after 4 weeks of DTG ($p<0.001$).
- Abnormal dreams in the IS vs DS arm at week 4 ($p<0.001$).
- Total Chol ($p<0.001$).

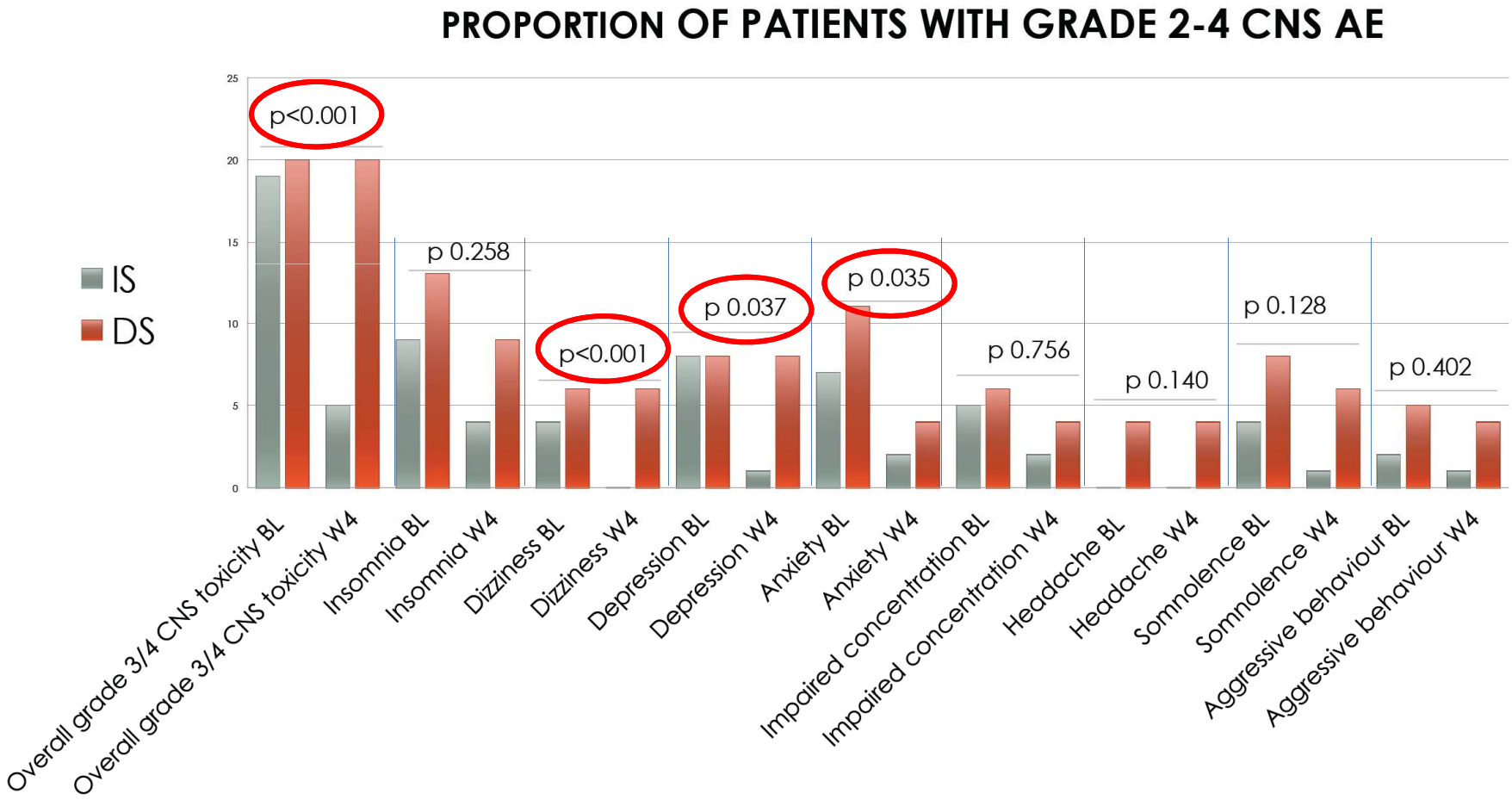
All patients maintained virological suppression.
No one D/C DTG.

M Bracchi. 22nd BHIVA Conference, #18

Switching EFV to DTG for CNS toxicity.

SSAT056 Interim analysis results.

Secondary endpoints.



M Bracchi. 22nd BHIVA Conference, #18

INI EMA SPCs. Psychiatric disorders.

(last updated)	Psych warning	Common (1% - <10%)	Uncommon (0.1% - 1%)
Raltegravir (9/03/2015)	Yes	abnormal dreams, insomnia, nightmare, abnormal behaviour, depression	mental disorder, suicide attempt, anxiety, confusional state, depressed mood, major depression, middle insomnia, mood altered, panic attack, sleep disorder, suicidal ideation, suicidal behaviour (particularly in patients with a pre-existing history of psychiatric illness)
Elvitegravir/c (24/05/2016)	No	insomnia, abnormal dreams	suicidal ideation and suicide attempt (in patients with a pre-existing history of depression or psychiatric illness), depression
DTG Tivicay, Triumeq (15/01/2016; 31/03/2016)	No	*Very common:* insomnia (Triumeq). *Common*: insomnia, abnormal dreams, depression, nightmare, sleep disorder	suicidal ideation or suicide attempt (particularly in patients with a pre-existing history of depression or psychiatric illness)

4.4 Special warnings and precautions for use

RAL: Depression, including suicidal ideation and behaviours, has been reported, particularly in patients with a pre-existing history of depression or psychiatric illness. Caution should be used in patients with a pre-existing history of depression or psychiatric illness.

4.7 All 3 (stronger for RAL): Dizziness may influence some patients' ability to drive and use machines.

Available at: http://www.ema.europa.eu/ema/ . Accessed May 25, 2016.

Conclusions & take homes

- ✓ **INI are among the safest class of ARV drugs we've had so far**.
- ✓ **Psych AEs have been reported with all them in RCT, at low rates**. All them have "common" psych AEs in their SPCs.
- ✓ **DTG drug levels do not** seem to **correlate with AEs**, robust data.
- ✓ Some **observational studies** are reporting unexpectedly high rates of D/C of DTG in real life. Their **methodological shortcomings** prevent drawing conclusions yet.
- ✓ Many **uncontrolled factors might be biassing** those analyses.

- ✓ There is a need to generate good-quality data in real-life settings.