EFFICACY AND SAFETY OF DOLUTEGRAVIR IN TREATMENT-NAIVE PEOPLE LIVING WITH HIV-1 STRATIFIED BY AGE: META-ANALYSIS OF 48-WEEK RESULTS FROM ARIA, FLAMINGO, SINGLE, AND SPRING-2

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Introduction

- People living with HIV (PLWH) are living longer because of advances in ART[1]
- Data on the efficacy and safety of ART regimens in older (aged ≥50 years) adults living with HIV (OALWH) are limited,[2] and OALWH have been historically underrepresented in clinical trials[3]
- Here, we evaluated the efficacy and safety profile of the INSTI DTG in ART-naive PLWH stratified by age group (<50, ≥50 to <65, and ≥65 years) from 4 phase III/IIIb clinical trials

Methods

Clinical Trials

- This meta-analysis combined data from the ARIA, FLAMINGO, SINGLE, and SPRING-2 trials (ClinicalTrials.gov identifiers: NCT01910402, NCT01449929, NCT01263015, and NCT01227824, respectively)[4-7]
- In each trial, ART-naive adults were randomized 1:1 to receive either a DTG- or comparator-based regimen (ATV/r in ARIA, DRV/r in FLAMINGO, EFV in SINGLE, and RAL in SPRING-2) in combination with 2 NRTIs for 48 weeks (Table 1)

Table 1. Characteristics of Clinical Trials

	Clinical trials			
	ARIA (N=495)	**FLAMINGO (N=484)**	**SINGLE (N=833)**	**SPRING-2 (N=822)**
Participant sex	100% female	85% male; 15% female	84% male; 16% female	86% male; 14% female
Masking	Open-label	Open-label	Double-blind	Double-blind
Intervention	DTG/ABC/3TC (n=248)	DTG + ABC/3TC or TDF/FTC (n=242)	DTG + ABC/3TC (n=414)	DTG + ABC/3TC or TDF/FTC (n=411)
Comparator	ATV/r + TDF/FTC (n=247)	DRV/r + ABC/3TC or TDF/FTC (n=242)	EFV/TDF/FTC (n=419)	RAL + ABC/3TC or TDF/FTC (n=411)

- Data were summarized by age group (<50, ≥50 to <65, and ≥65 years) and treatment (DTG and comparator)
- Unadjusted virologic suppression rates were estimated using a fixed-effects meta-analysis inverse-variance weighted combination of individual study estimates within age groups (<50 and ≥50 years)

Outcomes

- Baseline characteristics, including concomitant medications and comorbidities, were collected
- Endpoints at Week 48 were proportion of participants achieving virologic response (defined as plasma HIV-1 RNA <50 c/mL; FDA Snapshot algorithm) and change from baseline in mean CD4+ cell count
- Adverse events (AEs) were monitored and recorded

Results

Participants and Baseline Characteristics

- Overall, 2634 ART-naive PLWH were included in this pooled analysis (Table 2)

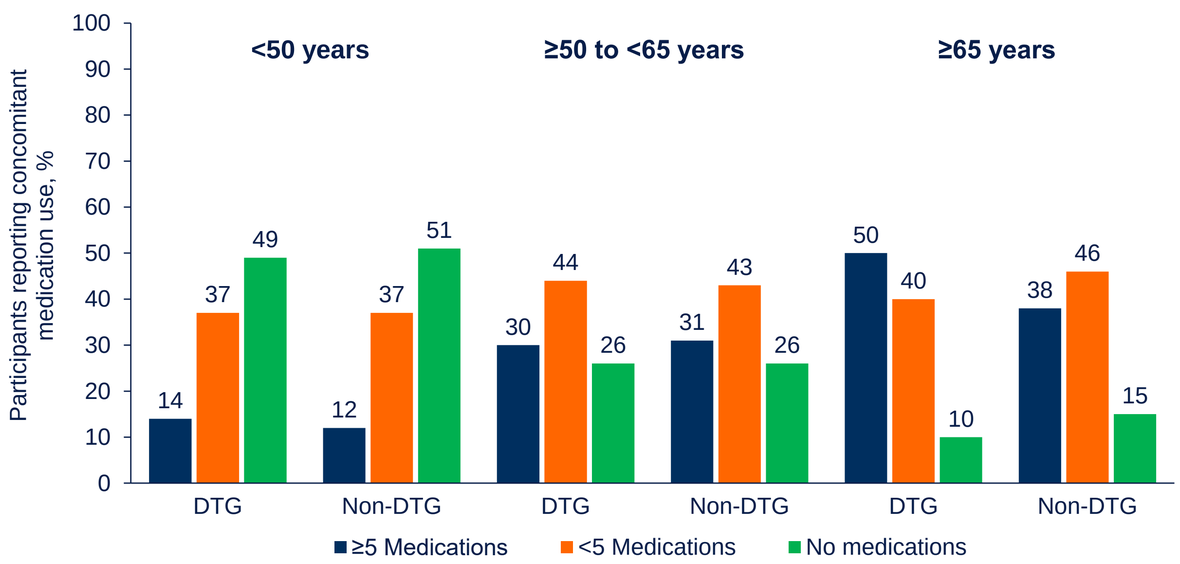
Table 2. Pooled Baseline Characteristics Stratified by Age Group

	<50 years		≥50 to <65 years		≥65 years	
n (%)	**DTG (N=1157)**	**Non-DTG (N=1158)**	**DTG (N=148)**	**Non-DTG (N=148)**	**DTG (N=10)**	**Non-DTG (N=13)**
CDC classification						
Asymptomatic or lymphadenopathy	989 (85)	976 (84)	118 (80)	123 (83)	7 (70)	10 (77)
Symptomatic, not AIDS	129 (11)	145 (13)	23 (16)	21 (14)	2 (20)	3 (23)
AIDS	39 (3)	37 (3)	7 (5)	4 (3)	1 (10)	0
Most prevalent HIV risk factors (>20% in any group)						
Homosexual contact	646 (57)[a]	641 (57)[a]	57 (39)[b]	61 (44)[b]	2 (20)	1 (8)[c]
Heterosexual contact	459 (41)[a]	451 (40)[a]	84 (58)[b]	68 (49)[b]	8 (80)	10 (83)[c]
HIV-1 RNA, c/mL						
>100,000	321 (28)	326 (28)	51 (34)	43 (29)	6 (60)	5 (38)
CD4+ cell count, cells/mm^3						
<200	167 (14)	164 (14)	28 (19)	19 (13)	4 (40)	2 (15)
200 to <350	390 (34)	372 (32)	52 (35)	47 (32)	4 (40)	4 (31)
≥350	600 (52)	622 (54)	68 (46)	82 (55)	2 (20)	7 (54)

[a]For DTG, n=1126; for non-DTG, n=1130. [b]For DTG, n=145; for non-DTG, n=140. [c]For non-DTG, n=12.

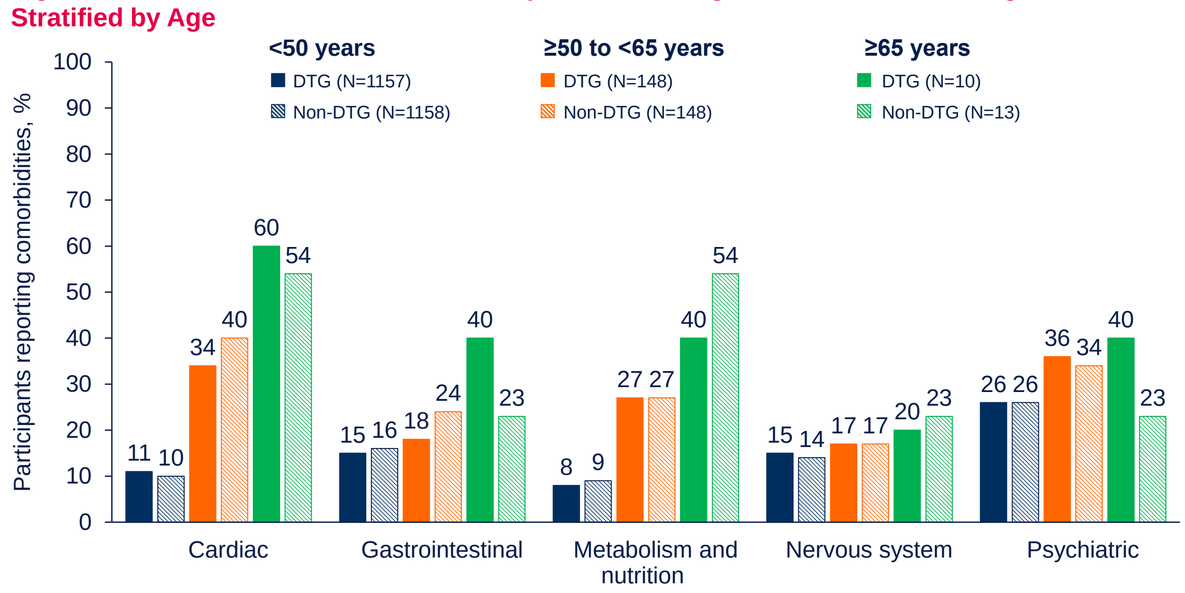
- Higher proportions of participants aged ≥50 years reported heterosexual contact as a risk factor for HIV compared with those aged <50 years
- Use of concomitant medications increased with age in the DTG and non-DTG groups (Figure 1)

Figure 1. Rates of Concomitant Medication Use in Participants Receiving DTG and Non-DTG Regimens Stratified by Age



- Generally, rates of comorbidities increased with age in both the DTG and non-DTG groups (Figure 2)
  - Rates of hypertension were higher in those aged ≥50 to <65 years (DTG, 31%; non-DTG, 37%) and those aged ≥65 years (DTG, 60%; non-DTG, 54%) relative to those aged <50 years (DTG, 9%; non-DTG, 7%)
  - Rates of type 2 diabetes were also higher in those aged ≥50 to <65 years (DTG, 8%; non-DTG, 13%) and those aged ≥65 years (DTG, 30%; non-DTG, 23%) relative to those aged <50 years (DTG, 1%; non-DTG, 2%)

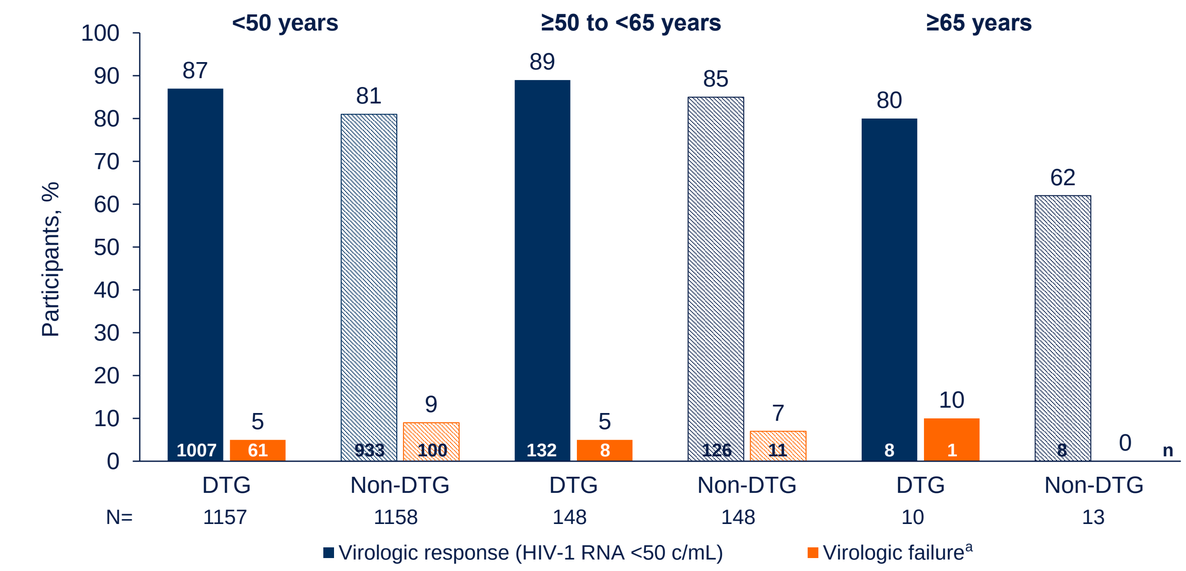
Figure 2. Rates of Comorbidities in Participants Receiving DTG and Non-DTG Regimens Stratified by Age



Virologic Response and CD4+ Cell Count at Week 48

- Rates of virologic response at Week 48 were generally similar within the DTG and non-DTG groups across age strata (Figure 3)
- Generally, across age strata, mean (SD) change from baseline in CD4+ cell count was comparable in the DTG and non-DTG groups (<50 years: 250.7 [180.4] vs 230.0 [176.6] cells/mm^3; ≥50 to <65 years: 249.6 [183.9] vs 235.9 [168.6] cells/mm^3; ≥65 years: 234.1 [120.1] vs 112.6 [301.5] cells/mm^3)
- Virologic response rates (%) between DTG and non-DTG groups were significantly different in favor of DTG for those aged <50 years (treatment difference, 6.2; 95% CI, 3.3-9.1; *P*<0.0001), whereas those aged ≥50 years showed no significant difference (treatment difference, 5.1; 95% CI, −2.4, 12.6; *P*=0.1819)

Figure 3. Combined Snapshot Virologic Outcomes at Week 48 Across Age Strata



[a]Includes HIV-1 RNA ≥50 c/mL, discontinuation due to lack of efficacy or other reason, or change in ART.

Safety

- For all age groups, participants in the non-DTG group experienced more adverse drug reactions and AEs leading to withdrawal by Week 48 than those in the DTG group (Table 3)

Table 3. Combined Safety Outcomes at Week 48

	<50 years		≥50 to <65 years		≥65 years	
n (%)	**DTG (N=1157)**	**Non-DTG (N=1158)**	**DTG (N=148)**	**Non-DTG (N=148)**	**DTG (N=10)**	**Non-DTG (N=13)**
All AEs	972 (84)	989 (85)	134 (91)	131 (89)	8 (80)	12 (92)
Serious AEs	81 (7)	75 (6)	21 (14)	20 (14)	1 (10)	3 (23)
Adverse drug reactions	406 (35)	567 (49)	57 (39)	70 (47)	3 (30)	7 (54)
AEs leading to withdrawal	33 (3)	73 (6)	2 (1)	9 (6)	0	3 (23)

Conclusions

- In OALWH, increased age was generally associated with higher rates of concomitant medication use and comorbidities
- Regardless of age, PLWH naive to ART who were treated with DTG-based regimens achieved similar increases from baseline in CD4+ cell count
- After 48 weeks of treatment, virologic response rates were high and significantly favored the DTG group vs the non-DTG group in participants aged <50 years. In participants aged ≥50 years, response rates were consistent with those in the younger age group, with no significant differences between treatment groups
- Overall AE rates were similar across treatment groups and age groups; adverse drug reactions and AEs leading to withdrawals occurred at lower rates in the DTG group vs the non-DTG group, regardless of age

Please join us on Thursday, 8th October, for one of the two live Meet the Experts Q&A sessions with our senior medical experts around our most recent data presented at HIV Glasgow 2020.

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References: 1. Nideröst and Imhof. *Gerontol Geriatr Med.* 2016;2:2333721416636300. **2.** Nguyen and Holodniy. *Clin Interv Aging.* 2008;3:453-472. **3.** Johnston and Heitzeg. *AIDS Res Hum Retroviruses.* 2015;31:85-97. **4.** Orrell et al. *Lancet HIV.* 2017;4:e536-e546. **5.** Clotet et al. *Lancet.* 2014;383:2222-2231. **6.** Walmsley et al. *N Engl J Med.* 2013;369:1807-1818. **7.** Raffi et al. *Lancet*. 2013;381:735-743.

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