# Update on 2 drug regimens

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# Disclosures

- Gilead – grants, honoraria
- Merck – grants, honoraria
- ViiV Healthcare - honoraria

# Outline

## Oral 2DR

- ART naives - GEMINI 1 & 2
- ART switch – TENGO
- ART switch - SWORD

## Long acting injectable 2DR

- ATLAS & FLAIR combined analysis

## Islatravir (MK-8591) plus doravirine 2DR

## Conclusions

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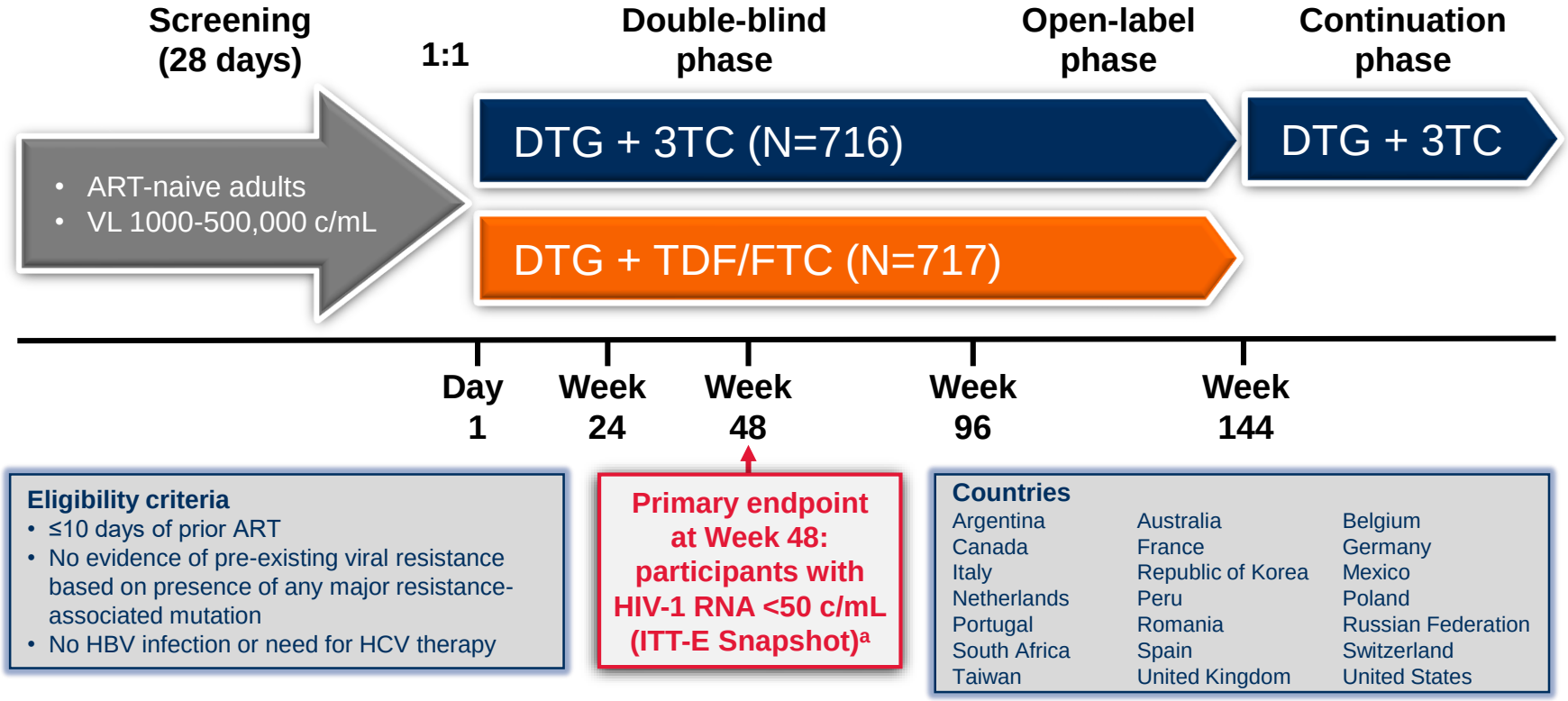
## Islatravir (MK-1598) plus doravirine 2DR

## Conclusions

# GEMINI-1 and -2 Phase III Study Designs

**Identically designed, randomized, double-blind, parallel-group, multicenter, non-inferiority studies**




**Baseline stratification factors:** plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL) and CD4+ cell count (≤200 vs >200 cells/mm$^3$).

[a]–10% non-inferiority margin for individual studies.

Cahn et al. *Lancet.* 2018 [Epub ahead of print].

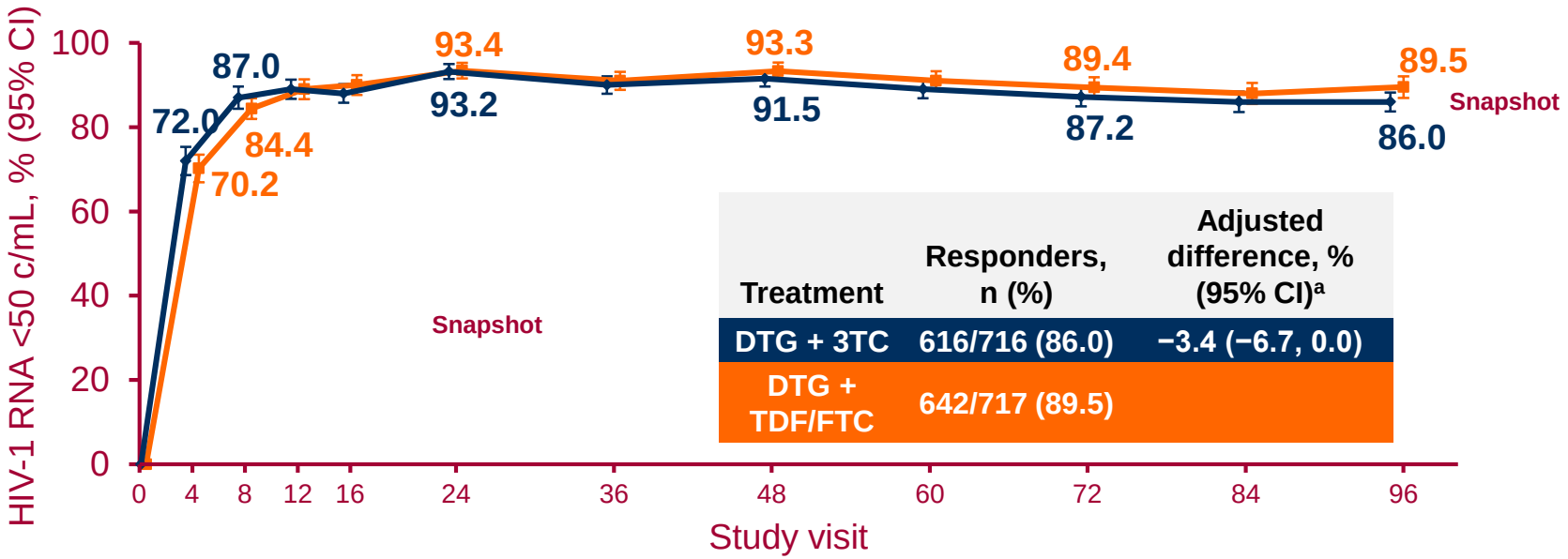
# Demographic and Baseline Characteristics for the Pooled GEMINI-1 and -2 Population

| Characteristic | DTG + 3TC (N=716) | DTG + TDF/FTC (N=717) |
|---|---|---|
| **Age, median (range), y** | 32.0 (18-72) | 33.0 (18-70) |
| ≥50 y, n (%) | 65 (9) | 80 (11) |
| **Female, n (%)** | 113 (16) | 98 (14) |
| **Race, n (%)** | | |
| White | 480 (67) | 497 (69) |
| African American/African heritage | 99 (14) | 76 (11) |
| Asian | 71 (10) | 72 (10) |
| Other | 66 (9) | 72 (10) |
| **Ethnicity, n (%)** | | |
| Hispanic or Latino | 215 (30) | 232 (32) |
| Not Hispanic or Latino | 501 (70) | 485 (68) |
| **HIV-1 RNA, median (range), $log_{10}$ c/mL** | 4.43 (1.59-6.27) | 4.46 (2.11-6.37) |
| ≤100,000 | 576 (80) | 564 (79) |
| >100,000 | 140 (20) | 153 (21) |
| >250,000 | 51 (7) | 46 (6) |
| >400,000 | 18 (3) | 24 (3) |
| >500,000[a] | 13 (2) | 15 (2) |
| **CD4+ cell count, median (range), cells/mm$^3$** | 427.0 (19-1399) | 438.0 (19-1497) |
| ≤200 | 63 (9) | 55 (8) |
| >200 | 653 (91) | 662 (92) |

[a]Participants were required to have HIV-1 RNA ≤500,000 c/mL at screening. Other than 1 participant enrolled without meeting study entry criteria, these participants had an observed increase in HIV-1 RNA between screening and baseline.

Cahn et al. *Lancet.* 2018 [Epub ahead of print].

# GEMINI: primary endpoint (snapshot HIV-RNA <50 c/mL) at week 96




| Treatment | Responders, n (%) | Adjusted difference, % (95% CI)[a] |
|---|---|---|
| DTG + 3TC | 616/716 (86.0) | −3.4 (−6.7, 0.0) |
| DTG + TDF/FTC | 642/717 (89.5) | |

**Non-inferiority criteria were met for GEMINI-1, GEMINI-2, and the pooled analysis[b]**

[a]Based on Cochran-Mantel-Haenszel stratified analysis adjusting for the following baseline stratification factors: plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL), CD4+ cell count (≤200 vs >200 cells/mm$^3$), and study (GEMINI-1 vs GEMINI-2). The upper limit of the 95% CI for the pooled analysis was 0.0007%.

[b]In GEMINI-1, HIV-1 RNA <50 c/mL (95% CI) was achieved in 300/356 participants (84.3% [80.5-88.1]) in the DTG + 3TC group and 320/358 (89.4% [86.2-92.6]) in the DTG + TDF/FTC group (adjusted treatment difference [95% CI], −4.9% [−9.8, 0.03]). In GEMINI-2, the corresponding values were 316/360 (87.8% [84.4-91.2]) and 322/359 (89.7% [86.5-92.8]), respectively (adjusted treatment difference [95% CI], −1.8% [−6.4, 2.7]).

Cahn et al. IAS 2019; Mexico City, Mexico. Slides WEAB0404LB.

# GEMINI 1 & 2: treatment emergent resistance at confirmed virological failure

| | | GEMINI-1 | | GEMINI-2 | | Pooled | |
|---|---|---|---|---|---|---|---|
| | **Variable, n (%)** | **DTG + 3TC (N=356)** | **DTG + TDF/FTC (N=358)** | **DTG + 3TC (N=360)** | **DTG + TDF/FTC (N=359)** | **DTG + 3TC (N=716)** | **DTG + TDF/FTC (N=717)** |
| Week 48 | CVW | 4 (1.1) | 2 (0.6) | 2 (0.6) | 2 (0.6) | 6 (0.8) | 4 (0.6) |
| Week 96 | CVW | 5 (1.4) | 4 (1.1)[a] | 6 (1.7) | 3 (0.8) | 11 (1.5) | 7 (1.0)[a] |
| | **Treatment-emergent resistance** | **0** | **0** | **0** | **0** | **0** | **0** |

[a]One participant met the criteria for CVW at Week 12 but was not reported at the Week 48 analysis because of a laboratory repo rting error identified after the Week 48 analysis.

Cahn et al. IAS 2019; Mexico City, Mexico. Slides WEAB0404LB.

# GEMINI 1 & 2: Adverse event profile

| n (%) | DTG + 3TC (N=716) | DTG + TDF/FTC (N=717) |
|---|---|---|
| **Any AE** | **591 (83)** | **609 (85)** |
| **AEs occurring in ≥10% of participants in either group** | | |
| Nasopharyngitis | 71 (10) | 114 (16) |
| Diarrhea | 89 (12) | 93 (13) |
| Headache | 79 (11) | 87 (12) |
| **Drug-related AEs[a]** | **140 (20)** | **179 (25)** |
| **Any Grade 2-5 drug-related AEs** | **50 (7)** | **57 (8)** |
| **Grade 2-5 drug-related AEs occurring in ≥1% of participants** | | |
| Headache | 8 (1) | 8 (1) |
| **AEs leading to withdrawal from the study** | **24 (3)** | **23 (3)** |
| **AEs of interest leading to withdrawal from the study** | | |
| Neuropsychiatric | 10 (1) | 5 (1) |
| Renal-related | 2 (<1) | 7 (1) |
| Osteoporosis | 0 | 2 (<1) |
| **Any serious AE[b]** | **64 (9)** | **67 (9)** |

- Increased weight was reported as an AE in 13 (1.8%) participants treated with DTG + 3TC and in 10 (1.4%) treated with DTG + TDF/FTC
  - Overall mean change from baseline was 3.1 kg in the DTG + 3TC group and 2.1 kg in the DTG +TDF/FTC group

[a]Relative risk (95% CI) for the DTG + 3TC vs DTG + TDF/FTC group was 0.78 (0.64, 0.95).
[b]3 deaths (acute myocardial infarction, n=1; Burkitt's lymphoma, n=1; coronary artery disease, n=1), 1 in GEMINI-1 and 2 in GEMINI-2; all were in the DTG + 3TC group and were considered unrelated to the study drug regimen.

Cahn et al. IAS 2019; Mexico City, Mexico. Slides WEAB0404LB.

# GEMINI 1 & 2: VL decline through 48 Weeks: Pooled ITT-E Population

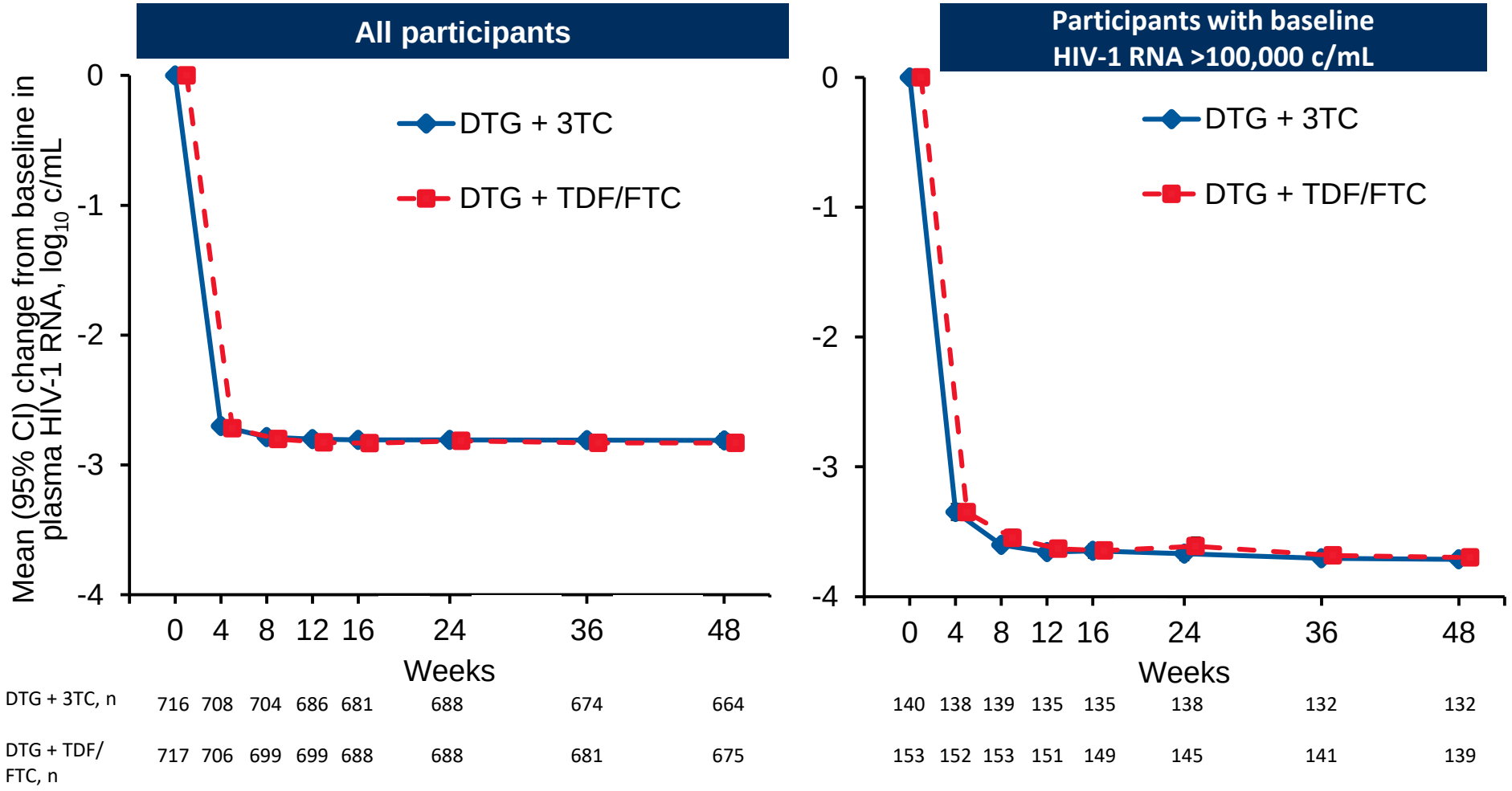
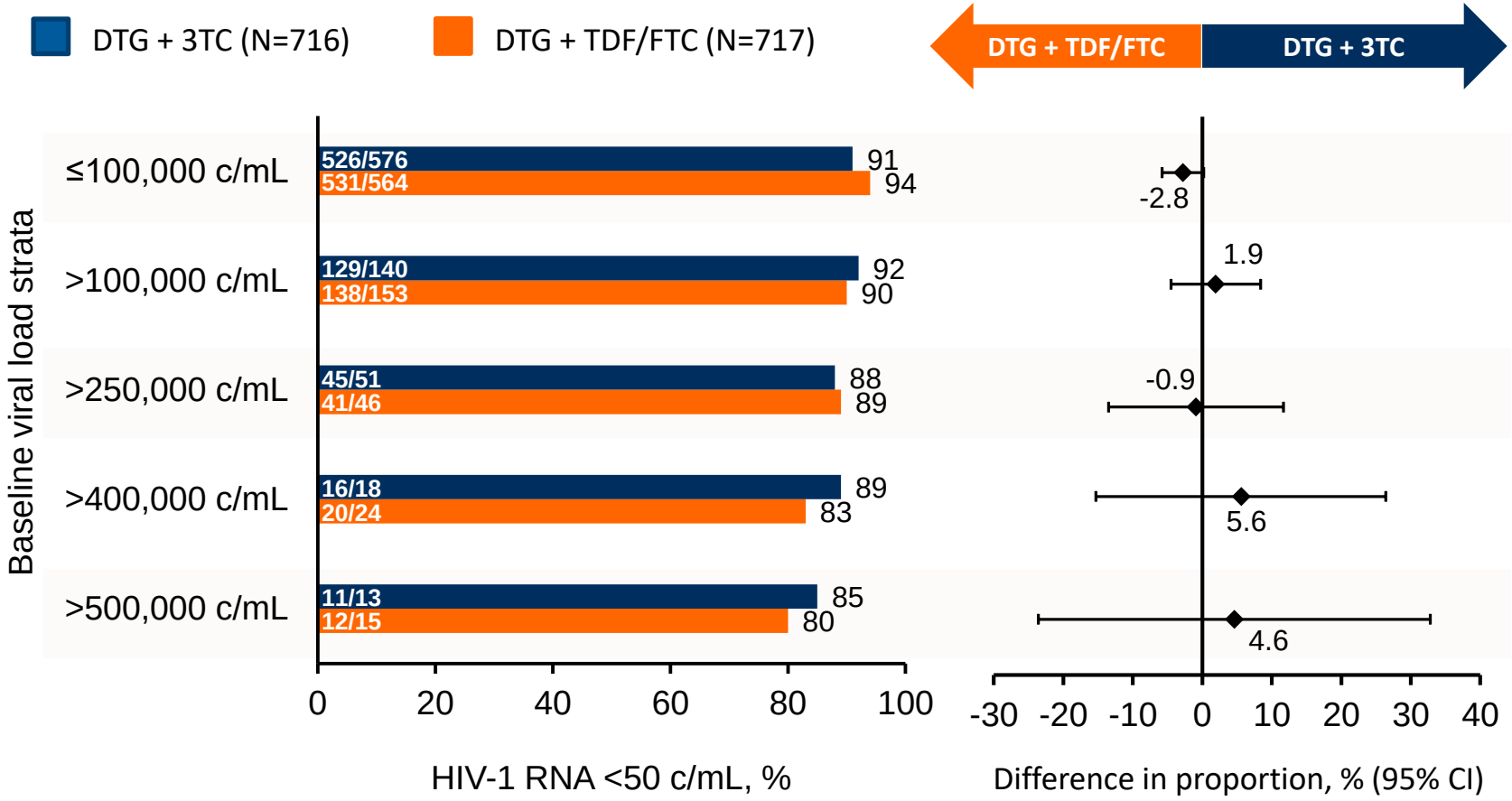



Figure on the left reproduced from Cahn et al. *Lancet.* 2018 [Epub ahead of print]. With permission from Elsevier.

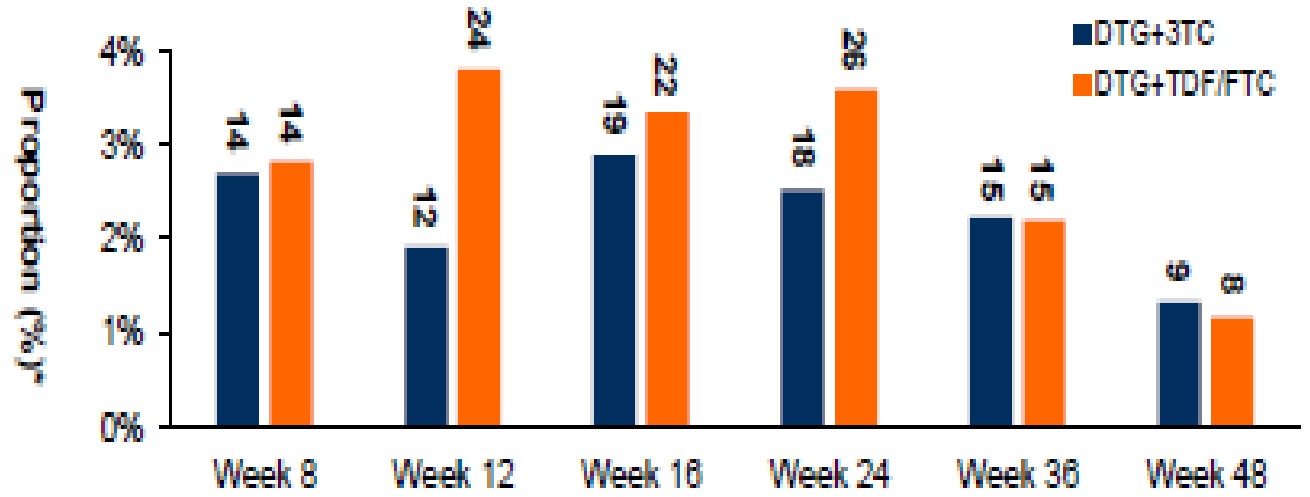
# GEMINI 1 & 2: Proportion of participants with VL <50 c/mL at Week 48 (snapshot analysis) by baseline VL: Pooled ITT-E Population




Cahn et al. *Lancet.* 2018 [Epub ahead of print].

Eron et al. HIV DART and Emerging Viruses 2018; Miami, FL. Oral Presentation #7.

# GEMINI 1 & 2: VL blip frequencies and number by visit week




*Percentages were calculated from number of blips (Table 1, category 1a) using previously suppressed (<50 c/mL) participant Ns, respectively, for DTG + 3TC and DTG + TDF/FTC at Wk 8 (N=517) and (N=496); Wk 12 (N=625) and (N=632); Wk 16 (N=657) and (N=659); Wk 24 (N=714) and (N=726); Wk 36 (N=674) and (N=683); and Wk 48 (N=678) and (N=691). Bold numbers on chart are # of blips at given week visits. Individual participants can have had more than one blip.

- Similar 'blip' frequencies were seen across arms by visit week.
- Cumulative occurrences: DTG + 3TC (N=87); DTG + TDF/FTC (N=109).

Underwood M, et al. IAS Mexico 2019. Abstract # MOPEB321

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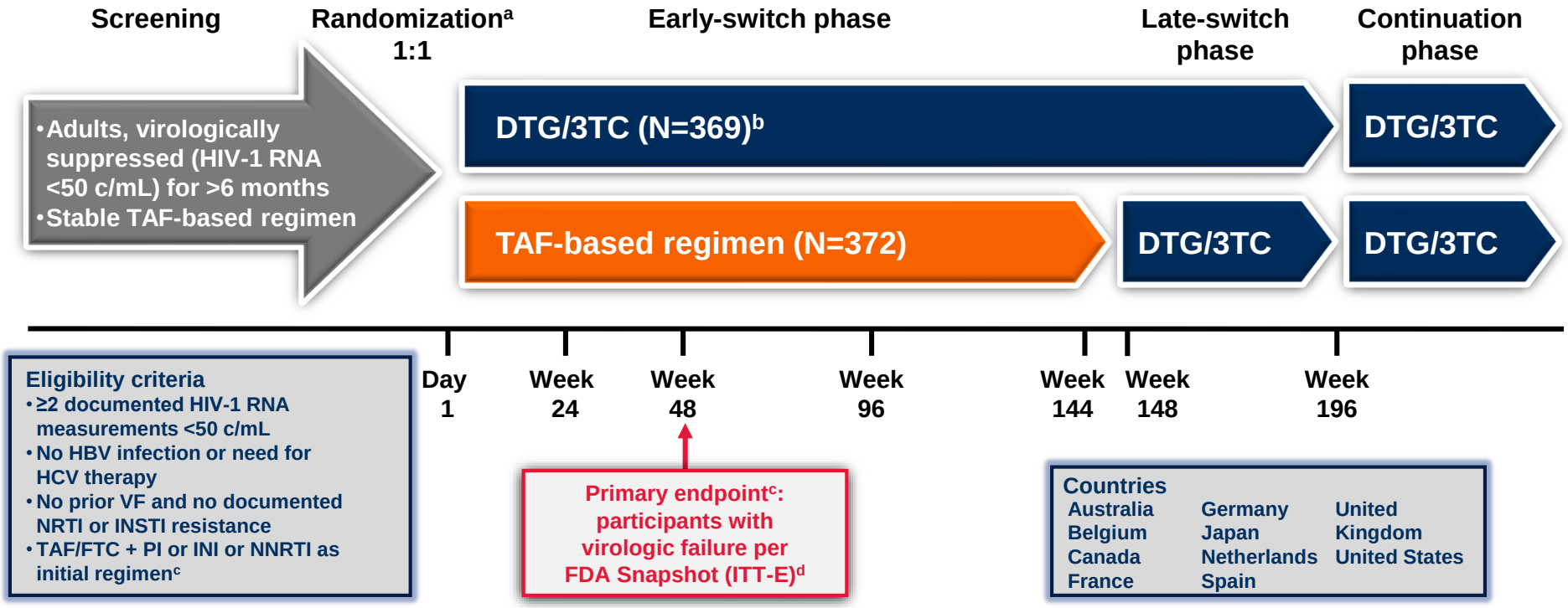
# TANGO Phase III Study Design

**Randomized, open-label, multicenter, parallel-group, non-inferiority study**

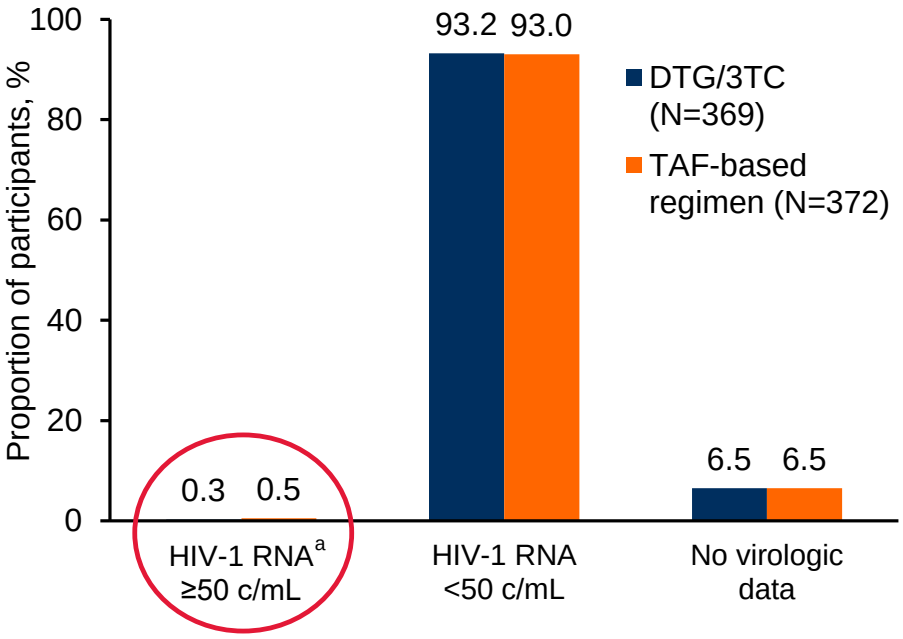



[a]Stratified by baseline third agent class (PI, INI, or NNRTI). [b]Two patients excluded who were randomized but not exposed to study drug. [c]Participants with initial TDF treatment who switched to TAF ≥3 months before screening, with no changes to other drugs in their regimen, were also eligible. [d]4% non-inferiority margin. [e]Includes participants who changed a background therapy component or discontinued study treatment for lack of efficacy before Week 48, or who had HIV-1 RNA ≥50 c/mL in the 48-week window.

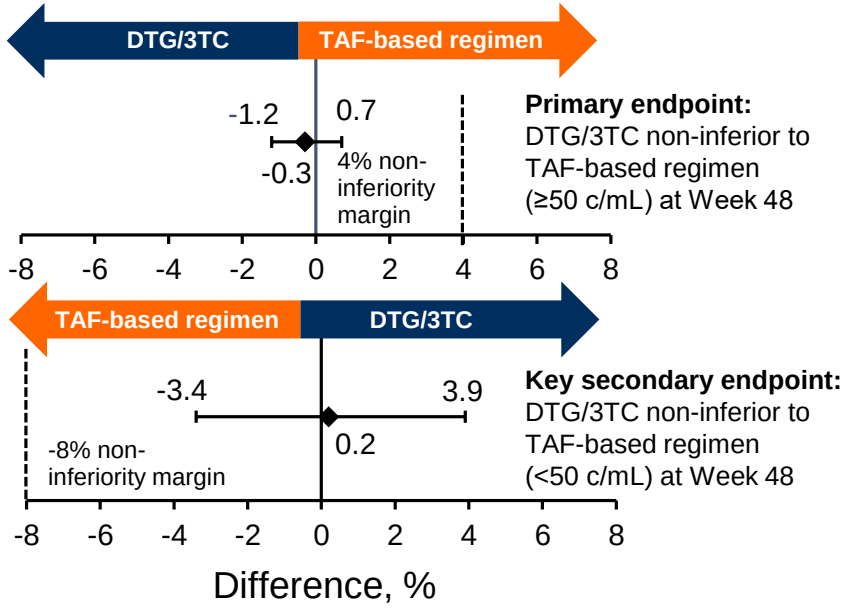
van Wyk et al. IAS 2019; Mexico City, Mexico. Slides WEAB0403LB.

# TANGO: primary endpoint (snapshot HIV-RNA <50 c/mL) at week 48

## Virologic outcomes




## Adjusted treatment difference (95% CI)[b]




- In the per-protocol population, 0/352 participants in the DTG/3TC group and 2/358 participants in the TAF-based regimen group had HIV-1 RNA ≥50 c/mL at Week 48 (adjusted difference, −0.6; 95% CI, −1.3 to 0.2)[b]

[a]Primary endpoint (Snapshot virologic non-response, ITT-E). [b]Based on Cochran-Mantel-Haenszel stratified analysis adjusting for baseline third agent class.

van Wyk et al. IAS 2019; Mexico City, Mexico. Slides WEAB0403LB.

# TANGO: Treatment emergent resistance at confirmed virological failure

| n (%) | DTG/3TC (N=369) | TAF-based regimen (N=372) |
|---|---|---|
| **Confirmed virologic withdrawal (CVW)[a]** | 0 | 1 (<1)[b] |
| **Observed resistance mutation at failure[c]** | 0 | 0 |

[a]One assessment with HIV-1 RNA ≥200 c/mL after Day 1 with an immediately prior HIV-1 RNA ≥50 c/mL.
[b]Treatment interrupted before suspected virologic withdrawal (VL, 38,042 c/mL) and resumed 3 weeks before VL retest (297 c/mL).
[c]Plasma HIV-1 RNA resistance genotype at failure is compared with baseline PBMC pro-viral resistance genotype.

van Wyk et al. IAS 2019; Mexico City, Mexico. Slides WEAB0403LB.

# TANGO: Adverse event profile

| n (%) | DTG/3TC (N=369) | TAF-based regimen (N=371) |
|---|---|---|
| **Any AE** | **295 (80)** | **292 (79)** |
| Nasopharyngitis | 43 (12) | 41 (11) |
| Upper respiratory tract infection | 31 (8) | 32 (9) |
| Diarrhea | 30 (8) | 26 (7) |
| Headache | 24 (7) | 17 (5) |
| Syphilis | 24 (7) | 13 (4) |
| Back pain | 21 (6) | 28 (8) |
| Fatigue | 20 (5) | 3 (1) |
| Bronchitis | 8 (2) | 20 (5) |
| **Any drug-related Grade 2-5 AE** | **17 (5)** | **3 (1)** |
| **Drug-related Grade 2-5 AEs occurring in ≥0.5%[a]** | | |
| Insomnia | 4 (1) | 0 |
| Constipation | 2 (1) | 1 (<1) |
| Flatulence | 2 (1) | 0 |
| Headache | 2 (1) | 0 |
| **AEs leading to withdrawal from the study** | **13 (4)[b]** | **2 (1)** |
| Drug-related AEs leading to withdrawal from the study | 9 (2) | 1 (<1) |
| **Any SAE[c]** | **21 (6)[b]** | **16 (4)** |

- At Week 48, a similar adjusted mean increase from baseline in weight of 0.8 kg was observed in both treatment groups
- Increased weight was reported as an AE in 3 (1%) participants treated with DTG/3TC and in 6 (2%) treated with a TAF-based regimen

SAE, serious adverse event.

[a]All drug-related AEs were of grade 2. [b]One fatal AE occurred (homicide). [c]No SAEs were drug related.

van Wyk et al. IAS 2019; Mexico City, Mexico. Slides WEAB0403LB.

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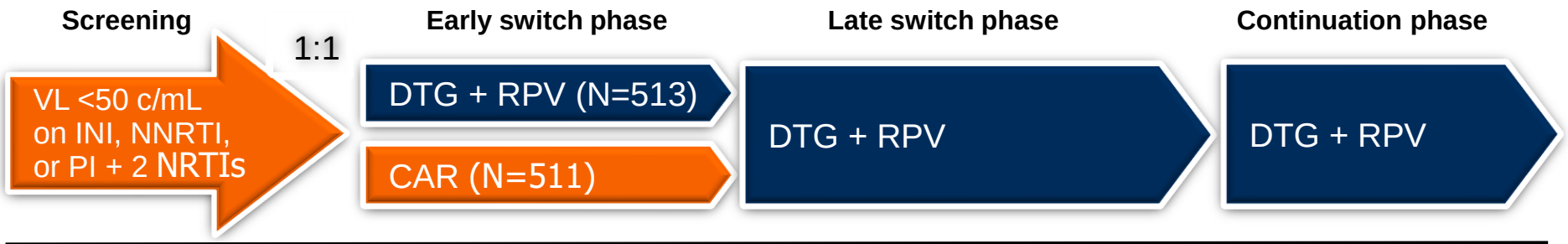
# SWORD 1 & 2
# Phase III Study Design

**Identically designed, randomized, multicenter, open-label, parallel-group, non-inferiority studies**




**Inclusion criteria**

- On stable CAR ≥6 months before screening
- 1st or 2nd ART with no change in prior regimen due to VF
- Confirmed HIV-1 RNA <50 c/mL during the 12 months before screening
- HBV negative

**Primary endpoint at 48 weeks: subjects with VL <50 c/mL (ITT-E snapshot)[a]**

**Countries**

Argentina, Australia, Belgium, Canada, France, Germany, Italy, Netherlands, Russia, Spain, Taiwan, United Kingdom, United States

[a]-8% non-inferiority margin for pooled data. -10% non-inferiority margin for individual studies

van Wyk et al. BHIVA 2019; Bournemouth, UK. Poster P008.

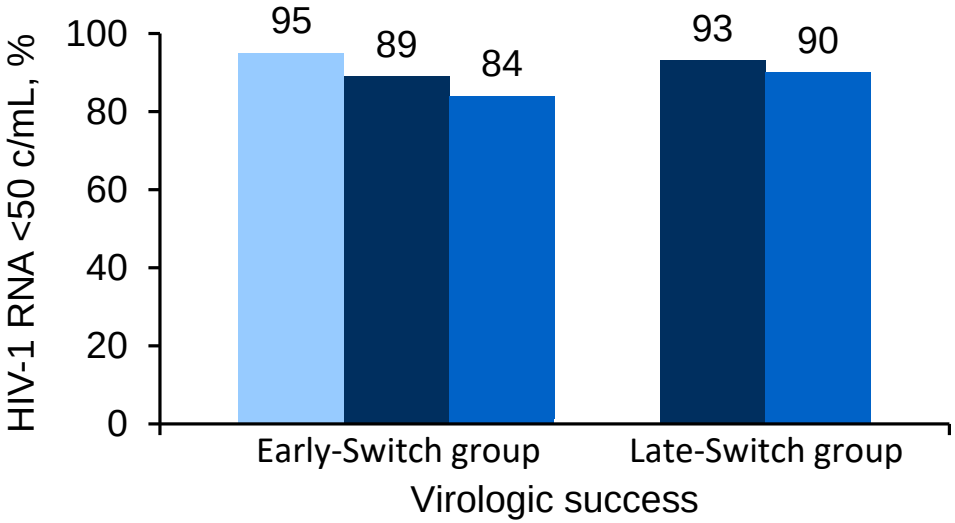
# SWORD 1 & 2: HIV-1 RNA <50 c/mL (FDA snapshot) at weeks 48, 100, and 148

**Study Disposition**

- Overall, 990 participants received DTG + RPV treatment (Early-Switch group, n=513; Late-Switch group, n=477)

**Virologic Efficacy**

- Through 148 weeks of treatment, DTG + RPV continued to be efficacious in the Early-Switch group
- Virologic efficacy in the Late-Switch group at Week 148 was similar to that in the Early-Switch group at Week 100




**Early-Switch group**

DTG + RPV, Day 1 to Week 48 (n=513)

DTG + RPV, Day 1 to Week 100 (n=513)

DTG + RPV, Day 1 to Week 148 (n=513)

**Late-Switch group**

DTG + RPV, Week 52 to Week 100 (n=477)

DTG + RPV, Week 52 to Week 148 (n=477)

van Wyk et al. BHIVA 2019; Bournemouth, UK. Poster P008.

# SWORD 1 & 2: confirmed virologic failure from week 100-148 in those exposed to DTG + RPV

- Through Week 148, there was a low number of confirmed virologic withdrawals (CVWs) across study populations who received DTG + RPV (1%; 11/990)
- Three CVWs occurred between the Week 100 analysis and Week 148

| Week of failure | Previous regimen | Viral loads, copies/mL[c] | Resistance mutations[b] | | | | Fold change | |
|---|---|---|---|---|---|---|---|---|
| | | | Baseline (GenoSure[d]) | | Confirmed virologic withdrawal | | | |
| | | | NNRTI | INSTI | NNRTI | INSTI | DTG | RPV |
| W112 | RAL/TDF/FTC | <u>118</u>; 230; 324 | None | E157Q, G193E, T97T/A | M230M/L | E157Q, G193E | 1.47 | 2 |
| W112 | DRV, RTV, TDF/FTC | <u>148</u>; 219; 307 | ND | | ND | | ND | |
| W136[e] | EFV/TDF/FTC | <u>4294</u>; 7247; 40,020; 3378 | NR[f] | | E138A, L100L/I | NR[f] | — | 4.14 |

ND, not determined; NR, not reported. [a]There was an additional participant with confirmed virologic withdrawal at Week 160. However, blood collected with the first elevated viral load was collected as a protocol deviation on the day of DTG + RPV reinitiation after treatment interruption due to injuries sustained in a motor vehicle accident. [b]Shading represents participants with NNRTI RAMs. [c]Underlined value denotes viral load when participant met virologic withdrawal. [d]HIV-1 baseline resistance testing was performed on integrated HIV-1 proviral DNA using GenoSure Archive® assay (Monogram Biosciences, South San Francisco, CA). On-study resistance testing used standard plasma-based genotypic and phenotypic resistance testing. [e]Participants in the Late-Switch group. [f]Sample failed testing.

van Wyk et al. BHIVA 2019; Bournemouth, UK. Poster P008.

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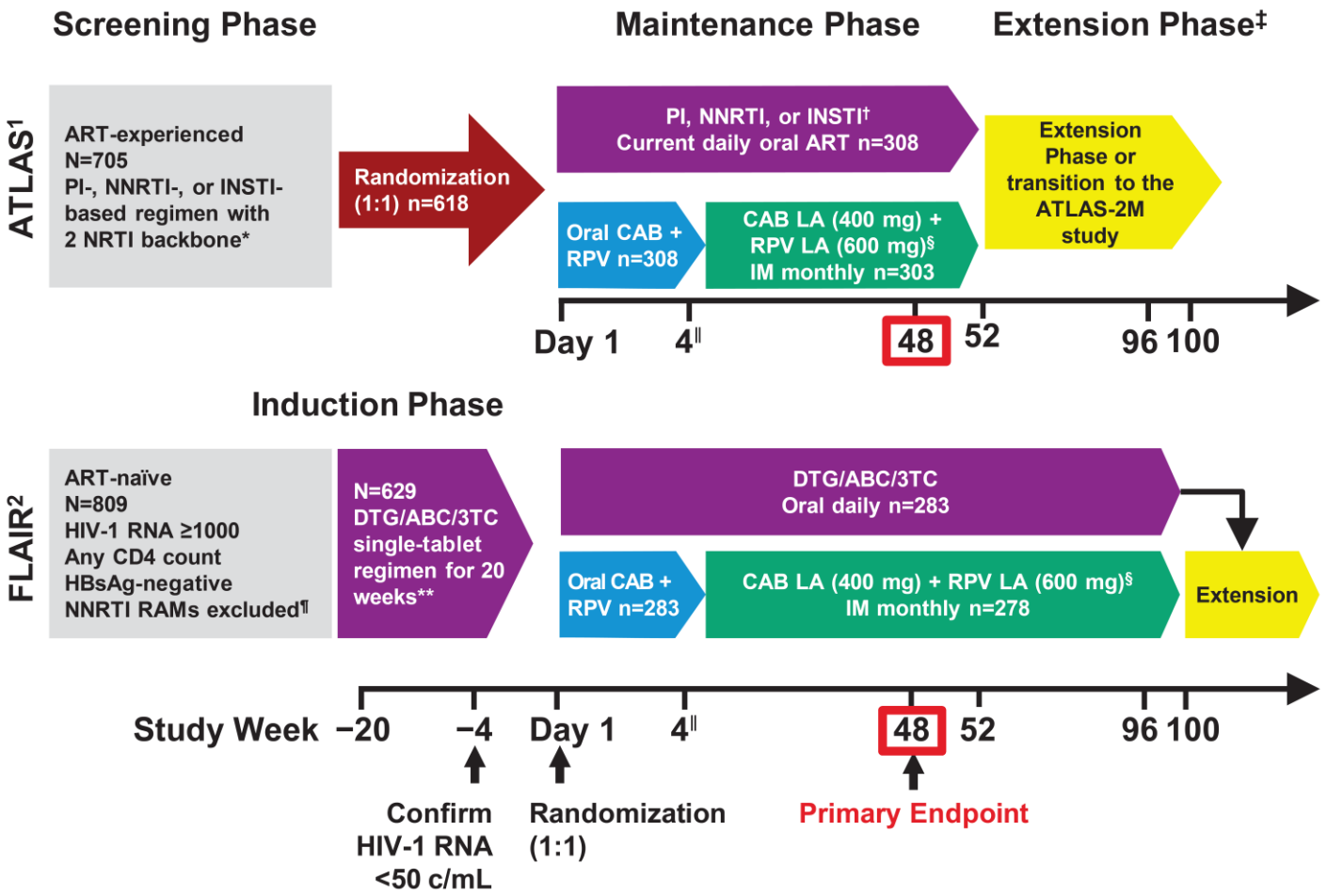
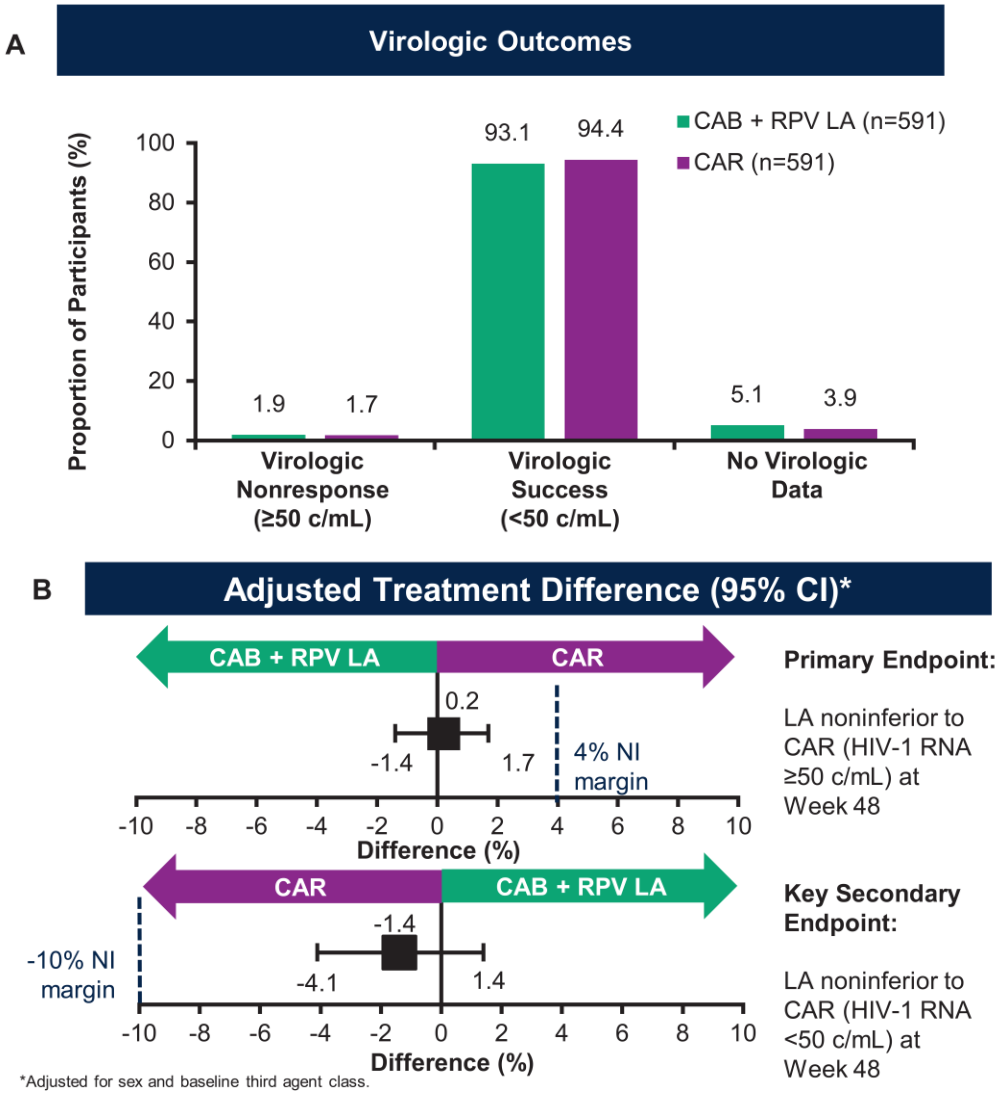
# ATLAS and FLAIR Study Design




*Uninterrupted ART ≥ 6 months and VL <50 c/mL at Screening, 2× VL <50 c/mL ≤12 months; †INSTI-based regimen capped at 40% of enrollment; Triumeq excluded from study; ‡Optional switch to CAB + RPV LA at Week 52 for those on CAR; §Participants who withdraw/complete IM CAB + RPV LA must complete 52 weeks of follow-up; ‖Participants received initial loading dose of CAB LA (600 mg) and RPV LA (900 mg) at Week 4. From Week 8 onwards, participants received CAB LA (400 mg) + RPV LA (600 mg) injections every 4 weeks; ¶NNRTI RAMs, but not K103N, were exclusionary; **DTG plus two alternative non-ABC NRTIs was permitted if participant was intolerant or HLA-B*5701-positive.

Overton et al. IAS 2019; Mexico City, Mexico. Poster MOPEB257.

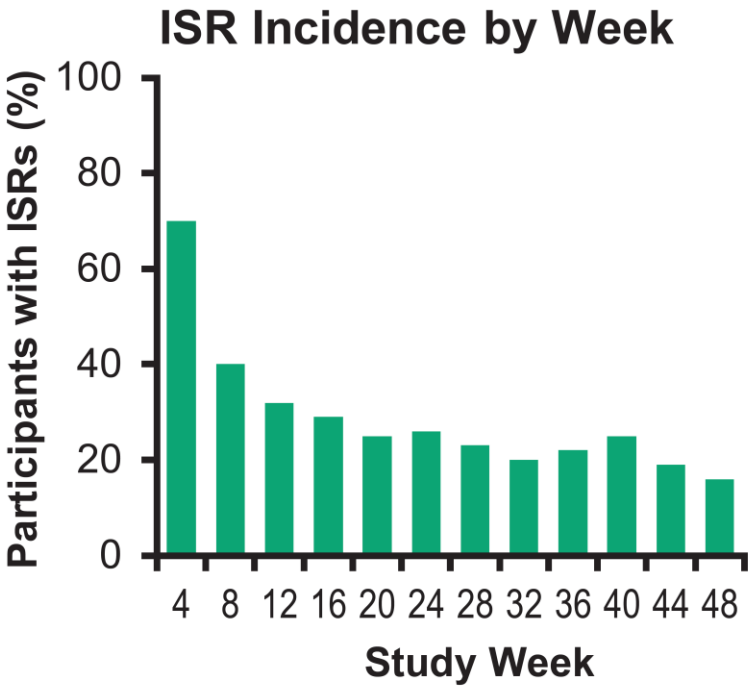
# ATLAS and FLAIR combined analysis: primary endpoint (ITT-E)




Overton et al. IAS 2019; Mexico City, Mexico. Poster MOPEB257.

# Pooled Injection Site Reactions

- The majority (99%, 3628/3663) of ISRs were Grade 1–2 and most (88%) resolved within ≤7 days




| Event | CAB + RPV LA N=591 |
|---|---|
| Participants receiving injections, n | 581 |
| Injections given, n | 14682 |
| ISR events, n (%) | 3663 (24.9) |
| Pain | 3087 (21.0) |
| Nodule | 140 (1.0) |
| Induration | 136 (0.9) |
| Swelling | 86 (0.6) |
| Grade 3 ISR pain | 32 (0.2) |
| Median duration of ISRs, days | 3 |
| Participants with ISR leading to withdrawal, n (%) | 6 (1) |

Bars represent incidence of onset ISRs relative to the most recent IM injection visit.

Overton et al. IAS 2019; Mexico City, Mexico. Poster MOPEB257.

Press Release 22 August 2019: ViiV reports ATLAS-2M has met its primary endpoint.

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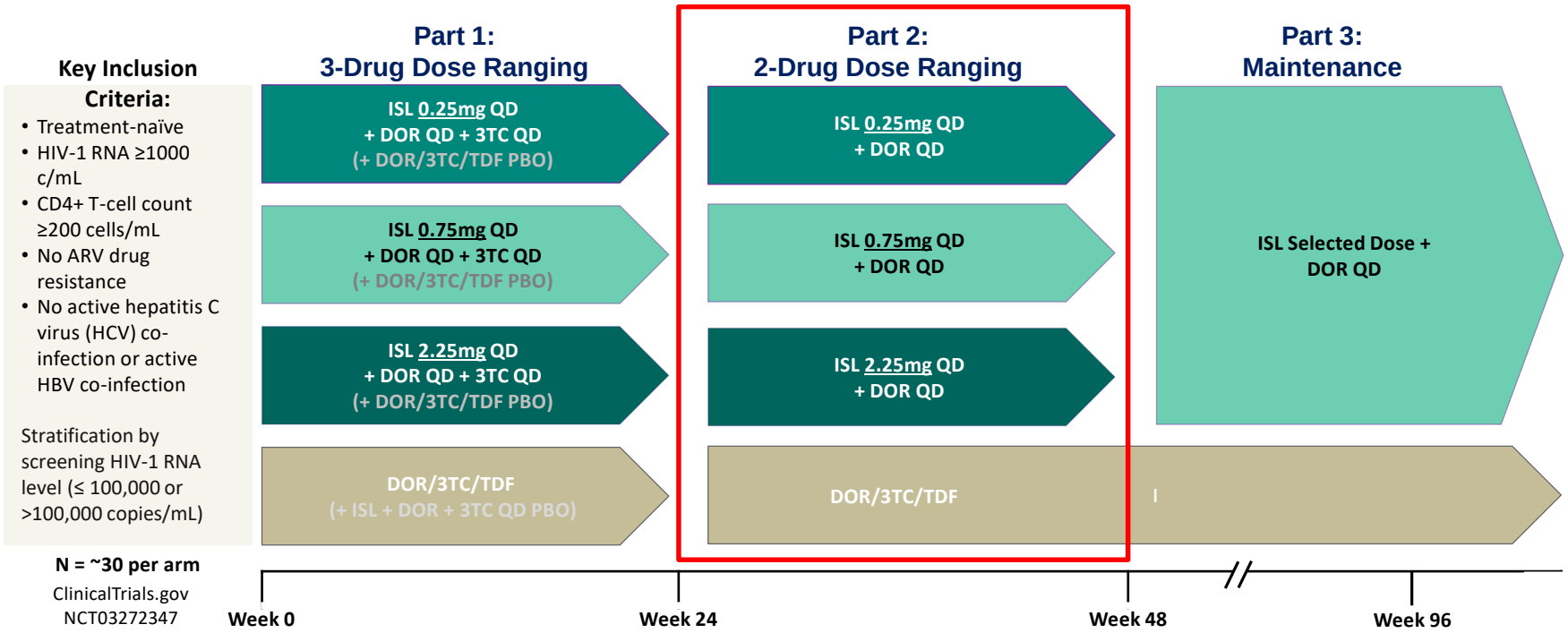
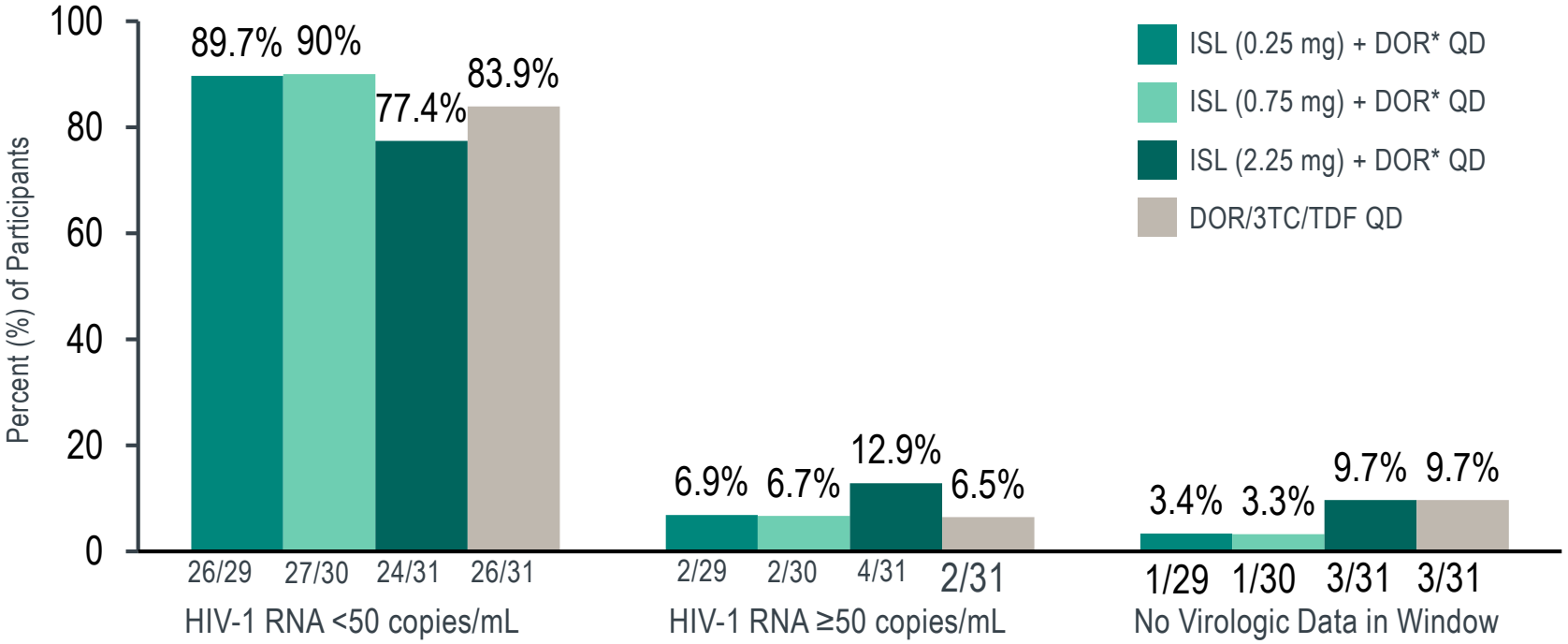
# MK-8591 Protocol 011: Phase 2 Dose Ranging Trial of ISL + DOR




After 24 weeks of dosing in Part 1, participants who are virologically suppressed (HIV-1 RNA <50 copies/mL) at the Week 20 visit and have not met any viral failure criteria are eligible to switch to Part 2 of the trial at Week 24. Participants with HIV-1 RNA levels ≥50 copies/mL at Week 20 will remain in Part 1 until the HIV-1 RNA is <50 copies/mL and they have not met any of the viral failure criteria, at which point they transition to Part 2 at their next visit.

Molina JM, et al. IAS Mexico 2019, Abstract WEAB0402LB

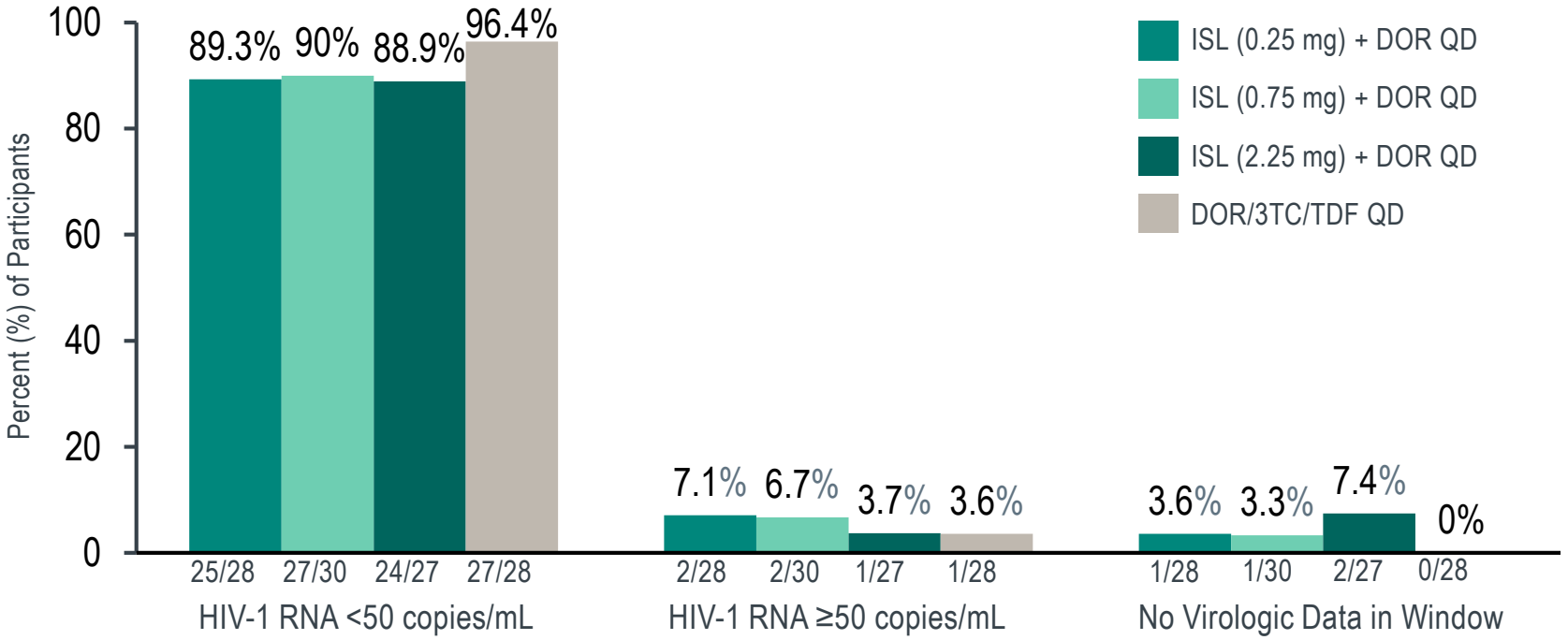
# Virologic outcomes through week 48 (FDA snapshot approach)




*Participants initially received ISL+DOR+3TC and switched to ISL+ DOR during the week 24-48 period of the study.

Molina JM, et al. IAS Mexico 2019, Abstract WEAB0402LB

# Virologic outcomes 24 weeks after entering Part 2 (FDA snapshot approach)

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# Conclusions

2DR DTG-3TC is non-inferior to 3DR over 96 weeks in ART naives

- More data required in use in women, high baseline VLs, M184V/I resistance (GART and proviral DNA) and test & treat

2DR switch to DTG/RPV or DTG/3TC appears safe and effective

Another drug company exploring 2DR is intriguing

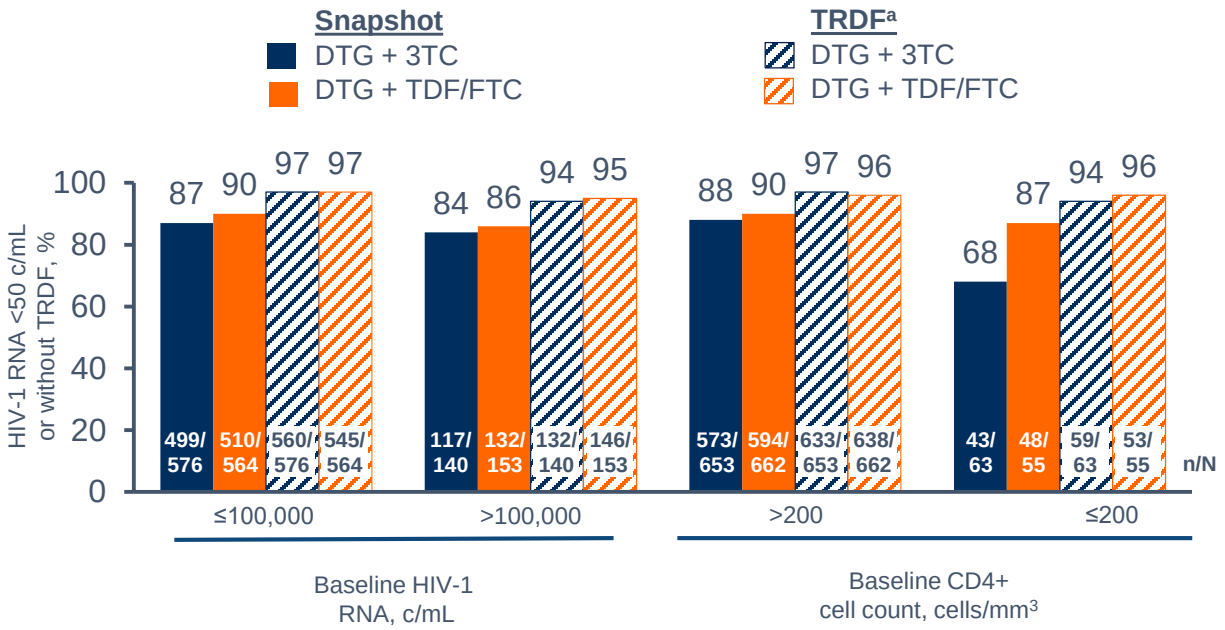
- But what can Merck partner with Islatravir?

Are we at a point when we can ask ‘why 3DR’?

# Back up slides

# GEMINI 1 & 2: proportion of participants with HIV RNA <50c/mL by baseline VL and CD4+ count:

## Snapshot and TRDF analysis




- **At Week 96, there were 3 confirmed virologic withdrawals in the DTG + 3TC group and 2 in the DTG + TDF/FTC group in the CD4 ≤ 200 stratum**

TRDF, treatment-related discontinuation equals failure. [a]TRDF was a pre-planned analysis at Week 96.

Cahn et al. IAS 2019; Mexico City, Mexico. Slides WEAB0404LB.

# SWORD 1 & 2: Adverse Events with onset through Week 52

| | Early switch phase[a] | |
|---|---|---|
| | DTG + RPV (n=513) n (%) | CAR (n=511) n (%) |
| **Any AE** | 395 (77) | 364 (71) |
| **AEs occurring in ≥5% of subjects in either group** | | |
| Nasopharyngitis | 49 (10) | 50 (10) |
| Headache | 41 (8) | 23 (5) |
| Upper respiratory tract infection | 24 (5) | 37 (7) |
| Diarrhea | 32 (6) | 27 (5) |
| Back pain | 15 (3) | 31 (6) |
| **Any Serious AEs[1]** | 27 (5) | 21 (4) |
| **Drug-related AEs** | | |
| Grades 1-2 | 89 (17) | 8 (2) |
| Grades 3-4 | 8 (2) | 1 (<1) |
| **AEs leading to withdrawal from the study** | 21 (4) | 3 (<1) |
| CNS AEs leading to withdrawal | 9 (2) | 1 (<1) |

[a]Data pooled across SWORD-1 and SWORD-2. [b]Two deaths in the study, both unrelated to study drug. DTG + RPV, Kaposi's sarcoma (n=1); CAR, lung cancer (n=1).

Llibre et al. CROI 2017; Seattle, WA. Slides 44LB.

# Resistance-Associated Mutations

- CVWs with resistance-associated mutations (RAMS) were low across both groups and were detected in 6 (0.6%) participants
  - RAMs were not detected at baseline in 4 of these participants; in 2 participants, GenoSure testing was not available at baseline
  - No participants had INSTI RAMs at CVW time point; 1 participant with only polymorphic INSTI V151V/I (no impact on DTG susceptibility) had INSTI RAM mixtures N155N/H and G163G/R at baseline

van Wyk et al. BHIVA 2019; Bournemouth, UK. Poster P008.