2025 IAS Conference Review: Part 1

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Disclosures

No conflicts of interest or relationships to disclose.

I did not attend the IAS Conference. Information presented here is based on reviews of available data.

I will discuss investigational antiretroviral agents.

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Disclaimer

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Outline

- ACTG 5391 (The DO-IT Trial)
- Investigational weekly oral two-drug combination (islatravir/ulonivirine)
- Updates on other investigational ART for HIV treatment

ACTG 5391 (The DO-IT Trial)

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ACTG 5391: The DO-IT Trial
Background

- Some studies found greater weight gain among PWH taking an INSTI compared to NNRTI; also with TAF compared to TDF
- *Research question*: for PWH with BMI ≥30 kg/m^2 who are taking an INSTI + TAF/FTC and have suppressed viral load, does switch to doravirine (DOR), with or without a switch to TDF/FTC, lead to greater weight loss as compared to continuing an INSTI + TAF/FTC

Source: Koethe J, et al. IAS 2025 Conference.

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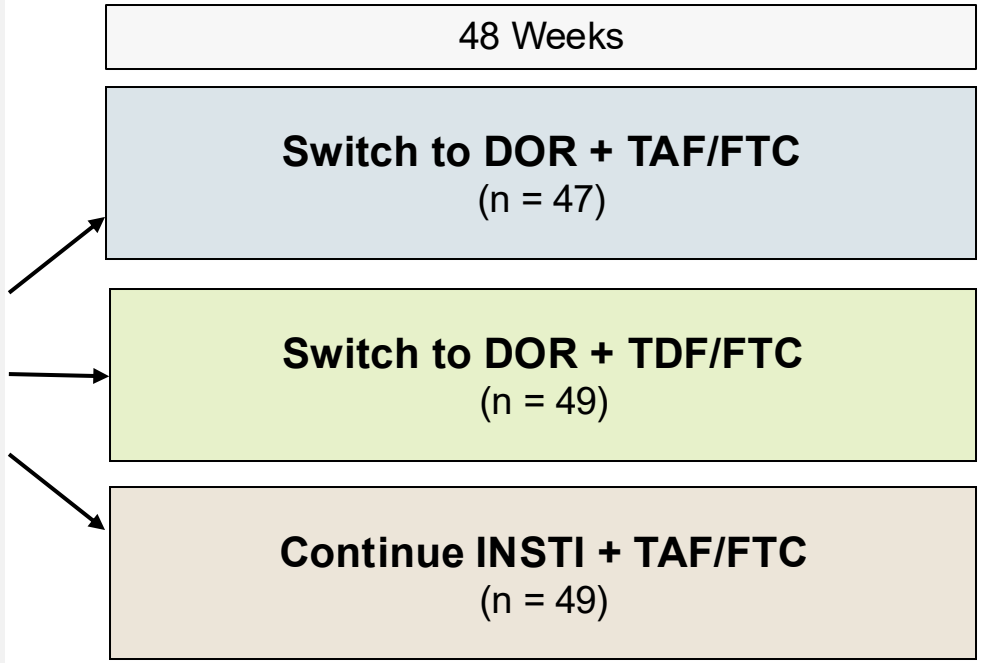
ACTG 5391: The DO-IT Trial
Study Design

- **Background**: 48-week, open-label, multicenter, superiority, randomized controlled trial; aimed for 150 participants, >50% female, >50% Black
- **Inclusion Criteria**
  - Age ≥18 years old
  - Original criteria: unintentional >10% weight gain in the 1-3 years after starting or switching to an INSTI + TAF/FTC
  - Amended criteria: BMI ≥30 kg/m^2 while taking an INSTI + TAF/FTC
  - Suppressed viral load
  - No weight loss meds or weight loss surgery
  - No documented or suspected resistance to DOR; also no K65R or M184V/I mutations
  - No prior TDF toxicity
  - No pregnancy, breastfeeding, osteoporosis/osteopenia, recent critical illness



Source: Koethe J, et al. IAS 2025 Conference.

ACTG 5391: The DO-IT Trial Results

Participant Characteristics	
Characteristic	**Median (or percentage where noted)**
Age	49
BMI	34.9 kg/m2
Waist circumference	111 cm
CD4 count	688
Time taking current INSTI + TAF/FTC	3.4 years
INSTI	86% BIC, 13% DTG, 1% RAL
*65% of participants had >10% weight gain in first 1-3 years of INSTI-based ART	

Source: Koethe J, et al. IAS 2025 Conference.

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ACTG 5391: The DO-IT Trial Results

Weight Change Per Trial Arm	
Trial Arm	**Median Weight Change (97.5% CI)**
Switch to DOR + TAF/FTC	-0.47 (-2.09, -1.14)
Switch to DOR + TDF/FTC	-2.73 (-4.22, -1.23)
Continue INSTI + TAF/FTC	-1.84 (-3.37, -0.30)

*All study arms lost weight

*There was no evidence that a switch to DOR affected 48-week changes in weight compared to continued INSTI + TAF/FTC; 97.5% CIs were <5 percentage points

*Also no safety differences (adverse effects, creatinine elevation, change in bone mineral density)

Source: Koethe J, et al. IAS 2025 Conference.

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ACTG 5391: The DO-IT Trial
Conclusions

- Switch to DOR, +/- change from TAF/FTC to TDF/FTC, did not reduce weight at 48 weeks for PWH with BMI >30, compared to continuing INSTI + TAF/FTC
- Female and Black participants did not derive significant benefit from a regimen change, nor did those with prior >10% weight gain in first 3 years of INSTI use
- Robust evidence that ART regimen changes are not effective in reducing weight among PWH with elevated BMI – other interventions needed

Source: Koethe J, et al. IAS 2025 Conference.

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ACTG 5391: The DO-IT Trial
Strengths & Limitations

- Strengths:
  - Prospective, randomized trial
  - Female and Black participants each comprised about 50% of enrollees
- Limitations:
  - Results may not be generalizable to PWH with BMI <30 kg/m^2 or outside US
  - Open-label design may have influenced participant behavior
  - Difficulty with enrollment led to amendment of inclusion criteria
  - Not clear if results would be similar with recent start/recent weight gain on ART

Source: Koethe J, et al. IAS 2025 Conference.

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Switch to Once-Weekly Oral NNRTI (MK-8507, Ulonivirine) Plus Islatravir After Virologic Suppression

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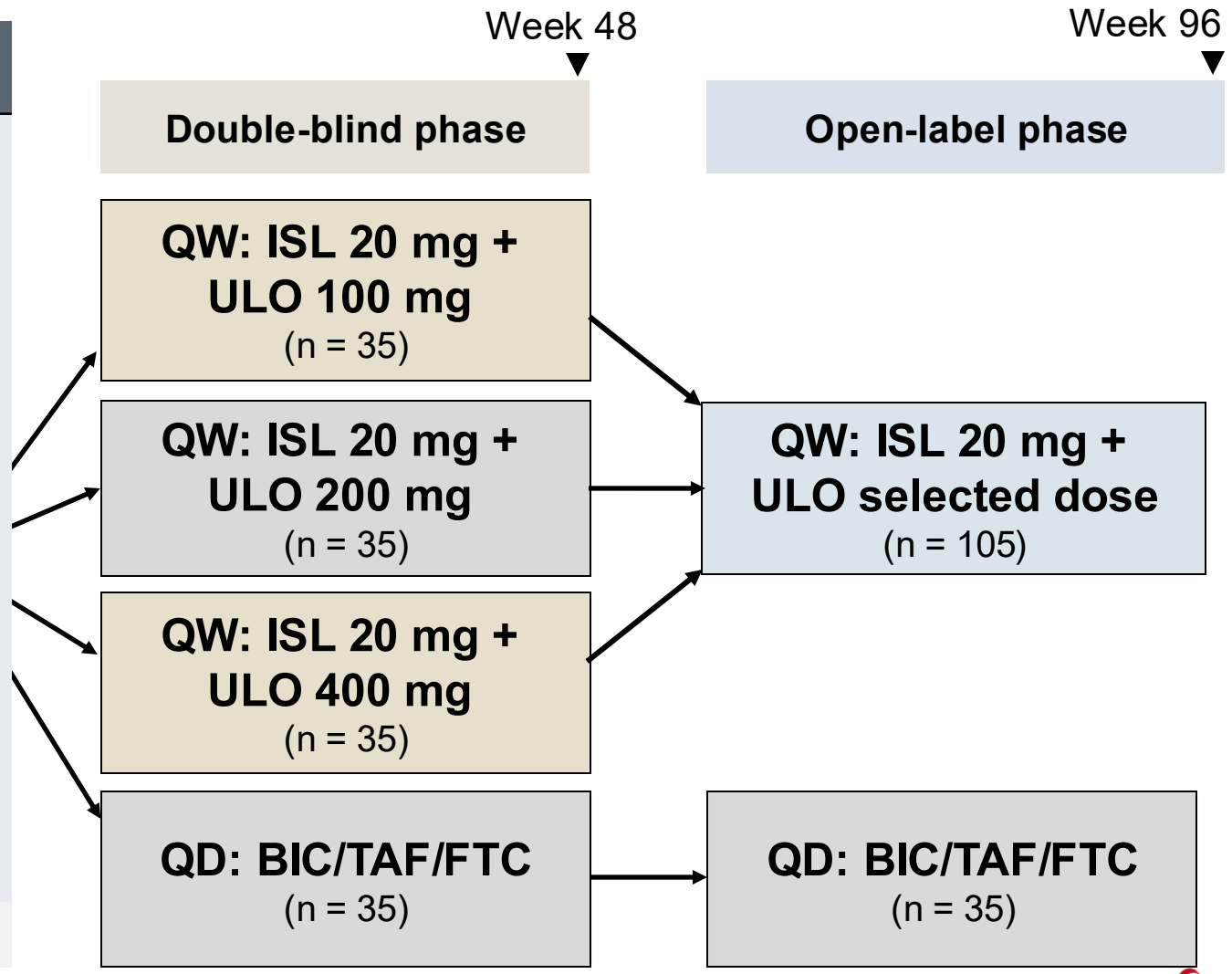
Study MK-8591B-060: Switch to ISL+ULO After Virologic Suppression on BIC/TAF/FTC
Study Design

Study Design: MK8591B-060

- **Background**: phase 2b, randomized, active-controlled, open-label study to evaluate a switch to islatravir (ISL, an NRTTI) plus ulonivirine (ULO, an NNRTI) once weekly for adults with virologic suppression on BIC/TAF/FTC

- **Enrollment Criteria:**
  - Adults with HIV-1 RNA <50 copies/mL for ≥6 months on BIC/TAF/FTC
  - No history of treatment failure
  - No known virologic resistance to NNRTIs
  - CD4 count ≥200 cells/mL
  - No active hep B or hep C infection

Randomized 1:1:1:1

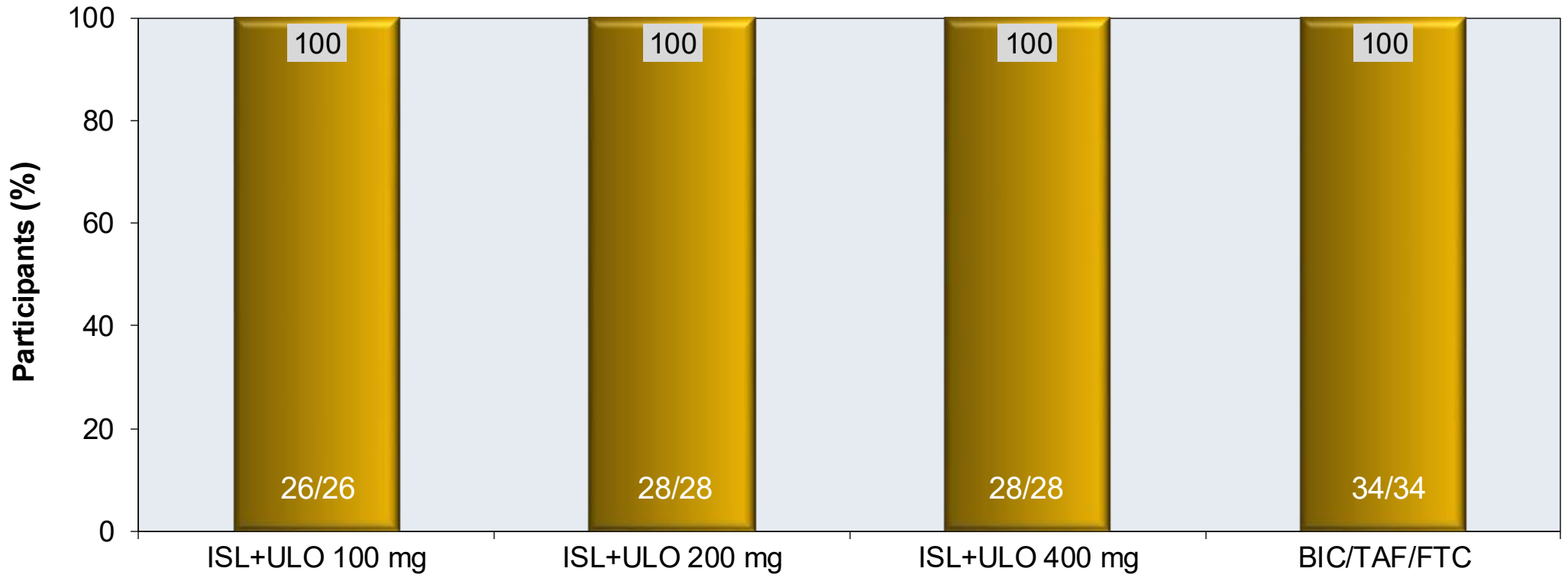


Source: Molina J-M, et al. IAS 2025 Conference.

Study MK-8591B-060: Switch to ISL+ULO After Virologic Suppression on BIC/TAF/FTC

Results

Proportion with Virologic Suppression at Week 24



CD4 and lymphocyte decline noted in all ISL arms by week 8-12. Trial stopped and labs recovered by week 132.

Source: Molina J-M, et al. IAS 2025 Conference.

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Study MK-8591B-060: Switch to ISL+ULO After Virologic Suppression on BIC/TAF/FTC
Conclusions

- Weekly oral ISL 20 mg + ULO effective maintained VL suppression at 24 weeks
- Switch to ISL+ULO generally well tolerated, except CD4/lymphocyte decline
- Development of weekly ISL+ULO resumed with ISL 2 mg plus ULO 200 mg

Source: Molina J-M, et al. IAS 2025 Conference.

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Investigational ART Updates

(some data based on a talk by Dr. Raj Gandhi at IAS 2025)

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Islatravir Clinical Trials Update

- Islatravir/doravirine (ISL/DOR):
  - Daily oral two-drug combination
  - Reduced ISL dose to 0.25 mg daily
    - Effective as switch when suppressed on BIC/TAF/FTC or other oral ART
  - ***Submitted to FDA for switch indication; FDA decision by April 28, 2026**
  - ISL/DOR vs. BIC/TAF/FTC as initial ART fully enrolled (results 2026)
  - ISL/DOR for heavily treatment-experienced PWH stopped

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Oral Lenacapavir Clinical Trials Update

- Islatravir/lenacapavir (ISL/LEN) oral weekly (lower ISL dose, 2 mg)
  - Phase 2: effective compared to BIC/TAF/FTC after VL suppressed
  - Phase 3 (results 2026):
    - ISLEND1: weekly ISL/LEN compared to BIC/TAF/FTC with suppressed VL
    - ISLEND2: weekly ISL/LEN compared to standard oral ART with suppressed VL
- Bictegravir/lenacapavir oral daily
  - ARTISTRY 1: switch from complex ART regimens effective (phase 2/3)
  - ARTISTRY 2: switch after virologic suppression on BIC/TAF/FTC (phase 3)
  - ARTISTRY 3: switch from complex ART (phase 3)

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Other Investigational ART Updates

- Weekly oral GS1720 (INSTI) and GS4182 (capsid inhibitor): **on hold**
- HRF-0071 (maturation inhibitor) dose finding study at IAS (phase 2a)
- Ibalizumab every 2 weeks IM (instead of IV) (phase 3 results available)
- Every 6-month dosing: lenacapavir + 2 bNAbs (phase 2)
- Every 12-month dosing: lenacapavir IM (moving into phase 3)

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Other Investigational ART Updates

- Phase 1:
  - VH-499: long-acting injectable capsid inhibitor (every 6 months)
  - VH-184: long-acting injectable third generation INSTI (every 6 months)
  - GS-3107: long-acting oral lenacapavir pro-drug (oral monthly)
  - GS-1219: long-acting injectable INSTI (every 6 months)
  - GS-3242: long-acting injectable INSTI (every 6 months)
  - GS-1614: long-acting injectable islatravir pro-drug (every 6 months)

Acknowledgment

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