CROI 2020 Review: Dual ART & HIV Cure

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Disclosures

No conflicts of interests or relationships to disclose.

Outline

- Dual ART
  - Dolutegravir/lamivudine initial ART: updated 96-week results
  - Islatravir + doravirine metabolic outcomes at 48 weeks
- HIV Cure:
  - Sustained HIV remission in the London Patient

Dolutegravir/Lamivudine (DTG/3TC) Initial ART: Updated 96-Week Results

What to Start
Recommended Initial ART Options

DHHS (Dec 2019)[1] Recommended for Most People With HIV	IAS-USA (July 2018)[2] Recommended Initial Regimens
BIC/FTC/TAF	BIC/FTC/TAF
DTG/ABC/3TC (if B*5701 neg) DTG + FTC/TAF or FTC/TDF	DTG/ABC/3TC (if B*5701 neg) DTG + FTC/TAF
RAL + FTC/TAF or FTC/TDF	
DTG/3TC (if VL <500k, no hepatitis B, baseline genotype result available)	

Abbreviations:
BIC – bictegravir, DTG – dolutegravir, ABC – abacavir, 3TC – lamivudine, FTC – emtricitabine
TDF – tenofovir disoproxil fumarate, TAF – tenofovir alafenamide

Sources:
1. DHHS: http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision Dec. 18, 2019.
2. IAS-USA: Saag MS, et al. *JAMA*. 2018;320:379-396.

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DTG + 3TC versus DTG + TDF-FTC as Initial ART
GEMINI 1 and 2: Background

Study Design: GEMINI 1 and 2

- **Background**:
  - Two identical, double-blind, multinational, noninferiority randomized controlled trials that compared initial antiretroviral therapy (ART) of DTG + 3TC versus DTG + TDF-FTC

- **Enrollment Criteria:**
  - Treatment-naïve adults
  - HIV RNA 1,000-500,000 copies/mL
  - No NRTI, INSTI, or major PI mutations
  - No chronic HBV
  - No need for HCV therapy
  - Not pregnant or breastfeeding

DTG + 3TC
(Dual ART)
n = 716

DTG + TDF-FTC
(Triple ART)
n = 717

Primary endpoint: % with HIV RNA <50 copies/mL at 48 weeks by ITT

Source: Cahn P, et al. Lancet. 2019;393:143-55.

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DTG + 3TC versus DTG + TDF-FTC as Initial ART
GEMINI 1 and 2: Baseline Characteristics

GEMINI 1 and 2 Baseline Characteristics		
Characteristic	**DTG + 3TC** (n = 716)	**DTG + TDF-FTC** (n = 717)
Age, years, median (IQR)	32 (26-40)	33 (26-42)
Female, n (%)	113 (16)	98 (14)
White, n (%)	480 (67)	497 (69)
Black or African American, n (%)	99 (14)	76 (11)
CD4 cell count, mean (SD)	462 (219.2)	461.3 (213.1)
CD4 count ≤200 cells/mm^3, n (%)	63 (9)	55 (8)
HIV RNA (log_{10} copies/mL)	4.42 (0.66)	4.45 (0.65)
≤100,000 copies/mL, n (%)	576 (80)	564(79)
>100,000 copies/mL, n (%)	140 (20)	153 (21)

Source: Cahn P, et al. Lancet. 2019;393:143-55.

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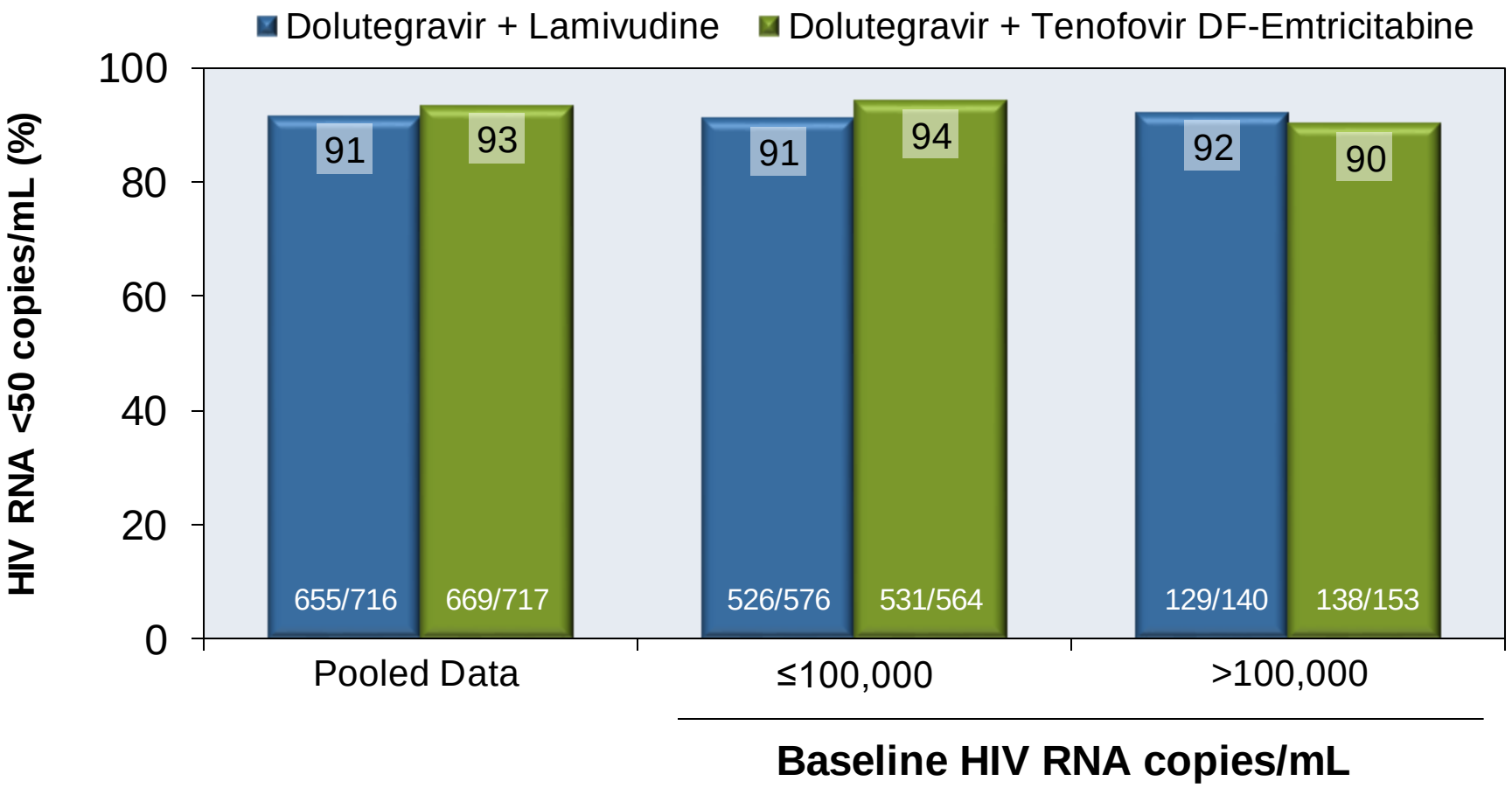
DTG + 3TC versus DTG + TDF-FTC as Initial ART
GEMINI 1 and 2: Results by Baseline HIV RNA Level

Week 48 Virologic Response (Intention-to-Treat Analysis)



Source: Cahn P, et al. Lancet. 2019;393:143-55.

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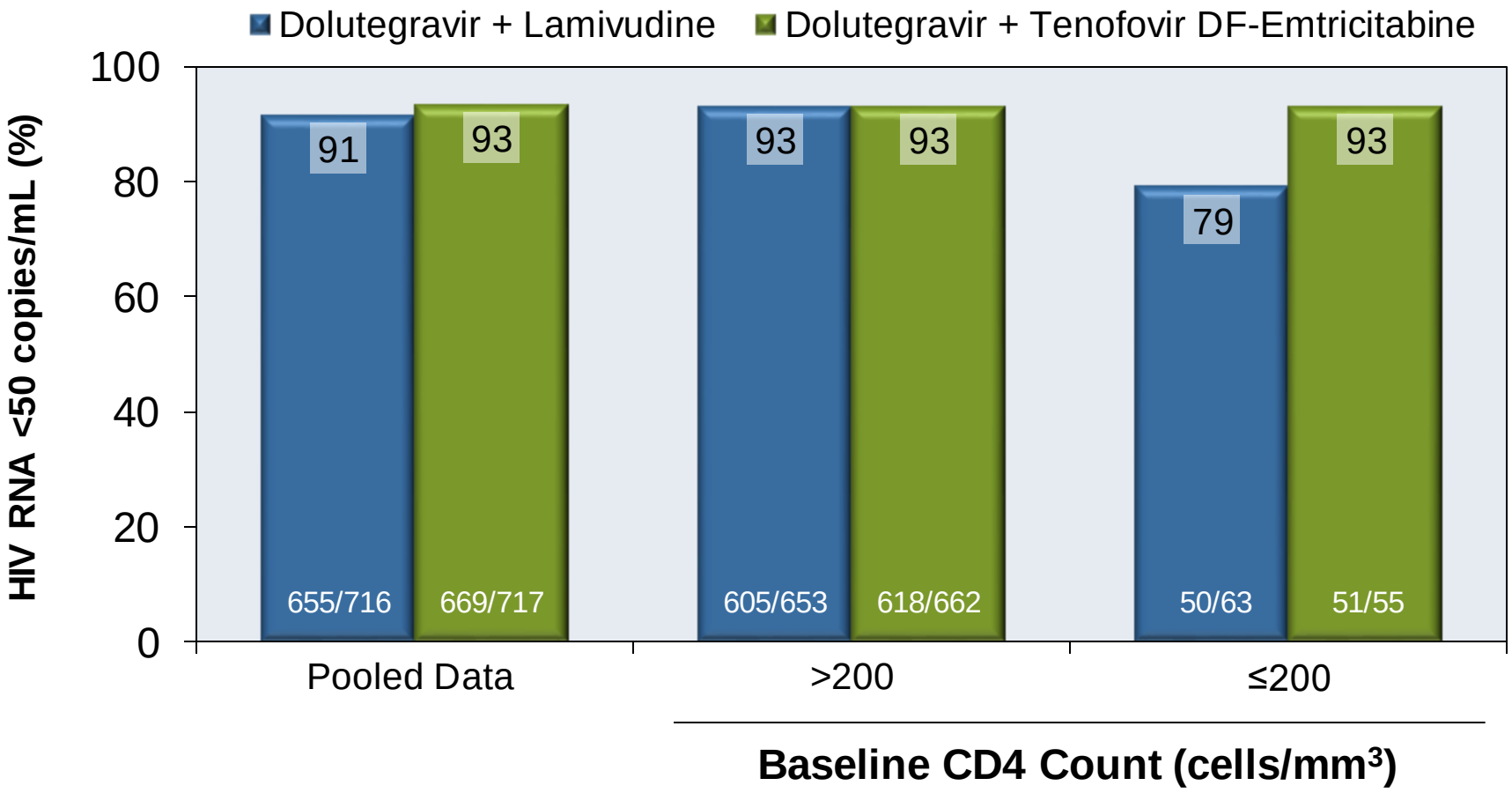
DTG + 3TC versus DTG + TDF-FTC as Initial ART
GEMINI 1 and 2: Results by Baseline CD4 Cell Count

Week 48 Virologic Response (Intention-to-Treat Analysis)



Source: Cahn P, et al. Lancet. 2019;393:143-55.

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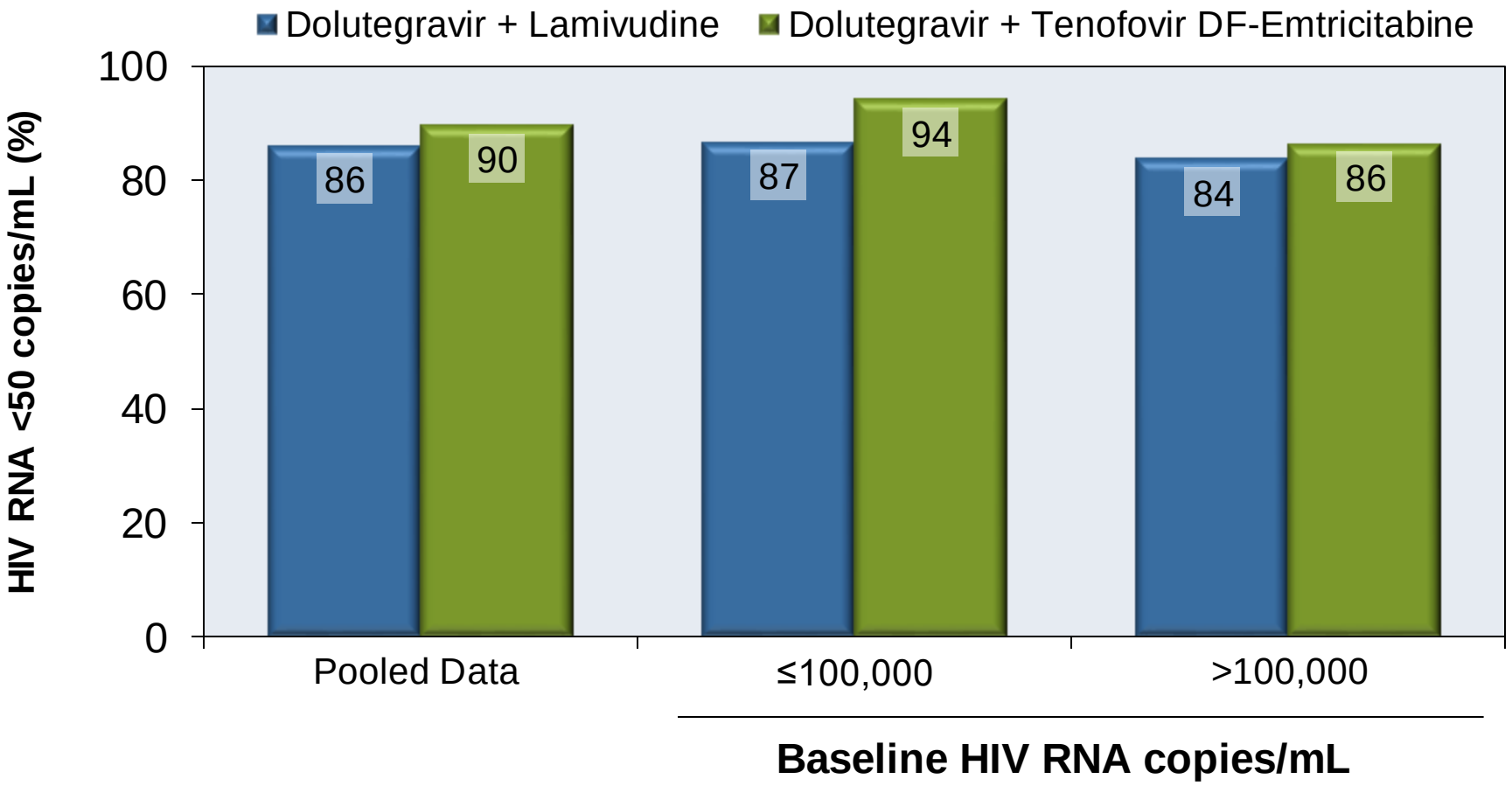
DTG + 3TC versus DTG + TDF-FTC as Initial ART
GEMINI 1 and 2: Results by Baseline HIV RNA Level

Week 96 Virologic Response (Intention-to-Treat Analysis)



Source: Cahn P, et al. JAIDS, 2020 March; 83(3):310-318.

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DTG + 3TC versus DTG + TDF-FTC as Initial ART
GEMINI 1 and 2: CROI 2020 Update

Confirmed virologic withdrawals and resistance analysis		
Total confirmed virologic withdrawals (CVW's)	**DTG + 3TC** (n = 11)	**DTG + TDF-FTC** (n = 7)
Baseline VL >100,000 copies/mL	4	2
Baseline CD4 <200 cells/mL	3	2
CVW viral load <1,000 copies/mL	4	4
CVW viral load >10,000 copies/mL	4	6
Adherent to study drugs	2	0
Non-adherent or treatment interruption	6	1
Unknown adherence	3	6
Emergent INSTI or RT resistance	**0**	**0**

Source: Underwood M, et al. CROI 2020. Abstract 483.

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DTG + 3TC versus DTG + TDF-FTC as Initial ART
GEMINI 1 and 2: CROI 2020 Update

- Overall low & comparable CVW's through 96 weeks across treatment arms; no pattern by baseline CD4 or viral load
- Among CVW's, no treatment-emergent genotypic or phenotypic INSTI or RT resistance occurred
- Most CVW's due to non-adherence
- Data support the durability and high barrier to resistance of DTG/3TC dual ART as initial therapy

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- *My question: should we offer this more often as initial ART?*

Source: Underwood M, et al. CROI 2020. Abstract 483.

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Oral Islatravir plus Doravirine Dual ART: Metabolic Outcomes

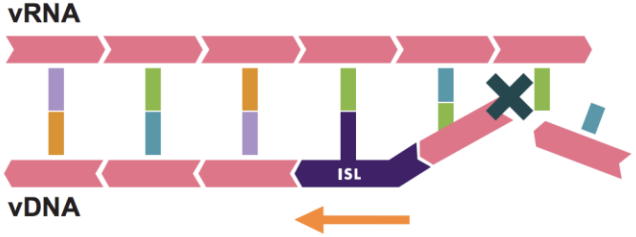
What is Islatravir (ISL)?

- NRTTI: nucleoside reverse transcriptase translocation inhibitor

Translocation Inhibition

- Translocation inhibition prevents opening of the RT nucleotide binding site
- Nucleotides cannot be incorporated into vDNA
- **Viral replication is inhibited**

Delayed Chain Termination



- ISL changes vDNA structure such that nucleotide incorporation is prevented
- As ISL is not in the RT active site, it is not susceptible to resistance-conferring mutations
- **Viral replication is inhibited**

Source: McComsey G, et al. CROI 2020. Abstract 686.

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Potential Advantages of Islatravir (ISL)

- Active against isolates with pre-existing NRTI resistance
- Potent viral load reduction plus high barrier to resistance
- Inhibitory quotient achieved with low doses
- Long intracellular half-life (190 hours with oral dosing)
- Potential for once-daily, once-weekly, or less frequent oral dosing; much less frequent for other formulations

Source: McComsey G, et al. CROI 2020. Abstract 686.

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Review of Doravirine (DOR)

- Most recently approved NNRTI
- Once-daily dosing with no food requirement
- Fewer drug-drug interactions than previous NNRTI's
- Better lipid effects compared to some previous NNRTI's
- In vitro activity against isolates with some common NNRTI mutations (K103N, Y181C, K103N/Y181C, G190A, E138K)

Source: McComsey G, et al. CROI 2020. Abstract 686.

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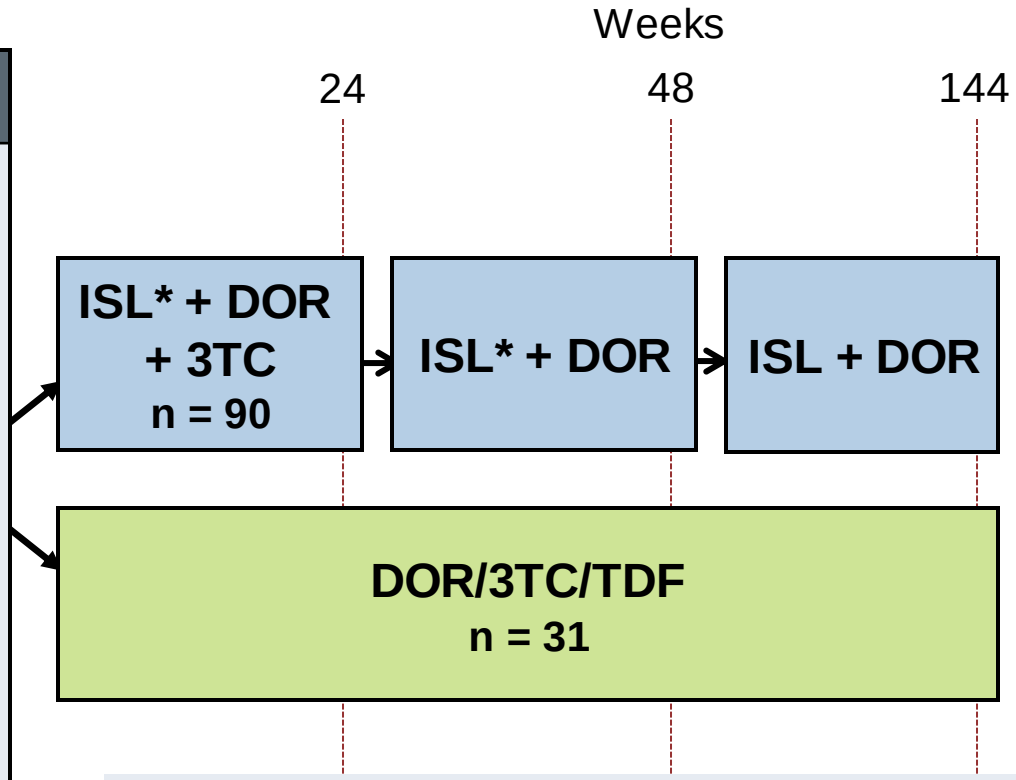
Oral ISL + DOR Dual ART Maintenance vs DOR/3TC/FTC
DRIVE2SIMPLIFY: Background

Study Design: DRIVE2SIMPLIFY

- **Background**:
  - International, randomized, double-blind phase IIb trial
- **Enrollment Criteria:**
  - Treatment-naïve adults
  - HIV RNA >1,000 copies/mL
  - CD4 T-cell count >200 cells/mL
  - No ARV drug resistance
  - No active HBV or HCV
- **Primary Endpoint**:
  - HIV RNA at 24 & 48 weeks; adverse events



*ISL dose: 0.25 mg, 0.75 mg, or 2.25 mg daily

Current analysis: weight; BMI; hip and spine BMD, peripheral & trunk fat by DXA; fasting plasma glucose; and lipid profile at 48 weeks

Source: McComsey G, et al. CROI 2020. Abstract 686.

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Oral ISL + DOR Dual ART Maintenance vs DOR/3TC/FTC
DRIVE2SIMPLIFY: Baseline Characteristics

- Baseline weight and metabolic characteristic consistent across groups (median BMI 23-24)
- Mean age 31 years, 93% male, 76% white
- Mean baseline CD4 count about 490 cells/mL
- 22% with baseline HIV RNA >100,000 copies/mL

Source: McComsey G, et al. CROI 2020. Abstract 686.

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Oral ISL + DOR Dual ART Maintenance vs DOR/3TC/FTC
DRIVE2SIMPLIFY: Results

DRIVE2SIMPLIFY: Metabolic Results at 48 Weeks

Characteristic	Combined ISL + DOR Groups (n = 90)	DOR/3TC/TDF (n = 31)
Mean % change in weight	3.8	3.0
Mean % change in hip BMD	-1.1*	-3.5
Mean % change in spine BMD	-1.3	-2.2
Mean % change in peripheral fat	10.2	9.6
Mean % change in trunk fat	15.0	12.9
Mean change in fasting markers (mg/dL)		
Glucose	2.3	-2.0
Total cholesterol	5.4	-6.5
HDL	4.3	0.8
LDL	-0.8	-4.7
Triglycerides	6.2	-10.9

Source: McComsey G, et al. CROI 2020. Abstract 686.

*p <0.05

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Oral ISL + DOR Dual ART Maintenance vs DOR/3TC/FTC
DRIVE2SIMPLIFY: Results

- Change in weight & BMI similar in ISL + DOR groups and DOR/3TC/TDF group, and consistent with average weight gain in general population (0.5-1.0 kg/year)
- ISL + DOR regimens had lower impact on hip BMD than DOR/3TC/TDF; spine BMD changes similar
- Changes in peripheral and trunk fat similar; changes in glucose and fasting lipids modest and similar
- Overall minimal effects on body composition and metabolic parameters supports phase 3 trials of ISL + DOR

- *Limitations: short follow-up, no TAF or INSTI comparison*

Source: McComsey G, et al. CROI 2020. Abstract 686.

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Sustained HIV Remission in the London Patient

Sustained HIV-1 Remission Following Homozygous CCR5 Delta32 Allogenic HSCT

"The London Patient" Case history

- 2003: HIV diagnosed
- 2013: Hodgkin lymphoma diagnosed. Started on EFV/FTC/TDF and VL suppressed; then changed to RAL + FTC/TDF in anticipation of chemotherapy (ABVD)
- Failed multiple rounds of chemotherapy and failed to mobilize cells for an auto-HSCT
- Allo-HSCT donor: 9/10 HLA match and also **homozygous for CCR5-delta-32 mutation**

Source: Gupta et al, CROI 2019, and *Nature* 2019.

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Sustained HIV-1 Remission Following Homozygous CCR5 Delta32 Allogenic HSCT

Allogeneic HSCT

- Conditioning chemotherapy
- May 2016: Stem cell infusion
  - Complications: gram-negative sepsis, colitis (possible mild GVHD), CMV and EBV reactivation (treated with ganciclovir and rituximab)
  - Fully engrafted – **all cells CCR5-delta32-minus**
- Sept. 2017: **Stopped ART**
- Feb. 2019: **VL not detected (18 months after ART stop)**

Source: Gupta et al, CROI 2019, and *Nature* 2019.

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Sustained HIV-1 Remission Following Homozygous CCR5 Delta32 Allogenic HSCT: CROI 2020 Update

Allogeneic HSCT

- T-cell chimerism maintained at 99%
- Peripheral HIV RNA undetectable (<1 copy/mL) at **30 months**
- Negative HIV DNA/RNA in CSF, gut tissue, & semen
- Low-level HIV DNA "fossils" in LN's and CD4 memory T cells
- Absent HIV-specific T cell immune response
- Cure (long-term remission) highly likely per mathematical model
  - Probability of cure >99% if >90% chimerism
  - Probability of cure >90% if >80% chimerism

Source: Gupta RV, et al. CROI 2020. Abstract 346LB.

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Sustained HIV-1 Remission Following Homozygous CCR5 Delta32 Allogenic HSCT

The London Patient	Timothy Brown (Berlin Patient)
• Homozygous for wt CCR5	• Heterozygous for d32 CCR5
• R5 using virus	• R5 using virus
• Hodgkin's lymphoma	• Acute myelogenous leukemia
• Single HSCT	• Two HSCTs
• No irradiation	• Total body irradiation
• Reduced intensity conditioning	• Full intensity conditioning
• T-cell depletion with aCD53	• T-cell depletion with ATG
• Mild GVHD	• Mild GVHD
• 100% T-cell donor chimerism	• 100% T-cell donor chimerism

Source: Gupta et al, CROI 2019.

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Other HSCT “Cure” Case Studies

Dusseldorf Patient

- Similar but only 4 months from HSCT
- Likely “cure”

Essen Patient

- Not cured - relapsed after HSCT due to recipient CXCR4 minority variants

Boston Patients

- Not cured – relapse after HSCT due to donors not CCR5 deletion homozygous

Sources: Jensen et al., CROI 2019. Hessen et al., *Viruses* 2015. Heinrich et al., *Annals of Intern Med* 2014.

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Conclusions About HIV Cure

- "Cure" or sustained remission is possible with allogeneic stem cell transplant if:
  - Recipient's HIV is 100% CCR5-using before transplant
  - Donor is CCR5-deletion homozygous
  - 100% chimerism/engraftment occurs (in other words, recipient becomes 100% CCR5-deleted)
- Key message: cure is possible, though not widely available; simpler treatments that delete CCR5 needed

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