AETC AIDS Education & Training Center Program Southeast

Pipeline drugs: HIV therapy

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Objectives

- Summarize recently approved and therapies in development for HIV treatment.
- Review options for injectable, long-acting, and oral medications for HIV treatment and prevention.
- Discuss therapies in development for HIV PrEP.

Classes of HIV Drug Therapy

Inhibition of HIV enzymes

- Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Integrase strand transfer inhibitors (INSTIs)
- Protease inhibitors (PIs)

Receptor-specific inhibition

- HIV:
  - Fusion inhibitor, enfuvirtide
- Human
  - CCR5 receptor antagonist, maraviroc

Classes of HIV Drug Therapy

Inhibition of HIV enzymes

- Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Integrase strand transfer inhibitors (INSTIs)
  - **Cabotegravir***
- Protease inhibitors (PIs)
- **Nucleoside reverse transcriptase translocation inhibitor (NRTTI), islatravir***

Receptor-specific inhibition

- HIV:
  - Fusion inhibitor, enfuvirtide
  - **Attachment inhibitor, fostemsavir***
  - **Capsid inhibitor, lenacapavir***
- Human
  - CCR5 receptor antagonist, maraviroc
  - **Post-attachment inhibitor, ibalizumab***

Why more new HIV drugs?

Unmet Needs in HIV Treatment

- Reduced pill burden
- Options for self administration
- Salvage therapies
- Novel alternatives for PrEP

Updates from CROI 2021

- Cabotegravir/rilpivirine
- Fostemsavir
- Ibalizumab
- Islatravir
- Lenacapavir
- Additional updates

Updates from CROI 2021

- **Cabotegravir/rilpivirine**
- Fostemsavir
- Ibalizumab
- Islatravir
- Lenacapavir
- Additional updates

Cabotegravir/rilpivirine (Cabenuva®)

- Approved in January 2021!
- Indications
  - Replace oral ART in patients with HIV viral load (VL) <50 for ≥3 months
  - On a stable antiretroviral regimen
  - No history of treatment failure
  - No known or suspected resistance to either cabotegravir or rilpivirine
  - Do not have active hepatitis B infection
  - Are not pregnant or plan on becoming pregnant
  - Are not receiving medications with significant drug interactions
- Dosing
  - Oral lead in period followed by monthly injections

Cabenuva. Prescribing information. ViiV Healthcare; 2021.
HHS Adults and Adolescents Antiretroviral Guidelines Panel Recommendation for the Long-Acting Injectable Antiretroviral Regimen of Cabotegravir and Rilpivirine. Department of Health and Human Services. February 2021.

Cabenuva® Dosing and Administration

Month 1
(2 tablets daily with food)
- Cabotegravir 30 mg once daily
- Rilpivirine 25 mg once daily

Month 2
2 initiation injections* (IM)
- Cabotegravir 600 mg (3 mL)
- Rilpivirine 900 mg (3 mL)

Month 3+
2 injections monthly* (IM)
- Cabotegravir 400 mg (2 mL)
- Rilpivirine 600 mg (2 mL)

IM = intramuscular

*Must be administered by a healthcare professional
*Patients may receive dose up to 7 days before or after scheduled visit

Cabenuva. Prescribing information. ViiV Healthcare; 2021.

Cabenuva® Clinical Pearls

- An option for simplified maintenance therapy
- Well-tolerated, injection site reaction most common
  - Occurred in ~80% of participants at least 1x
- Anti-convulsants and anti-mycobacterial agents contraindicated
  - Cabotegravir alone: Antacids, polyvalent cations
- Virologic failure not common (1.2%), cross-resistance possible

Cabenuva. Prescribing information. ViiV Healthcare; 2021.

Summary of Key Studies

ATLAS (N=616)[1]

- Phase 3, open-label, multi-center trial
- Participants randomized to continue current oral therapy or switch to monthly IM injections of cabotegravir/rilpivirine
- HIV VL <50 copies/mL found in **92.5%** of cabotegravir/rilpivirine participants compared to **95.5%** of those receiving oral therapy at week 48 (adjusted difference -3%, 95% CI -6.7 to 0.7), met criteria for **noninferiority**

ATLAS-2M[2,3]

- Phase 3, multi-center, open-label trial (ongoing)
- Treatment-experienced participants randomized to cabotegravir/rilpivirine administered every 8 weeks or every 4 weeks
- HIV VL ≥50 copies/mL shown in 2% of q8week group compared to 1% in q4week group, met criteria **for noninferiority**
- Sustained at week 96, with 90-91% of participants with HIV VL <50 copies/mL in both arms

FLAIR[4]

- Phase 3, open-label trial
- Participants randomized to continue therapy with DTG/ABC/3TC or switch to oral cabotegravir/rilpivirine followed by monthly injection
- HIV VL <50 copies/mL found in **93.6%** of cabotegravir/rilpviriine participants vs **93.3%** receiving DTG/ABC/3TC (adjusted difference, 0.4%, 95% CI -3.7 to 4.5), met criteria for **noninferiority**
- Cabotegravir/rilpivirine group had **higher treatment satisfaction**

1. Swindells S, Andrade-Villanueva JF, Richmond GJ, et al. *N Engl J Med.* 2020;382(12):1112-1123. doi: 10.1056/NEJMoa1904398
2. Overton ET, Richmond G, Rizzardini G, et al. *Lancet.* 2021;396(10267):1994-2005. doi: 10.1016/S0140-6736(20)32666-0.
3. Jaeger H, Overton ET, Richmond G, et al. CROI 2021, abstract #401.
4. Orkin C, Arasteh K, Hernandez-Mora, MG. *N Engl J Med.* 2020;382(12):1124-1135. doi: 10.1056/NEJMoa1909512.

HPTN084 LA Cabotegravir (PrEP)

- Multi-site, double-blind, double-dummy, randomized trial (N=4,566)[1,2]
- LA cabotegravir (IM Q8 weeks after oral lead in) vs FTC/TDF in cisgender women and transgender men at risk of acquiring HIV
- LA cabotegravir was superior to daily FTC/TDF in preventing HIV infection
  - Similar results to HPTN083 study (cisgender men and transgender women)[3]
- Approval for PrEP in 2022?!

LA = Long acting
FTC/TDF = emtricitabine/tenofovir disoproxil fumarate
HPTN = HIV Prevention Trials Network Study
PrEP = Pre-exposure prophylaxis

1. HPTN084 Study Summary. Accessed at www.hptn.org/research/studies/hptn084.
2. Landovitz RJ et al. Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women. *N Engl J Med.* 2021;285:595-608.
3. Landovitz RJ et al. AIDS 2020, #OAXLB01.

Assessment Question 1

A 27-year-old male is being seen for follow-up in your HIV clinic. He has no baseline resistance, NKDA, no current medications besides ART. His viral loads over the past 6 months have been undetectable. He has been vaccinated against HBV. He heard about a new injectable option for HIV treatment. Which of the following would be most appropriate to educate the patient on?

A. Cabotegravir/rilpivirine is only available as an oral solution.

B. Cabotegravir/rilpivirine is only appropriate for treatment naïve patients.

C. Cabotegravir/rilpivirine injections can only be administered by a healthcare provider.

D. Cabotegravir/rilpivirine cannot be used concomitantly with acetaminophen.

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Updates from CROI 2021

- Cabotegravir/rilpivirine
- **Fostemsavir**
- Ibalizumab
- Islatravir
- Lenacapavir

Fostemsavir (Rukobia®) Clinical Pearls

- Approved in August 2020
- Indications
  - Treatment experienced adults
  - Multidrug-resistant HIV-1 infection
  - Failing current ART due to resistance, intolerance, or safety concern
- Dosing
  - 600 mg tablets given twice daily with or without food
- Contraindicated with strong CYP3A4 inhibitors
- Nausea most common ADE

Rukobia. Prescribing Information. ViiV Healthcare; 2020.

Rukobia® Mechanism of Action

- gp120 attachment inhibitor

Temsavir attaches directly to gp120 on HIV cell surface
- Fostemsavir is prodrug of temsavir (active moiety)

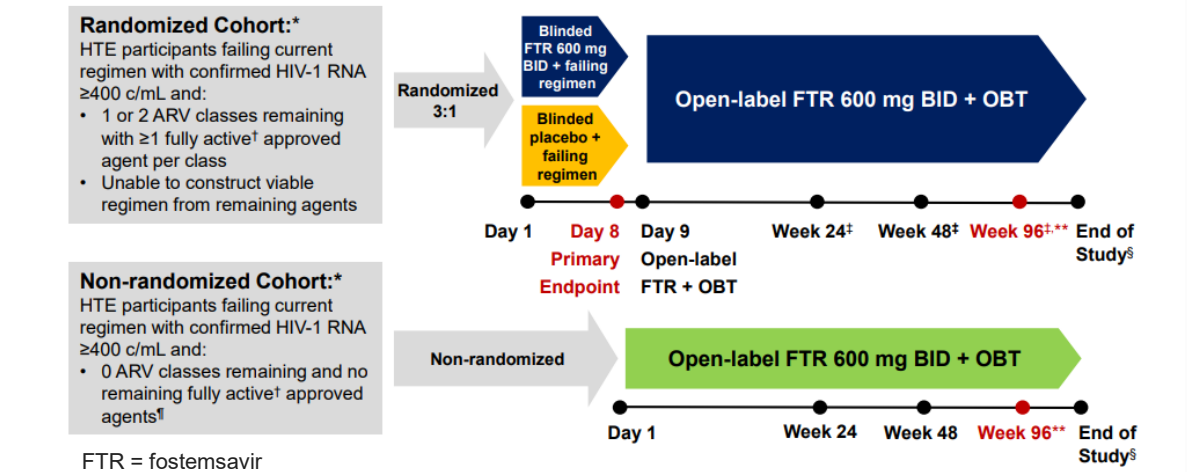
Binds near CD4 binding site, locks gp120 into closed confirmation
- Closed confirmation does not allow for attachment

No interaction between virus/host cell
- Prevents first step of viral entry

Rukobia. Prescribing Information. ViiV Healthcare; 2020.

Summary of Key Studies

- **BRIGHTE study (N=371)**
  - Phase 3, multi-center, randomized controlled trial, heavily treatment experienced (HTE) participants
  - Week 48[1]
    - Rate of virologic response was 53% at week 24 and 54% at week 48 (HIV VL <40 copies/mL)
  - Week 96[2,3]
    - Rates of virologic suppression increased to 60% at week 96
    - CD4 count increased by 205 cells/uL from baseline to week 96 (randomized cohort)



FTR = fostemsavir
OBT = optimized background therapy

1. Kozal M, Aberg J, Pialous G, et al. *N Engl J Med.* 2020;382(13):1232-1243. doi: 10.1056/NEJMoa1902493
2. Lataillade M, Lalezari JP, Kozal M, Aberg JA, Pialoux G, Cahn P. *Lancet HIV.* 2020;7(11):E740-E751. doi: 10.1016/S2352-3018(20)30240-X
3. Lataillade et al. IAS 2019; Mexico City, Mexico. Slides MOAB0102.

Updates from CROI 2021

- Cabotegravir/rilpivirine
- Fostemsavir
- **Ibalizumab**
- Islatravir
- Lenacapavir

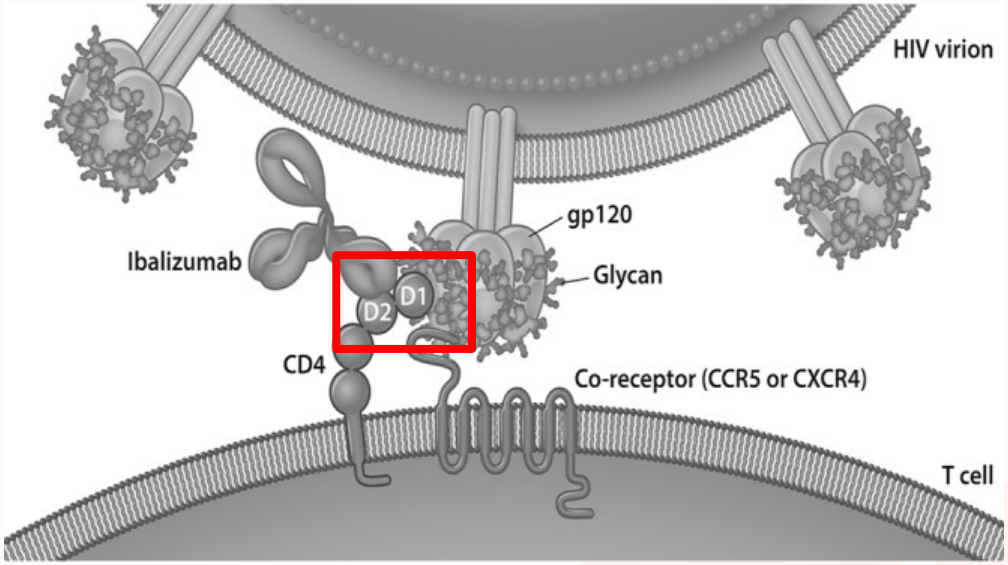
Ibalizumab (Trogarzo®) Clinical Pearls

- Approved in 2018
- Indications
  - Treatment experienced adults
  - Multi-drug resistant HIV-1 infection
  - Failing current ART
- Dosing
  - Single loading dose of 2,000 mg IV followed by 800 mg IV Q2 weeks (available only as 2 mL vial containing 150 mg/mL)
- Non-specific ADEs: diarrhea, dizziness, nausea, rash

Trogarzo®. Prescribing Information. Theratechnologies Inc. 2018.

Trogarzo® Mechanism of Action

- Post-attachment inhibitor



Trogarzo®. Prescribing Information. Theratechnologies Inc. 2018.
Beccari MV, Mogle BT, Sidman EF, et al. *Antimicrob Agents Chemother.* 2019;63(6):e00110-19. doi: 10.1128/AAC.00110-19

Summary of Key Studies

- Single group, open label, phase 3 study (N=40)[1]
- Ibalizumab was added to optimized background regimen (OBR) for individuals failing ART (≥3 class resistance)
- Unique study design → added ibalizumab after day 7
- 83% of participants had decrease in VL from baseline ($p<0.001$) in intention-to-treat population on day 14
  - Viral suppression found in 56% of patients after week 96[2]
- Similar CD4 counts between groups

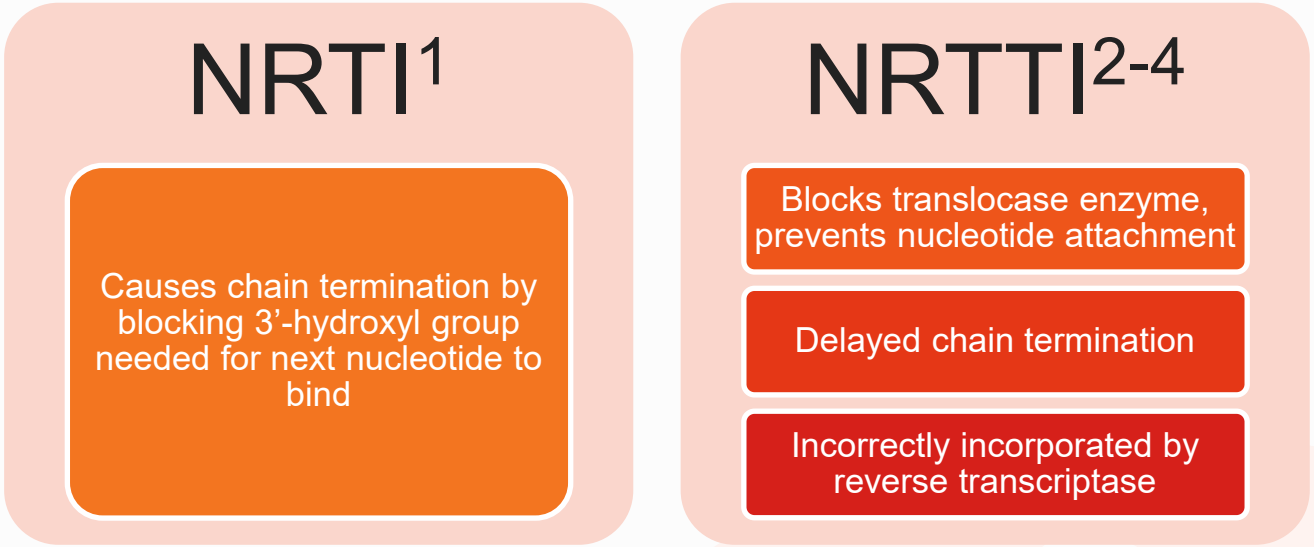
1. Emu B, Fessel J, Schrader S,e t al. *N Engl J Med.* 2018;379(7):645-654. doi: 10.1056/NEJMoa1711460.
2. Emu B, et al. CROI 2019. Abstract #85.

Updates from CROI 2021

- Cabotegravir/rilpivirine
- Fostemsavir
- Ibalizumab
- **Islatravir**
- Lenacapavir

Islatravir Mechanism of Action

- NRTTI → first in its class



NRTI = nucleoside reverse transcriptase inhibitor
NRTTI = nucleoside reverse transcriptase translocation inhibitor

1. Anderson PL, Yager J, Fletcher CV. *Pharmcotherapy: a pathophysiologic approach, 11e.* McGraw-Hill.
2. Michailidis E, Huber AD, Ryan EM, et al. *J Biol Chem*. 2014;289(35):24533-24548. doi:10.1074/jbc.M114.562694
3. Michailidis E, Marchand B, Kodama EN, et al. *J Biol Chem*. 2009;284(51):35681-35691. doi:10.1074/jbc.M109.036616
4. Markowitz M, Sarafianos SG. *Curr Opin HIV AIDS*. 2018;13(4):294-299. doi:10.1097/COH.0000000000000467

Islatravir Clinical Pearls

- Extended half life
- High barrier to resistance
- Activity against NRTI resistant strains
- Few ADEs and drug interactions based on initial studies
- Undergoing clinical studies for oral options (HIV treatment/PrEP), injections (HIV treatment/PrEP), yearly implant (HIV PrEP)

Source: Clinicalinfo.hiv.gov/en/drugs/islatravir/patient

Summary of Key Studies (HIV Treatment)

Treatment	Duration	Primary endpoint	Results	Trial
Molina et al[1] ISL + DOR + 3TC (randomized 1:1:1:1)	24 weeks	Viral load <50 copies/mL	Reported in ~90% of participants in all arms	Phase 2B
AIDS 2020[2,3] ISL alone vs DOR/3TC/TDF	48 weeks	Safety analysis	HA, nausea, diarrhea most common ADE	Phase 2B
Ongoing NCT04223778 NCT04223791 NCT04233216 NCT04233879 NCT04003103	Varies from 26 to 144 weeks	Switch studies, comparison to Biktarvy, treatment simplification	Pending (will evaluate both tx naïve and tx exp patients)	Phase 3

1. Molina JM, Yazdanpanah Y, Saud AA, et al. *Lancet HIV.* 2021;8(6):E324-333. doi: 10.1016/S2352-3018(21)00021-7
2. Orkin et al. AIDS 2020. Abstr OAB0302.
3. DeJesus et al. AIDS 2020. Abstr OAB0305.

Summary of Key Studies (HIV PrEP)

Treatment	Duration	Primary endpoint	Results	Trial
Ongoing ISL once daily vs FTC/TDF (NCT04644029) ISL once daily vs FTC/TDF or FTC/TAF (NCT04652700)	ISL as oral tablet administrated once monthly	Incidence rate per year of confirmed HIV infections	Pending	Phase 3
Ongoing ISL in adults at low risk of HIV infection	ISL as once monthly injection	Pending	Pending	Phase 1/2
Other -Long-acting subdermal implant of ISL	ISL as once monthly injection	Pending	Pending	Phase 1

Source: Islatravir Clinical Program Overview, Merck. October 2021.

Assessment Question 2

Which of the following is the proposed mechanism of action of islatravir?

A. Nucleoside reverse transcriptase inhibitor (NRTI)

B. Integrase strand transfer inhibitor (INSTI)

C. Fusion inhibitor

D. Nucleoside reverse transcriptase translocation inhibitor (NRTTI)

Assessment Question 2

Which of the following is the proposed mechanism of action of islatravir?

A. Nucleoside reverse transcriptase inhibitor (NRTI)

B. Integrase strand transfer inhibitor (INSTI)

C. Fusion inhibitor

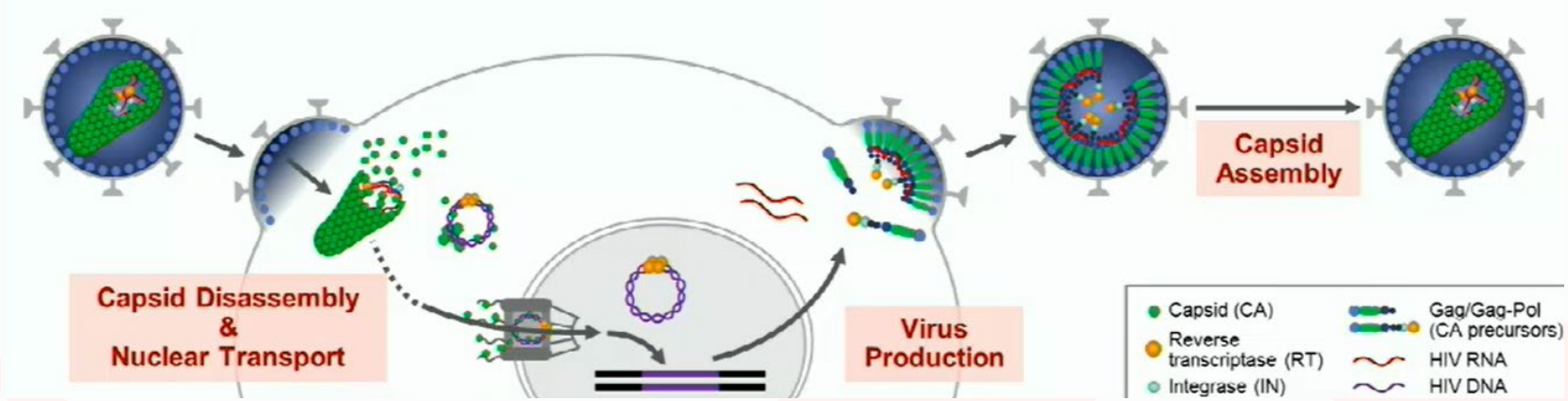
D. Nucleoside reverse transcriptase translocation inhibitor (NRTTI)

Updates from CROI 2021

- Cabotegravir/rilpivirine
- Fostemsavir
- Ibalizumab
- Islatravir
- **Lenacapavir**

Lenacapavir Mechanism of Action

- Capsid inhibitor → first in its class (multiple MOA)



Graphic from presentation given by Sagar et al at CROI 2019

Sager et al. CROI 2019, abstract #141.
Carnes SK, Sheehan JH, Aiken C. *Curr Opin HIV AIDS.* 2018;13(4):359-365.

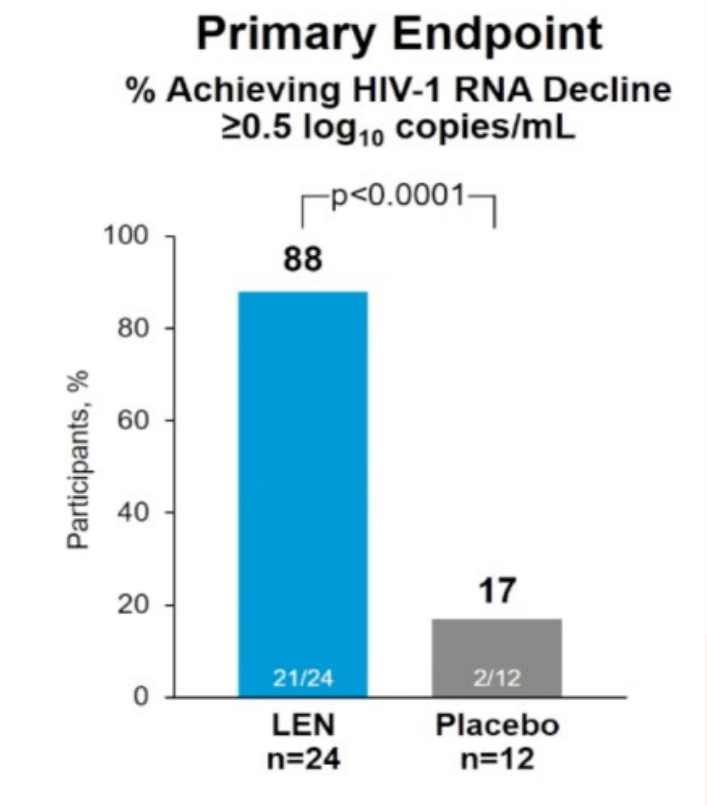
Lenacapavir Clinical Pearls

- Undergoing development as component of long-acting HIV therapy as well as for HIV PrEP
- Several abstracts presented at CROI depicting:
  - Drug interactions[1]
  - Antiviral activity in treatment experienced patients[2]
  - Resistance profile[3]
  - Dose adjustments[4]
- IAS 2021 conference[5]:
  - Phase 2/3 CAPELLA data
  - CALIBRATE study (phase 2 trial)

1. Begley et al. CROI 2021. Abstract #89.
2. Segal-Maurer et al. CROI 2021. Abstract #127.
3. Callebaut et al. CROI 2021. Abstract #128.
4. Jogiraju et al. CROI 2021. Abstract #375.
5. IAS Conference. July 2021. Press Release.

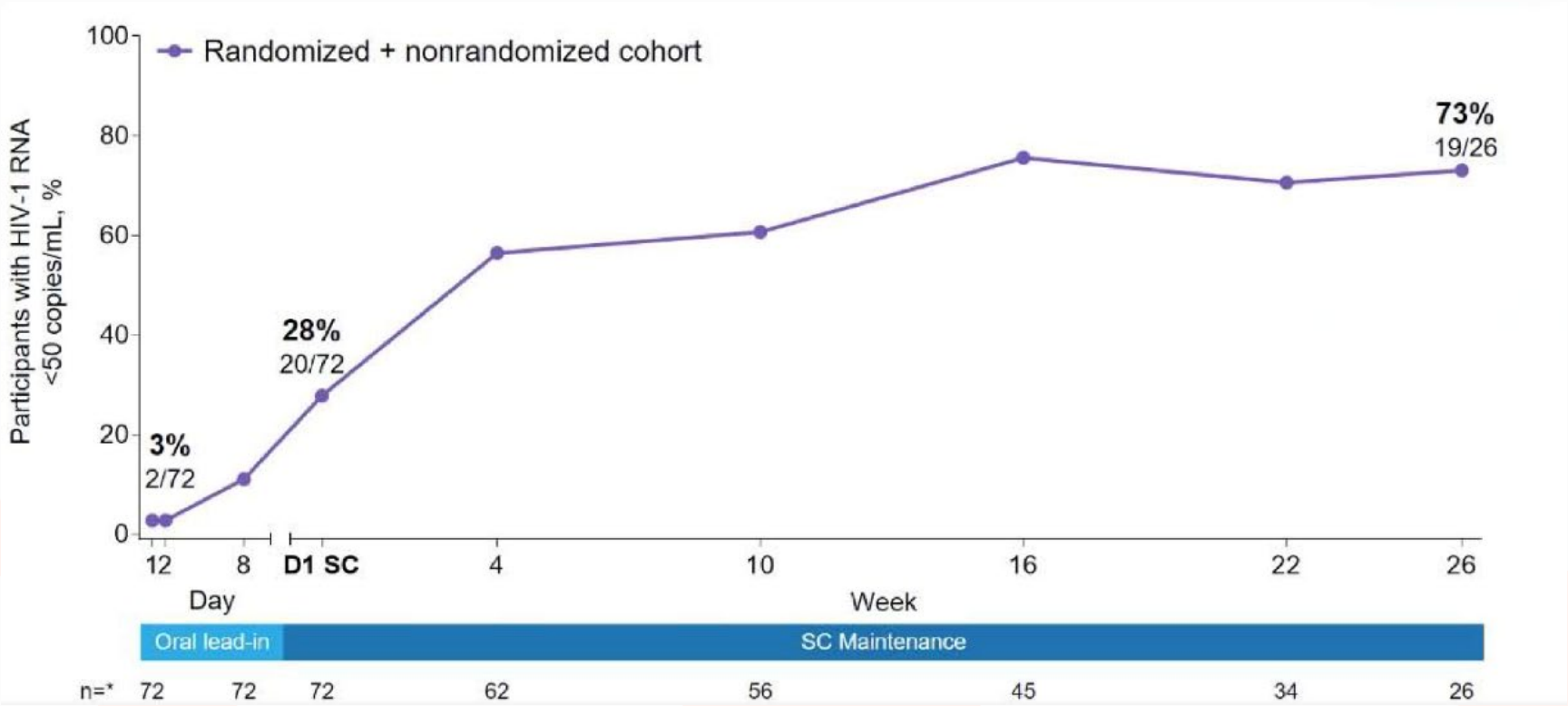
Summary of Key Studies

- CAPELLA (2021)
  - 2 treatment arms examining oral vs subcutaneous lenacapavir
  - Add-on to failing ART with resistance
  - Combination with optimized background treatment
  - Maintained high rates of virologic suppression through 26 weeks



Segal-Maurer et al. CROI 2021. Abstract #127.

Summary of key studies (continued)



Segal-Maurer S, et al. CROI 2021. Abstract #127.

Additional Updates

- IMPAACT 2010 results[1]
- GSK3640254 phase II results[2]
- Collaboration with Merck for islatravir/lenacapavir combined long acting injectable[3]

1. Chinula et al. CROI 2021. Abstract #177.
2. Jeffrey et al. CROI 2021. Abstract #421.
3. Merck Press Release. Accessed at https://www.merck.com/news/gilead-and-merck-announce-agreement-to-jointly-develop-and-commercialize-long-acting-investigational-treatment-combinations-of-lenacapavir-and-islatravir-in-hiv-2/

Key Takeaways

- Several new medications have (and will) entered the HIV drug market with novel mechanisms of action
- Options for injectable, long-acting, and oral medications may improve HIV treatment landscape for treatment naïve and experienced patients
- Novel options for PrEP may include q6 months injections and implantable devices