Future Horizons: Innovations Shaping the ART Landscape

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Disclosures

- Speaker's Bureau: Gilead and ViiV
- Consultant: Gilead, Merck, ViiV, Abbott, AbbVie

Objectives

1. Describe current trends in HIV treatment.

2. Identify investigational HIV drugs in development.

3. Discuss emerging future strategies in HIV management.

Evolution of ART: Past to Present

1985-89

1987
Zidovudine (NRTI)

HIVinfo.NIH.gov

1990-94

1991
Didanosine* (NRTI)

1992
Zalcitabine* (NRTI)

1994
Stavudine* (NRTI)

1995-99

1995
Lamivudine (NRTI)
Saquinavir Mesylate* (PI)

1996
Indinavir* (PI)
Nevirapine (NNRTI)
Ritonavir (PI)

1997
Combivir* (FDC)
Delavirdine* (NNRTI)
Nelfinavir* (PI)
Saquinavir* (PI)

1998
Abacavir (NRTI)
Efavirenz (NNRTI)

1999
Amprenavir* (PI)

2000-04

2000
Didanosine EC* (NRTI)
Kaletra (FDC)
Trizivir* (FDC)

2001
Tenofovir DF (NRTI)

2002
Stavudine XR* (NRTI)

2003
Atazanavir (PI)
Emtricitabine (NRTI)
Enfuvirtide (FI)
Fosamprenavir* (PI)

2004
Epzicom* (FDC)
Truvada (FDC)

2005-09

2005
Tipranavir* (PI)

2006
Atripla* (FDC)
Darunavir (PI)

2007
Maraviroc (CA)
Raltegravir (INSTI)

2008
Etravirine (NNRTI)

2010-14

2011
Complera (FDC)
Nevirapine XR (NNRTI)
Rilpivirine (NNRTI)

2012
Stribild (FDC)
Truvada (PrEP)

2013
Dolutegravir (INSTI)

2014
Cobicistat (PE)
Elvitegravir* (INSTI)
Triumeq (FDC)

2015-19

2015
Evotaz (FDC)
Genvoya (FDC)
Prezcobix (FDC)

2016
Descovy (FDC)
Odefsey (FDC)

2017
Juluca (FDC)
Raltegravir HD (INSTI)

2018
Biktarvy (FDC)
Cimduo (FDC)
Delstrigo (FDC)
Doravirine (NNRTI)
Ibalizumab-uiyk (PAI)
Symfi (FDC)
Symfi Lo (FDC)
Symtuza (FDC)
Temixys* (FDC)

2019
Dovato (FDC)
Descovy (PrEP)

2020-24

2020
Fostemsavir* (AI)
Tivicay PD (INSTI)

2021
Cabenuva (FDC)
Cabotegravir (INSTI)
Cabotegravir (PrEP)

2022
Triumeq PD (FDC)
Lenacapavir (CI)

2024
Rilpivirine PED (NNRTI)

Drug Class Abbreviations:
AI: Attachment Inhibitor; **CA:** CCR5 Antagonist; **CI:** Capsid Inhibitors; **FDC:** Fixed-Dose Combination; **FI:** Fusion Inhibitor; **INSTI:** Integrase Inhibitor; **NNRTI:** Non-Nucleoside Reverse Transcriptase Inhibitor; **NRTI:** Nucleoside Reverse Transcriptase Inhibitor; **PE:** Pharmacokinetic Enhancer; **PI:** Protease Inhibitor; **PAI:** Post-Attachment Inhibitor; **PrEP:** Pre-exposure prophylaxis

***Note:** Approvals are for HIV treatment, unless otherwise indicated. Drugs in gray are no longer available and/or are no longer recommended for use in the United States by the HHS HIV/AIDS medical practice guidelines. These drugs may still be used in fixed-dose combination formulations. Fixed-dose combination brand products in gray may be available as generics.

Future Interventions

INSTIs
- CAB-ULA Q4M
- GS-1720 Oral QWk
- VH-184 LA Inj
- GS-6212 Q3M
- GS-1219 Q6M
- GS-3242 Q6M
- ULA BIC Q6M
- ULA pro-CAB ≥Q6M
- DTG Implant Q6M

PIs
- GS-9770 Oral QWk, unboosted

Capsid Inhibitors
- VH-289
- VH-499
- GS-4182 pro-LEN

Maturation Inhibitor
- VH-937 QWk

NNRTIs
- MK-8507 Oral QWk
- GS-5894 Oral QWk

bNAbs
- ABBV-181
- ABBV-382
- TMB-380
- N6LS (+CAB)
- ZAB, TAB (+LEN)
- SAR441236
- VRCO7-523LS (+CAB)
- PGDM1400 + PGT121 + VRC07-523LS
- TMB-365 + VRC07-523LS

NRTTIs
- Islatravir
- MK-8527 Oral QWk(ART) or QM (PrEP)
- GS-1614 ISL prodrug;

Adapted from: Thompson, M. The Future of HIV Care (and Prevention), ACTHIV 2024.

Emerging Technologies

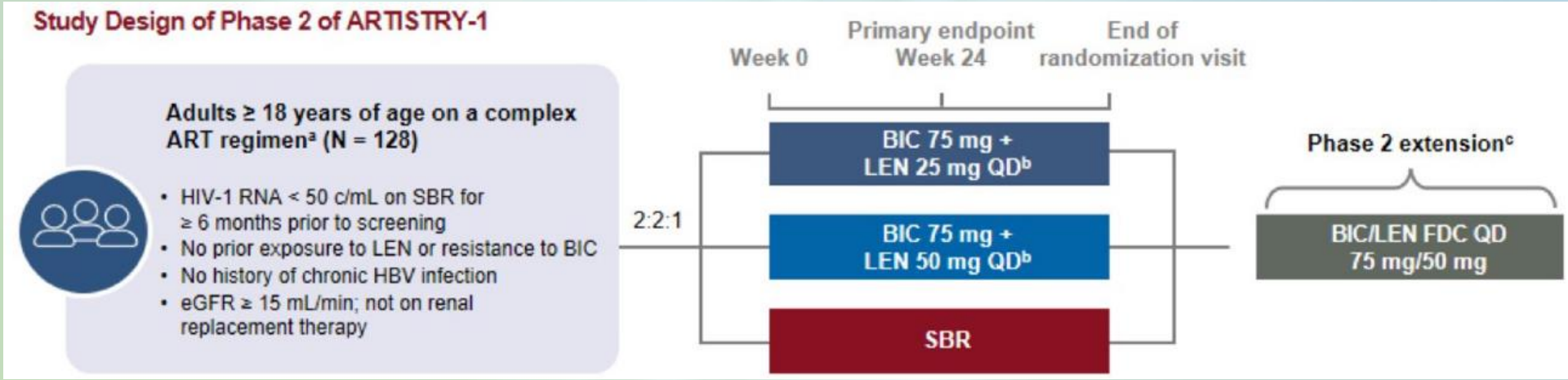
- Long-Acting and Ultra Long-Acting (ULA)
- Gene-Based Therapies
- Immunotherapy
  - Monoclonal Therapy
- Functional Cure

Long-Acting ART

- MK-8527 (PrEP)
  - NRTTI
  - single doses of MK-8527 as low as 0.5 mg achieved ≥1 log10 decreases in HIV-1 RNA at Day 7[1]
  - Longer T ½ than ISL
- GS-1720
  - INSTI
  - Single dose of 450mg has T½ 9.4 days
  - > 2 log decline for 150, 450, 900 mg dose levels
  - Target therapeutic range reached in all participants in 450 mg and 900 mg arms
  - No treatment emergent resistance in 150 mg and 450 mg arms; testing ongoing in 30mg and 900 mg cohorts

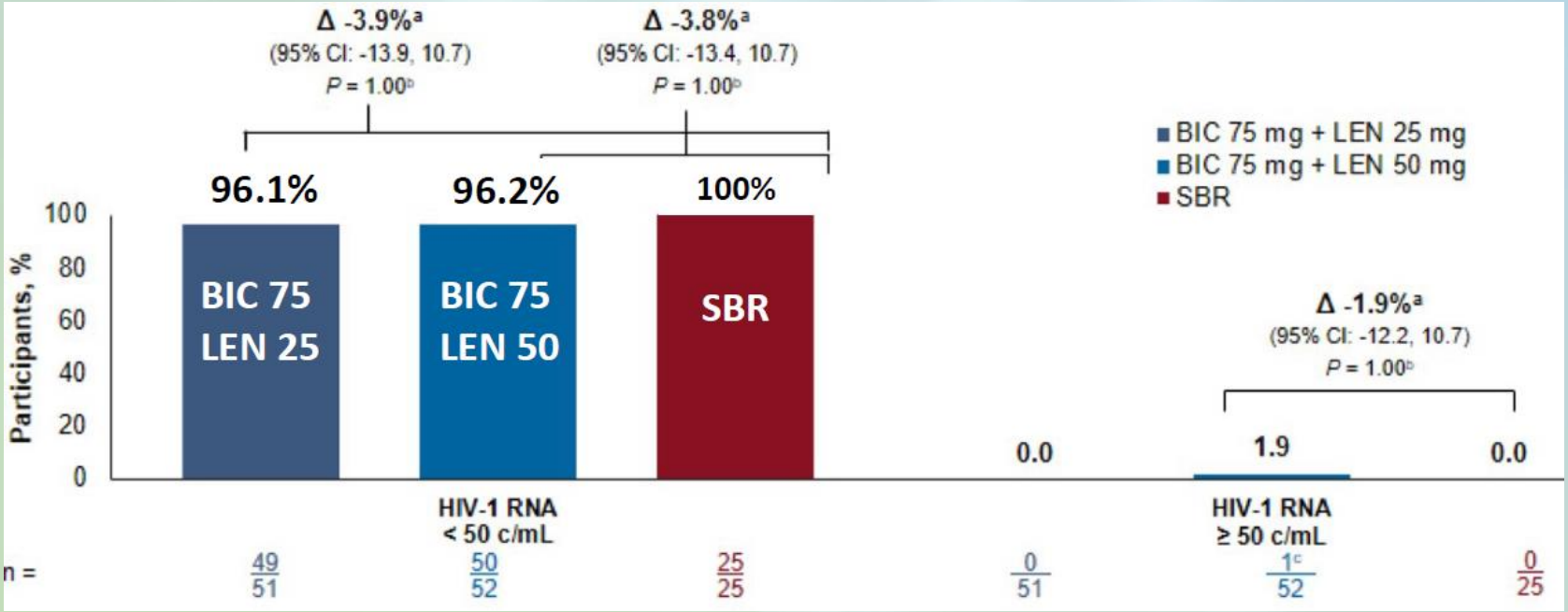
Carstens, et al. CROI 2024, Abstract 115,
Fichtenbaum, et. al. CROI 2024, Abstract 116.

ARTISTRY-1: Phase 2 Study of Switch to Daily BIC + LEN in Individuals on a Complex HIV Treatment Regimen



Data: Mounzer, et al. CROI 2024, Abstract 642,

ARTISTRY-1: Virologic Outcomes at Week 24



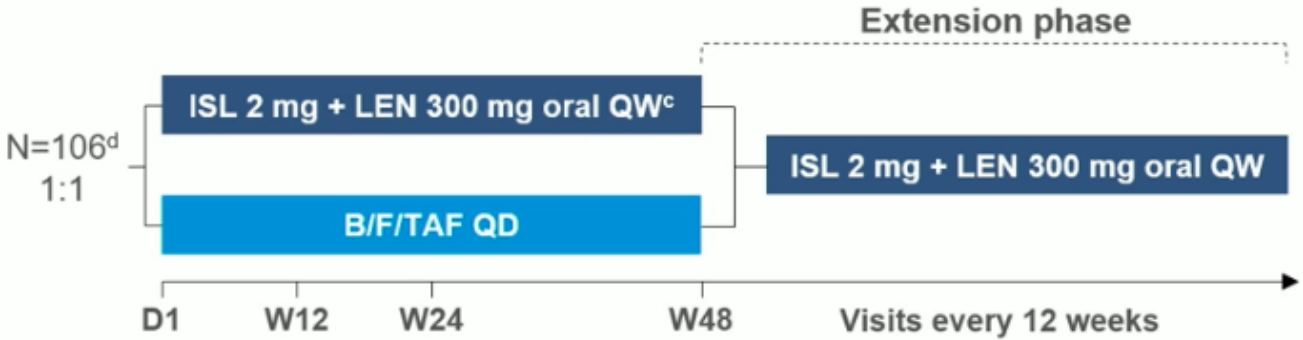
Data: Mounzer, et al. CROI 2024, Abstract 642,

Weekly ISL + LEN in PWH: A Phase 2 Study

A Phase 2, open-label, active-controlled study in virologically suppressed PWH[a]

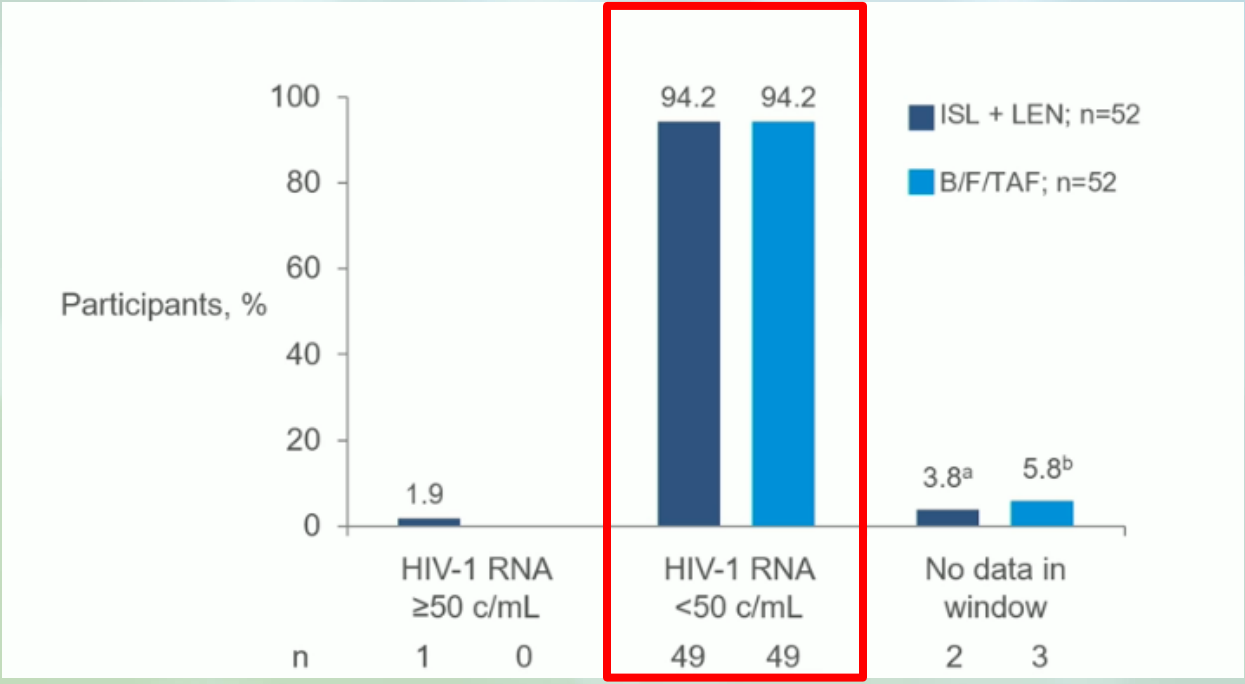
Inclusion criteria

- Aged ≥18 years
- Viral load <50 c/mL on B/F/TAF[b]
- No history of virologic failure
- CD4 count ≥350 cells/µl
- Lymphocytes ≥900 cells/µl
- No HBV infection



Colson et al. CROI 2024, Abstract 208

Weekly ISL + LEN in PWH: Virologic Efficacy at Week 24



Colson et al. CROI 2024, Abstract 208

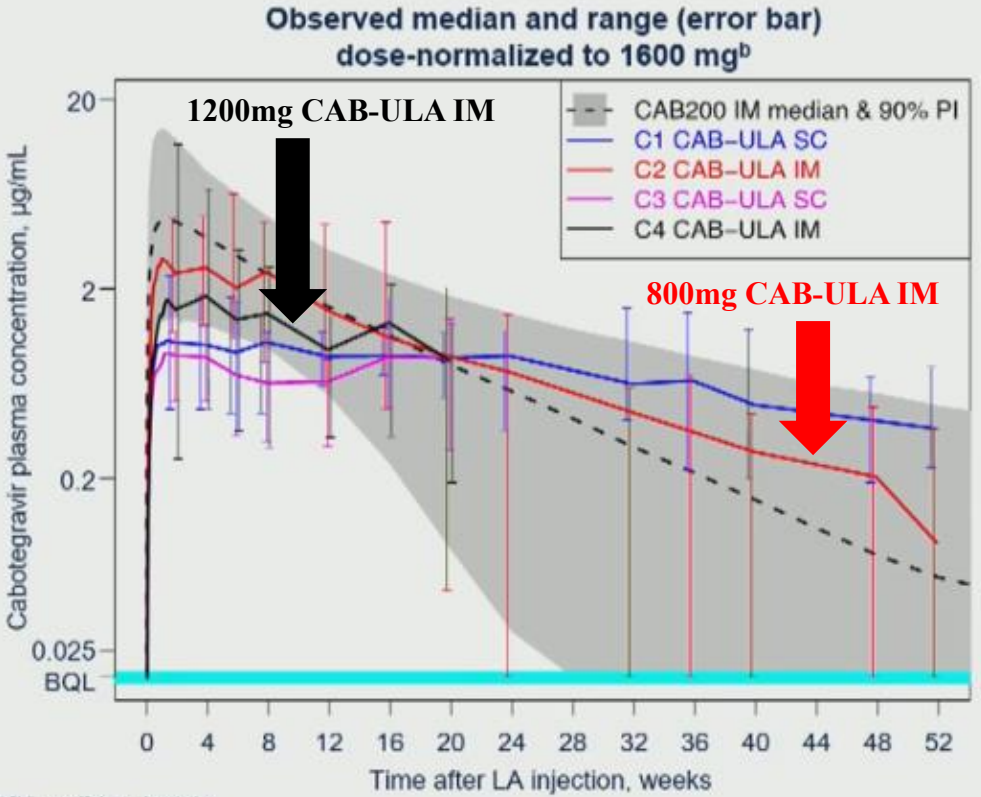
CAB-ULA PHARMACOKINETICS

Part C: CAB-ULA

Parameter, geometric mean (%CVb)	SC C1 800 mg (2 mL) (n=8)	SC C3 1200 mg (3 mL) (n=8)	IM C2 800 mg (2 mL) (n=8)	IM C4 1200 mg (3 mL) (n=8)
Cmax, µg/mL	0.7 (35.5)	0.8 (39.0)	1.8 (53.5)	1.8 (148)
tmax, hours	570 (158)	349 (147)	298 (136)	383 (107)

CAB-ULA has slower absorption and longer $t_{1/2}$ than CAB200 IM

- PK profiles were flatter than CAB200 IM
- CAB-ULA Cmax was lower with SC than IM; both were lower than CAB200 IM[1]
- tmax was longer than CAB200 IM[1]
- **CAB-ULA $t_{1/2}$ for SC and IM was predicted to be >6x and >2x the $t_{1/2}$ of CAB200 IM, respectively[1,a]**

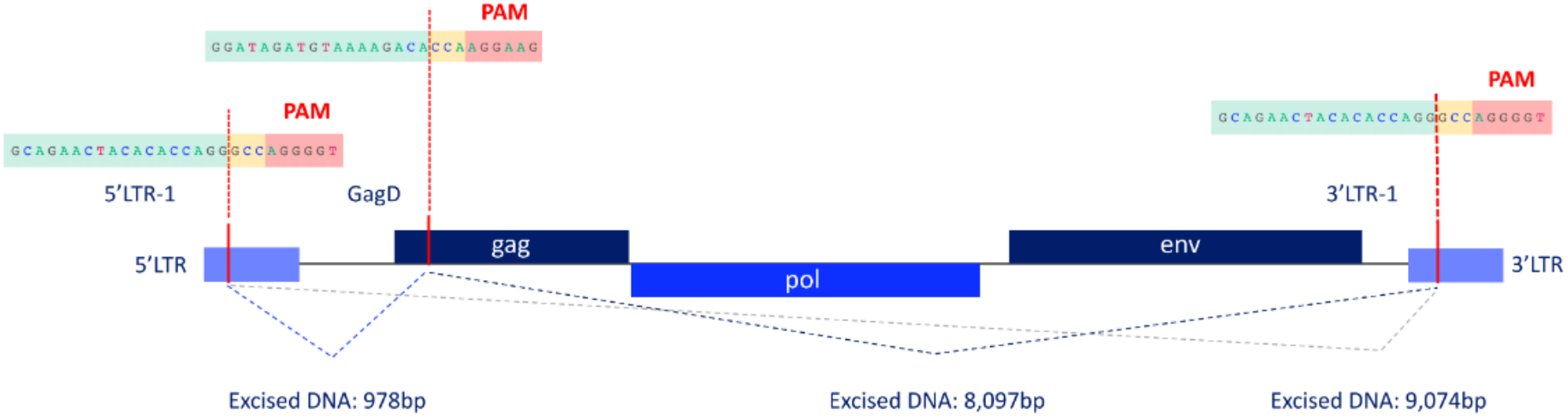


BQL, below quantification limit of 0.025 µg/mL; CAB, cabotegravir; Cmax, maximum observed plasma concentration; %CVb, coefficient of variation;

Han, et al. CROI 2024. Abstract 130

Gene-based Therapies

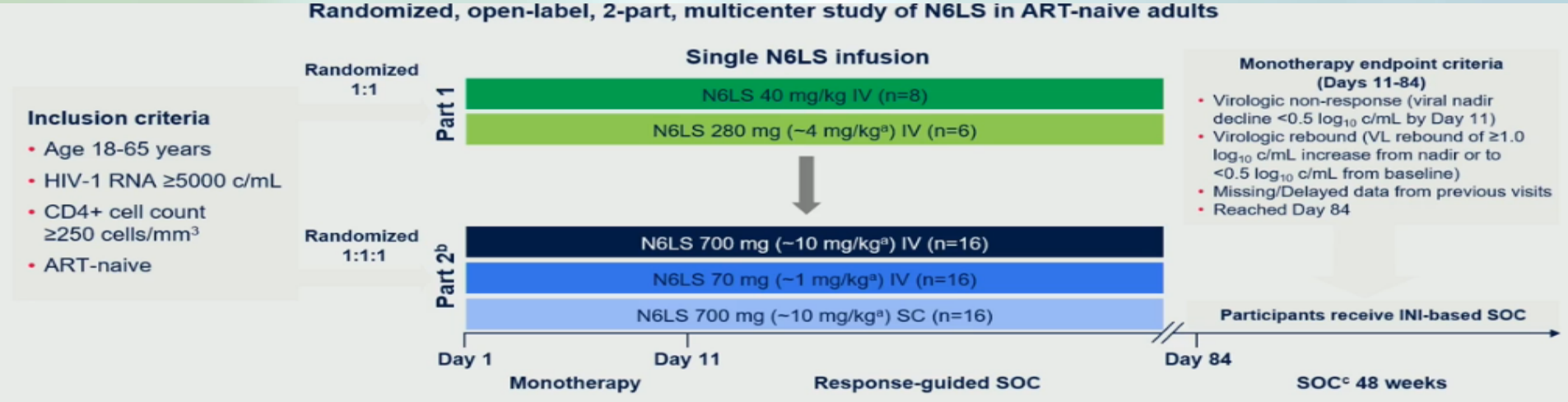
- CRISPR/Cas9
  - Excision EBT-101
    - Safe and well tolerated but did not prevent viral rebound in three participants who stopped antiretroviral treatment



Excision BioTherapeutics. Excision BioTherapeutics announces data from the phase 1/2 trial of EBT-101 in hiv and in vivo efficacy data in herpes virus and hepatitis B. Press release, 13 May 2024.

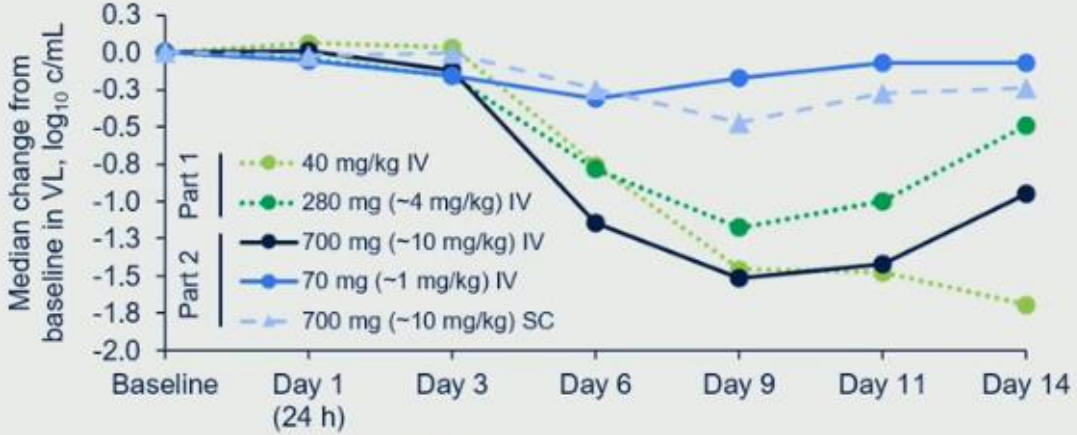
Immunotherapy

- N6LS
  - VH3810109 (N6LS) in Adults With HIV-1 Who Are ART-Naive-: Phase IIa BANNER Efficacy Data
  - Robust antiviral effect when given at 40 mg/kg IV in PLWH



Losos, et al. CROI 2024; Oral Abstract 117

BANNER Part 2: SC Antiviral Activity



- Lower exposures were observed with SC vs IV administration using the same N6LS dose
- Lower SC exposure due to first-pass lymphatic elimination
- The SC response was as expected when considering N6LS exposures achieved

	Part 1				Part 2
Viral dynamic measures, median (range)	N6LS 40 mg/kg IV (N=8)	N6LS 280 mg IV (~4 mg/kg[a]) (N=6)	N6LS 700 mg IV (~10 mg/kg[a]) (N=16)	N6LS 70 mg IV (~1 mg/kg[a]) (N=16)	N6LS 700 mg SC (~10 mg/kg[a]) (N=16)
Viral nadir from baseline, log_{10} c/mL	−1.72 (−2.60, −0.60)	−1.18 (−2.18, −0.30)	−1.54 (−2.22, −0.41)	−0.43 (−1.29, −0.12)	−0.50 (−2.13, −0.09)
Time to viral nadir, days	16 (5-21)	9 (7-16)	9 (6-27)	7 (2-23)	9 (1-50)
Time to viral rebound among responders, days	35 (12-78) [n=8]	18 (14-29) [n=5]	22 (14-43) [n=14]	13 (10-22) [n=7]	17 (11-63) [n=8]

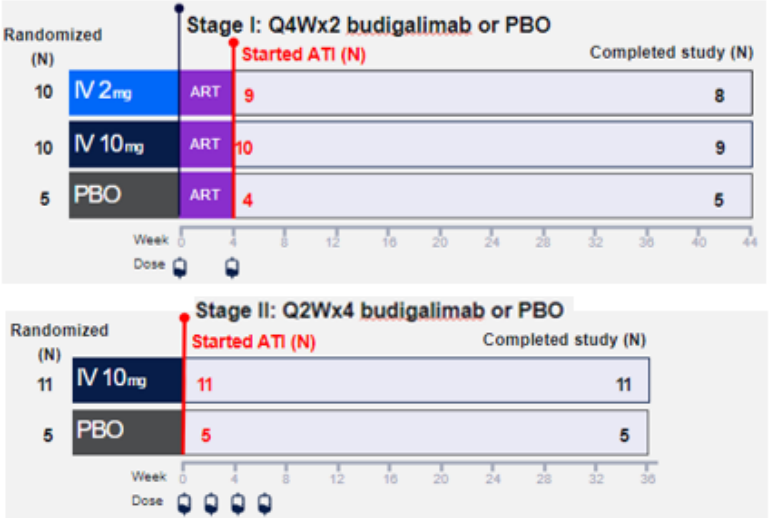
IV, intravenous; N6LS, VH3810109; SC, subcutaneous; VL, viral load.
[a]For a 70-kg individual.

Krishnan: Biomarker signatures in Phase 1b study with PD-1 inhibitor, budigalimab, in PLWH undergoing ATI (1 of 2) (oral)

Study M19-939 (NCT04223804) is a Phase 1b randomized double-blind study investigating low-dose budigalimab in PLWH undergoing ATI

Key study details

- Budigalimab is an investigational humanized, recombinant IgG1 L234A L235A mAb
- Study objective: identify potential efficacious dose and regimen of budigalimab with favorable safety in PLWH
- Study outcomes: safety, PK, PD-1 receptor saturation, biomarkers, and viral kinetics



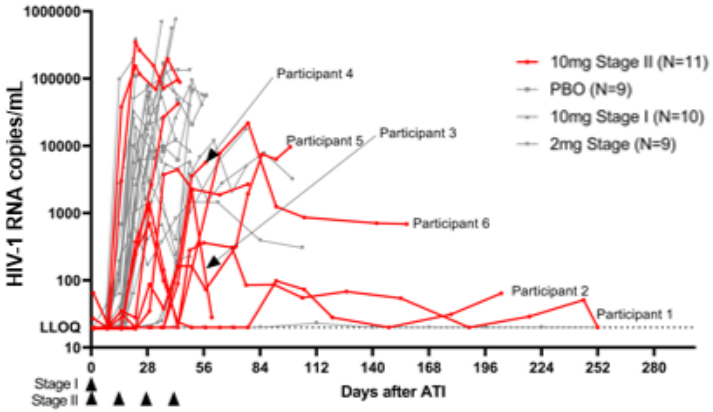
Baseline Characteristics	Stage I: Q4W×2			Stage II: Q2W×4	
	Placebo N=5	2 mg IV N=10	10 mg IV N=10	Placebo N=5	10 mg IV N=11
Male	5 (100)	10 (100)	10 (100)	5 (100)	10 (91)
Age, y	44 (14)	42 (13)	47 (14)	49 (11)	47 (14)
HIV-1 disease, y	11 (13)	9 (8)	13 (9)	19 (6)	11 (7)
CD4+ cell count, cells/uL	652 (143)	887 (263)	785 (175)	680 (160)	775 (203)
Viral suppression on ART, y	10 (12)	7 (5)	13 (9)	16 (5)	11 (6)
%CD8+ PD-1+ cells	**45 (14)**	**39 (16)**	**42 (15)**	**42 (23)**	**41 (7)**

Data are expressed as number (%) or mean [SD]

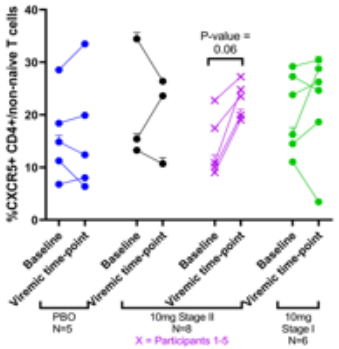
Krishnan: Biomarker signatures in Phase 1b study with PD-1 inhibitor, budigalimab, in PLWH undergoing ATI (2 of 2) (oral)

Biweekly administration of budigalimab 10 mg IV for 4 doses led to delayed viral rebound and/or ART-free viral control in 6 of 9 participants who completed dosing, with 2 participants remaining off ART until the end of the study

VL kinetics during ATI



% T follicular helper-like cells



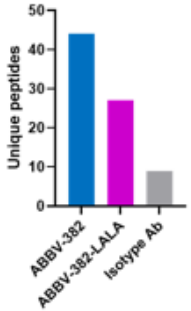
Key findings:

- Budigalimab administered for short duration at low doses was well tolerated in PLWH. Target engagement was observed at all doses with near-complete PD-1 receptor saturation for ~10 weeks post-ATI with four 10-mg biweekly IV doses
- Trends in budigalimab-dependent increase in T follicular helper-like cells, CD8+CXCR5+ cells, and CD4+CCR6+ cells were observed in participants with low viral load
- Viremia during ATI was associated with increased CD8+ T-cell activation, proliferation, differential transcriptomic trajectories, and TCR clonality/diversity

Krishnan, et al. CROI 2024; Oral 106

Ng: ABBV-382, an anti-α4b7 Ab that enhances HIV-1 antigen presentation for immune-mediated viral control (poster)

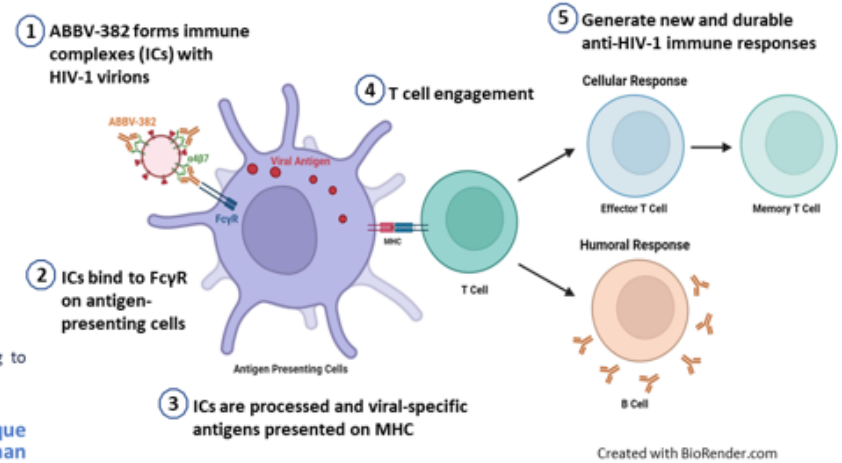
ABBV-382 inhibits HIV-1 replication/cell-to-cell spread via direct antagonism of the interaction of α4β7 with its cognate ligand MAdCAM-1 or HIV-1 gp120. Additionally, ABBV-382 can bind to α4β7 incorporated in the HIV-1 virions to form immune-complexes that can bind to FcγRs expressed on antigen-presenting cells and enhance viral antigen presentation to T cells, potentially inducing immune responses to control viral replication



g. 5D. Number of identified unique peptides mapping to IV-1-Gag-GFP in the indicated samples

ABBV-382 treated cells presented more unique HIV-1 peptides in MHC class II complex than those treated with ABBV-382 LALA or isotype control Ab

Proposed model for the immune modulation mediated by ABBV-382



Key study details:

- ABBV-382 is a novel anti-human α4β7 mAb with preserved Fc functionality
- ABBV-382 was evaluated in vitro in biochemical, virological, immunosafety, and immunopeptidomics studies to characterize its properties and determine its mechanisms of action for immune-mediated HIV-1 control
- ABBV-382, in combination with budigalimab, an anti–PD-1 mAb, is being studied in a Phase 2 study examining ART-free viral control

Functional Cure?

Summary

- Moving Away from Daily Drugs
- New Direction → Weekly Oral Dosing
- bNAbs Expanding
- Innovative Delivery Systems

THANK YOU!