Investigational Approaches to Antiretroviral Therapy: New Strategies and Novel Agents

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IAS–USA

Learning Objectives

After attending this presentation, learners will be able to:

- List several two-drug combinations that are being evaluated for initial or maintenance therapy
- Describe characteristics of the long acting injectable antiretroviral therapy in late-stage development
- Describe the mechanisms of action and potential uses of 2 entry inhibitors in development for patients with resistant virus

Outline of the Talk

- New Two-drug Strategies for Initial ART and treatment switch (long-acting therapy)
- Novel Agents for Resistant Virus
- New Agents in Early Development

ARS Question 1

- Your "go to" initial ART is
  1. Bictegravir/FTC/TAF
  2. Dolutegravir/abacavir/lamivudine
  3. Dolutegravir plus TAF (or TDF)/FTC
  4. Elvitegravir/cobi/TAF (or TDF)/FTC
  5. Darunavir/r (or cobi) plus TAF(or TDF)/FTC
  6. Rilpivirine/TAF (or TDF)/FTC
  7. Something else

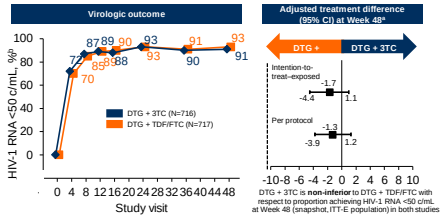
What is needed for initial therapy?

- We have convenient, safe, effective unboosted integrase inhibitor therapy – do we need something else?
- Alternatives to INSTI – based therapy?
  - NNRTI – based therapy
    - with better tolerability,
    - less resistance and fewer dosing restrictions?
  - PI - based therapy
    - more convenient
    - Fewer drug-drug interactions
- Exposure to fewer agents?
  - Two drug combinations
- Alternative dosing strategies

Two Drug Regimens for Initial Therapy

- Rationale
  - "nuc-sparing" – a need that seems less critical now
    - advanced renal disease or TFV or ABC intolerance
  - Minimize ARV exposure for therapy that will last for decades
  - Cost
- Strategies
  - Boosted PI plus INSTI (NEAT 001)
  - Boosted PI plus 3TC (GARDEL and ANDES studies)
  - Dolutegravir plus 3TC (PADDLE, A5353, GEMINI)

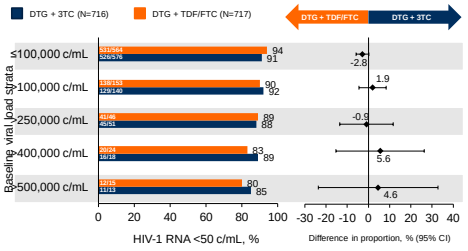
Snapshot Analysis by Visit: Pooled ITT-E Population



[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) and CD4+ cell count (≤200 vs >200 cells/mm³). [b]Calculated from a repeated measures model adjusting for study, treatment, visit (repeated factor), baseline plasma HIV-1 RNA, baseline CD4+ cell count, treatment and visit interaction, and baseline CD4+ cell count and visit interaction.

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

Proportion of Participants With Plasma HIV-1 RNA <50 c/mL at Week 48 (Snapshot Analysis) by Baseline Plasma HIV-1 RNA

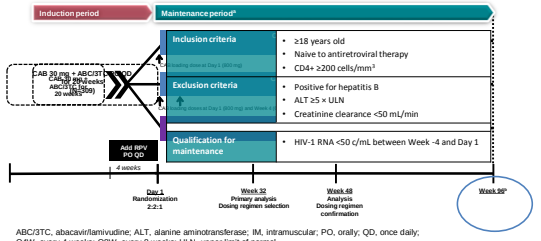


Cahn et al. *Lancet*. 2018 [Epub ahead of print].

ARS Question 2

- Based on the GEMINI 48 week data, in what setting will you use dolutegravir/3TC?
  1. As initial therapy with any baseline viral load
  2. As initial therapy in specific patients with lower viral loads
  3. As maintenance therapy in patients who are suppressed on 3-drug treatment
  4. I will wait until we have longer term (96 week data) with DTG/3TC to decide
  5. Only when insurance companies tell me to use it
  6. Something else

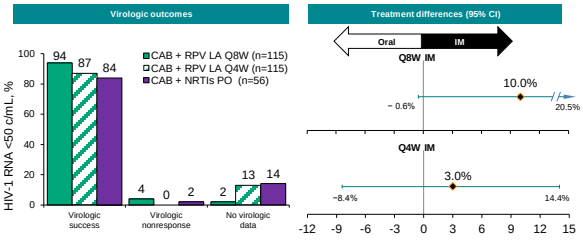
LATTE-2: Study of Long Acting Cabotegravir and Rilpivirine – 96 week data



ABC/3TC, abacavir/lamivudine; ALT, alanine aminotransferase; IM, intramuscular; PO, orally; QD, once daily; Q4W, every 4 weeks; Q8W, every 8 weeks; ULN, upper limit of normal.
[a]Subjects who withdrew after at least 1 IM dose entered the long-term follow-up period. [b]Subjects can elect to enter Q4W and Q8W LA extension phase beyond Week 96.

Eron et al. IAS 2017; Paris, France. Slides MOAX0205LB.

Comparable Response Across Arms
Week 96 HIV-1 RNA <50 c/mL by Snapshot (ITT-ME)



CAB, cabotegravir; CI, confidence interval; IM, intramuscular; ITT-ME, intent-to-treat maintenance exposed; LA, long acting; NRTI, nucleoside reverse transcriptase inhibitor; PO, orally; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

Eron et al. IAS 2017; Paris, France. Slides MOAX0205LB.

Latte 2 Outcomes at 160 Weeks

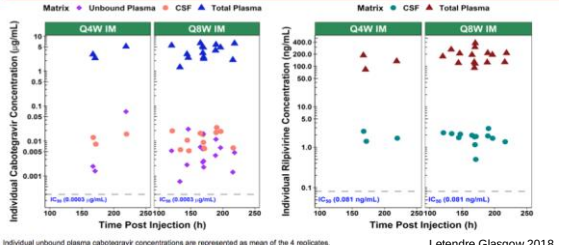
258 completed MP with 252 entering EP

Table 1. Snapshot Outcomes at Week 160

Outcome at W160[a]	Q8W IM n (%)	Q4W IM n (%)	Optimized Q8W IM n (%)	Optimized Q4W IM n (%)
Snapshot (ITT-ME)	N=115	N=115	N=34	N=10
HIV-1 RNA <50 c/mL	**104 (90)**	**95 (83)**	**33 (97)**	**10 (100)**
HIV-1 RNA ≥50 c/mL	**5 (4)**	**0**	**1 (3)**	**0**
Data in window not <50 c/mL	1 (<1)[b]	0	0	0
DC for lack of efficacy	1 (<1)	0	1 (3)	0
DC for other reason while not <50 c/mL	3 (3)[c]	0	0	0
No virologic data in window	**6 (5)**	**20 (17)**	**0**	**0**
W/D due to AE or death	1 (<1)	12 (10)[d]	0	0
W/D due to other reasons	5 (4)[e]	8 (7)[f]	0	0

[a]Data presented for the randomized Q8W/Q4W IM arms are inclusive of MP and EP. Data presented for the optimized Q8W/Q4W IM arms are inclusive of on-treatment events occurring from the first date of first injection in the EP. W100, 977 c/mL. [b]>50 c/mL at W96 and did not qualify for EP. [c]Added in EP: CAD; MI (death); motor neuron disease. [d]Relocation; entered LTFU; burden of travel; lost to FU. [e]Added in EP: PD; lost to FU; WD by patient.

Relationship Between CAB and RPV Concentration in Plasma and CSF



Individual unbound plasma cabotegravir concentrations are represented as mean of the 4 replicates.
CSF, cerebrospinal fluid; IM, intramuscularly; Q4W, every 4 wk; Q8W, every 8 wk.

Letendre Glasgow 2018

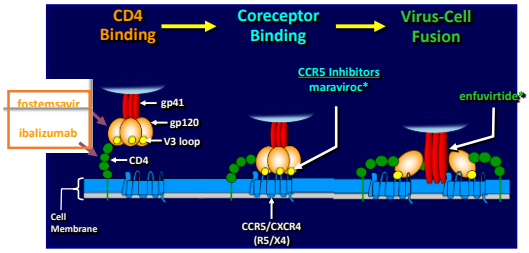
LA CAB and LA RPV Phase III studies

- **ATLAS** – randomized, open label, non-inferiority study in participants stably suppressed on 3-drug ART comparing CAB LA 400 mg + RPV LA 600 mg q 4 weeks with maintenance of current ARV regimen (2 NRTIs plus an INI, NNRTI, or a PI). **618 participants** were randomized (1:1) to continue current ART or switch to oral therapy with CAB 30 mg + RPV 25 mg daily for 4 Weeks followed by Q4 weekly CAB LA + RPV LA injections.
- **FLAIR** - randomized, open label, non-inferiority study in ART-naïve adult participants comparing CAB LA 400 mg + RPV LA 600 mg q 4 weeks to remaining on ABC/DTG/3TC over 48 weeks. **631 participants** started ABC/DTG/3TC for 20 weeks and those with HIV RNA <50 c/mL after 16 weeks were randomized at 20 weeks to continue ABC/DTG/3TC or switch to oral therapy with CAB 30 mg + RPV 25 mg daily for 4 week, followed by monthly CAB LA + RPV LA injections
- **Both studies met their primary endpoints at 48 week (ViiV Press Releases)**
- **ATLAS-2M** study compares q 8 wk CAB LA + RPV LA to q 4 wk CAB LA + RPV LA over a 48-week treatment period in approximately 1020 adult HIV-1 infected subjects.

Recently approved or in Phase III

NEW THERAPY FOR RESISTANT VIRUS

HIV Entry Inhibitors

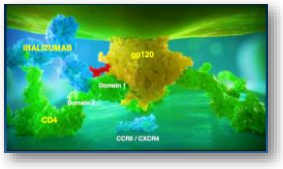


* = FDA approved

Slide courtesy of Trip Gulick, MD; Adapted from Moore JP, *PNAS* 2003;100:10598-10602.

Ibalizumab

- Humanized monoclonal Ab: binds CD4 on host cells; blocks HIV entry (post attachment inhibitor)[1]
- Active against CCR5 and CXCR4 tropic HIV
- No cross resistance with other ARVs[2]
- IV infusion: 2,000 mg loading dose then 800 mg every 2 wks
  - Duration of infusion: 15-30 min



[1]Emu B et al, Abstract 1686, IDWeek 2017; [2]Weinheimer S et al, CROI 2018
Slide courtesy of Raj Gandhi

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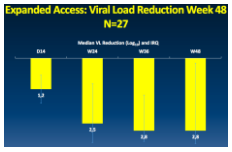
Ibalizumab in Persons with Multi-Drug Resistant HIV

- Phase 3 trial: 40 heavily treatment experienced pts with 3-class ARV resistance, ≥1 active drug
- Primary endpt: VL drop >0.5 $\log_{10}$ c/mL:
  - 3% during control period
  - 83% after loading dose
- Regimen optimized at day 14
  - Wk 24: VL <200 in 50%
  - Expanded access: viral suppression to wk 48

Approved March 6, 2018

Week 24 Ibalizumab + OBR	
Percent with VL<50 copies	43%
Percent with VL<200 copies	50%
Mean VL decrease	1.6 $\log_{10}$
Percent with ≥1.0 $\log_{10}$ reduction	55%
Percent with ≥2.0 $\log_{10}$ reduction	48%



Emu B et al, Abstract 1686, IDWeek 2017; Weinheimer S et al, CROI 2018, #561

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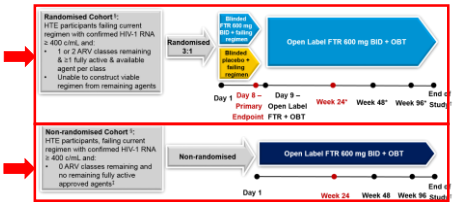
Fostemsavir (FTR): Oral HIV Attachment Inhibitor

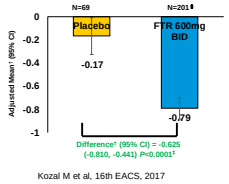
- Prodrug of temsavir: binds to gp120, inhibits HIV attachment to CD4
- Phase 3 trial in heavily treatment experienced patients with VF (BRIGHTE)



Kozal M et al, 16th EACS, 2017
Slide courtesy of Raj Gandhi

Fostemsavir (FTR): Phase 3 Trial (BRIGHTE)

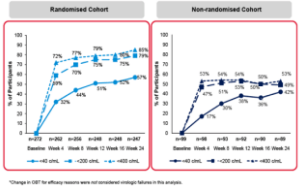
Mean VL Change at day 8



Kozal M et al, 16th EACS, 2017

"Regulatory submissions are currently anticipated to take place in the 2019/2020 timeframe"

Virologic response through wk 24 (observed analysis)



At wk 24, 54% of randomized and 36% of non-randomized ppts who received FTR + OBR achieved VL <40

Slide courtesy of Raj Gandhi
https://www.viivhealthcare.com/media/press-releases/2017/october/viiv-healthcare-announces-positive-phase-3-results-from-the-brighte-study-of-fostemsavir-in-heavily-treatment-experienced-patients-with-hiv.aspx

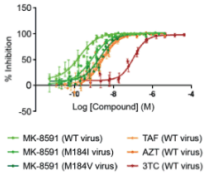
BRIGHTE: Efficacy at Wk 48 (FDA Snapshot)

Outcome at Wk 48, n (%)	Randomized Cohort (n = 272)	Nonrandomized Cohort (n = 99)
HIV-1 RNA < 40 c/mL (virologic success)	146 (54)	38 (38)
HIV-1 RNA < 200 c/mL/< 400 c/mL	187 (69)/191 (70)	43 (43)/44 (44)
HIV-1 RNA ≥ 40 c/mL (virologic failure)	104 (38)	52 (53)
▪ Data in window not below threshold	72 (26)	33 (33)
▪ D/c for lack of efficacy	6 (2)	2 (2)
▪ D/c for other reason while not below threshold	9 (3)	3 (3)
▪ Change in OBT	17 (6)	14 (14)
No virologic data	22 (8)	9 (9)
▪ D/c due to AE or death	15 (6)	8 (8)
▪ D/c due to other reasons	5 (2)	1 (1)
▪ Missing data during window but on study	2 (< 1)	0
Median CD4+ cell count change vs BL, cells/mm³ (IQR)	127 (54 to 204)	35 (-1 to 121)

Aberg. Glasgow 2018. Abstr O344A. Reproduced with permission.

NOVEL AGENTS IN EARLY DEVELOPMENT

MK-8591 is More Potent Against WT and M184V/I Viruses Than Approved NRTIs



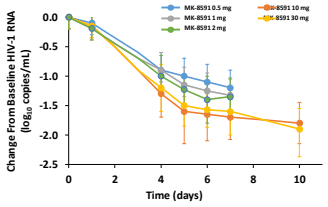
Compound	Virus	IC_{50} (nM)	
		$HIV_{NL4-3-GFP}$ [a]	HIV_{RTMS} [b]
MK-8591	WT	0.2 ± 0.1 (n = 68)	0.2 ± 0.1 (n = 6)
	M184I	1.0 ± 0.4 (n = 9)	ND
	M184V	1.6 ± 0.3 (n = 10)	ND
TAF	WT	2.8 ± 0.8 (n = 22)	ND
AZT	WT	2.6 ± 0.3 (n = 5)	10.1 ± 3.9 (n = 4)
TDF	WT	73.3 ± 37.1 (n = 20)	48.0 ± 29.5 (n = 4)
3TC	WT	112.3 ± 19.9 (n = 10)	144 ± 68 (n = 4)

Results are geometric means ± standard deviations with number of replicates displayed in parentheses.
[a] IC_{50} were determined by quantification of GFP positive PBMCs infected with a HIV reporter virus in the presence of increasing compound concentrations and 10% normal human serum.
[b] IC_{50} were determined by monitoring p24 production from infected PBMCs in the presence of increasing compound concentration and 10% fetal bovine serum.

Long-acting NRTTI: MK-8591 (EFdA)

- Nucleoside RT translocation inhibitor (NRTTI)
- Half life of active anabolite: ≈80-130 hr
- Humans: single oral dose as low as 0.5 mg suppressed HIV RNA for >7 days

Phase 1b, single-dose, monotherapy study
Study population: ART naïve (N=30)

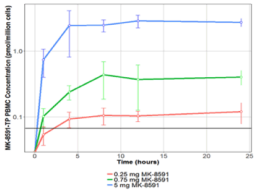


Grobler et al CROI 2017 #435
Matthews et al IAS 2017 #TUPDB0202LB

Long-acting NRTTI: MK-8591 (EFdA)

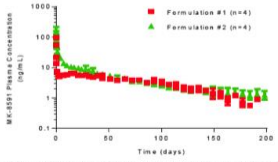
- Study in healthy volunteers: daily doses as low as 0.25 mg expected to lead to HIV suppression
- Phase 2b trial in people with HIV, in combination with doravirine (NNRTI) and 3TC, has started (DRIVE2Simplify)
  - Daily dosing
- Potential for once weekly or even once monthly dosing
  - "Partners wanted"

MK-8591 achieve target levels with only 0.25 mg dose



Matthews RP et al CROI 2018 #26
https://clinicaltrials.gov/ct2/show/NCT03272347

MK-8591 Parenteral Formulations Release Effective Drug Levels for >180 days

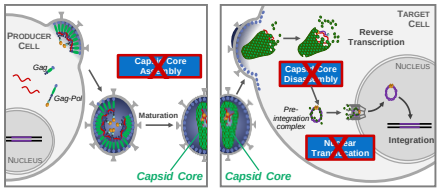


- Low dose amenable to extended-duration parenteral formulation
- >180-day extended release from solid state formulations after a single injection in rat
- Data suggest the potential to provide coverage for durations up to 1 year

Grobler et al CROI 2016

GS-6207

HIV Capsid Acts at Multiple Stages in the Viral Life Cycle

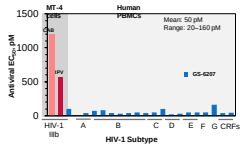


Gilead's capsid inhibitors inhibit HIV capsid function, resulting in aberrant core assembly/disassembly via multiple steps in HIV replication cycle

Tse W, et al. CROI 2017. Seattle, WA. Oral #38

GS-6207: Novel HIV Capsid Inhibitor with Long-Acting Potential

Potency



	EC_{50} (nM)[a]	$paEC_{95}$ (nM)[b]
GS-6207	**0.10 ± 0.01**	**4.0 ± 0.4**
EFV	0.79 ± 0.06	44 ± 3
RPV	0.57 ± 0.03	45 ± 2
DTG	1.34 ± 0.14	156 ± 16
ATV	7.23 ± 0.50	150 ± 11

GS-6207 is a potent inhibitor of all major HIV-1 subtypes

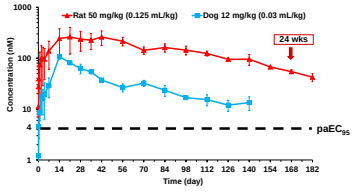
GS-6207 is more potent than currently marketed ARVs

ATV, atazanavir, DTG, dolutegravir. EFV, efavirenz. paEC, protein-adjusted effective concentration. RPV, rilpivirine
[a] EC_{50}, CC_{50}, and Hill slope values (mean ± SD) obtained from at least 3 independent experiments performed in quadruplicate
[b] EC_{95} = EC_{50} X $(95/5)^{1/Hill\ slope}$; $paEC_{95}$ = human serum shift X EC_{95}

Zheng J, et al. IDWeek 2018. San Francisco, CA. Poster #539

GS-6207: Novel HIV Capsid Inhibitor with Long-Acting Potential

Plasma PK in Rats and Dogs Following a Single SC Dose*

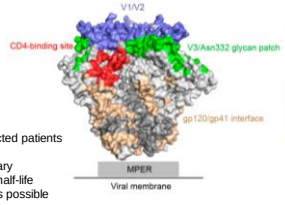


- Single subcutaneous injection maintains plasma concentrations well above $paEC_{95}$ for >24 weeks in dogs
- PK supports long acting administration, potentially Q3M or longer, in humans

paEC95, plasma-binding-adjusted effective concentration required to inhibit replication by 95%
* 400 mg/mL dose concentration

Zheng J, et al. IDWeek 2018. San Francisco, CA. Poster #539

Broadly Neutralizing Antibodies against HIV



CD4-binding site
b12, VRC01, VRC07, NIH45-46, 3BNC117, VRC-PG04

V1/V2
PG9, PG16, CH01-04, PGT141-145, PGDM1400

V3/Asn332 glycan patch
PGT121-123, PGT125-131, PGT135, 10-1074, 2G12

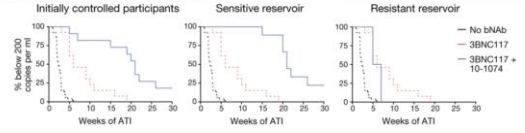
gp120/gp41-interface
PGT151, 35O22, 8ANC195

MPER
2F5, 4E10, 10E8

Phase 2 studies in HIV infected patients
Clear antiretroviral activity
Combinations likely necessary
Can be modified for longer half-life
Every 3 to 6 month infusions possible

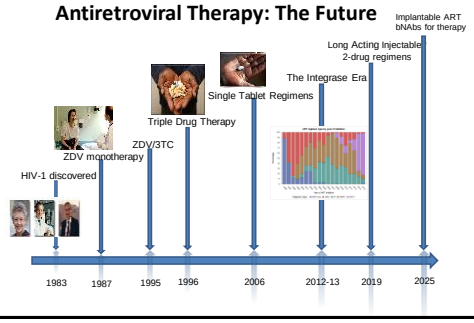
ARTICLE September 27, 2018

Combination therapy with anti-HIV-1 antibodies maintains viral suppression



Combination bNAb, long-acting bNAb being studied for treatment, prevention

Antiretroviral Therapy: The Future



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- Chloe Orkin
- Kathleen Squires
- Trip Gulick
- Raj Gandhi
- Jay Glober

Question-and-Answer

Investigational Approaches to Antiretroviral Therapy: New Strategies and Novel Agents
Joseph J. Eron, Jr, MD

SUGGESTED READINGS

Emu B, Fessel J, Schrader S, et al. Phase 3 study of ibalizumab for multidrug-resistant HIV-1. *N Engl J Med.* 2018;379(7):645-654.

Margolis DA, Gonzalez-Garcia J, Stellbrink HJ, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. *Lancet.* 2017;390(10101):1499-1510.

Mendoza P, Gruell H, Nogueira L, et al. Combination therapy with anti-HIV-1 antibodies maintains viral suppression. *Nature.* 2018;561(7724):479-484.

Saag MS, Benson CA, Gandhi RT, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2018 recommendations of the International Antiviral Society-USA panel. *JAMA.* 2018;320(4):379-396.

US Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0. Accessed on December 7, 2018.