Long-Acting Antiretrovirals for HIV

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Disclosures

None

Single Tablet ART Regimens: 2018

TDF/FTC/EFV (2006)

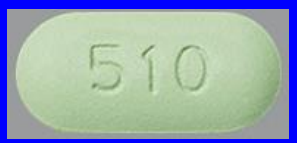
TDF/FTC/RPV (2011)

TDF/FTC/EVG/cobi (2012)

ABC/3TC/DTG (2014)

TAF/FTC/EVG/cobi (2015)

TAF/FTC/RPV (2016)



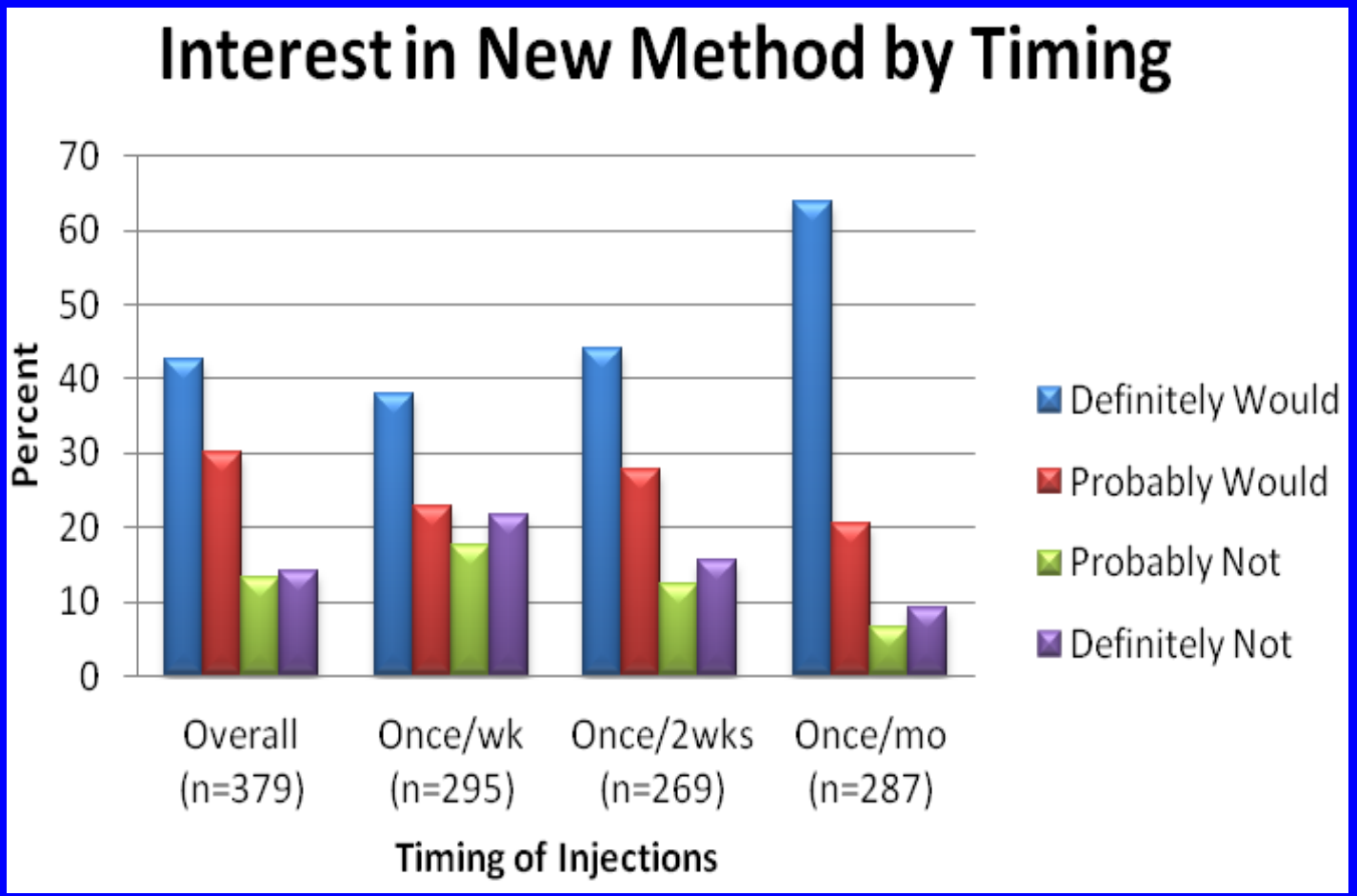
TAF/FTC/DRV/c (investigational)

Long-Acting: What's the attraction?

- Infrequent dosing
  - Longer drug half-lives
- Lower drug doses needed (nanoformulations)
- Addresses adherence
- Addresses pill fatigue
- Possibility of directly observed therapy (DOT)
- Tissue targeting (lymph node/macrophage uptake)
- Protection of health privacy
- Could avoid treatment-related HIV stigma

NanoART Survey - Results

HIV+ U.S. pts currently prescribed ART (N=400)
68% men, 53% African American, mean age 47



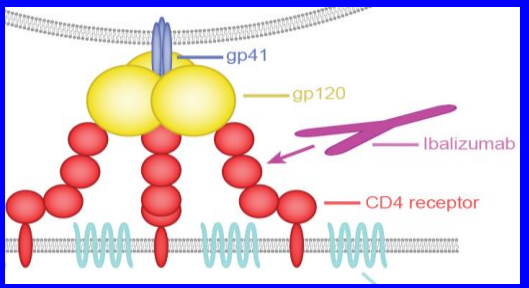
48% “very concerned” about side effects
35% concerned about needles

Williams, *Nanomedicine (London)* 2013;8:1807

Long Acting ART in Clinical Development

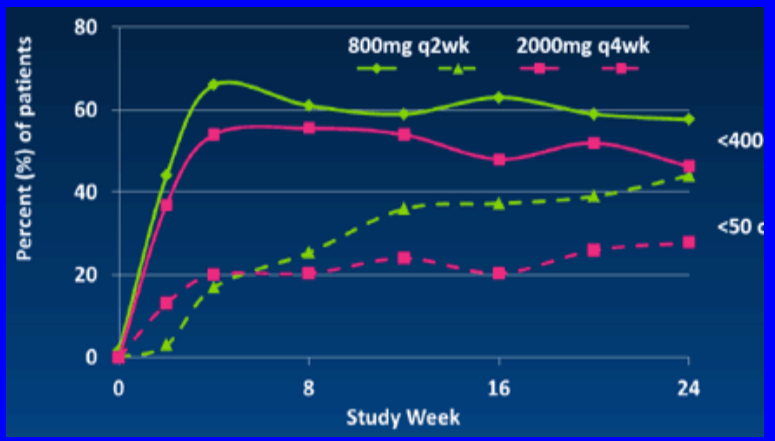
- Approved
  - ibalizumab (IBA)
- Phase 3
  - cabotegravir (CAB)-LA
  - rilpivirine (RPV)-LA
- Phase 2
  - albuvirtide
  - EFdA (MK-8591)
  - PRO 140
  - broadly-neutralizing monoclonal antibodies
    VRC01, 3BNC117, 10-1074, PGT121

Ibalizumab (IBA): HIV Entry Inhibitor



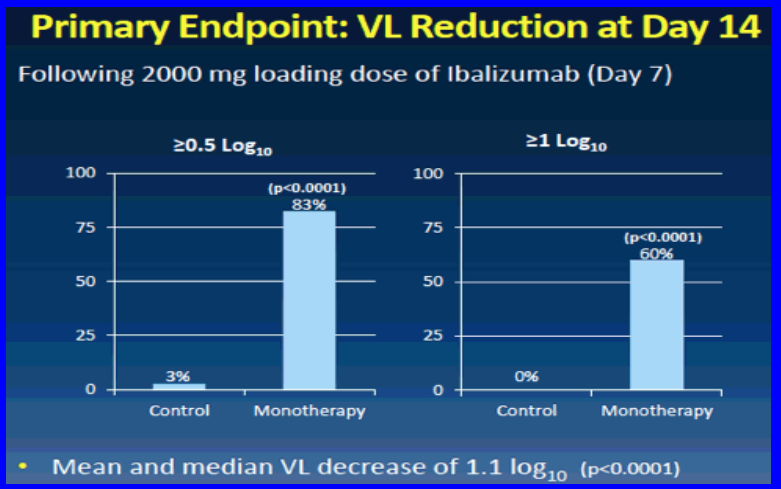
- Monoclonal antibody; IV, SC
- Binds to CD4 receptor
- Dosing every 1-4 weeks
- Phase 1a Kuritzkes JID 2004;189:286
- Phase 1b Jacobson AAC 2009;53:450
- Phase 2a Norris IAS 2006 #TuPE0058
- Phase 2b Khanlou IDSA 2011 #LB9
  - Rx-experienced; 3-class resistance; (N=113)
  - baseline susceptibility to IBA not different for those with drug resistance to NRTIs, NNRTIs, PIs, IIs, ENF or MVC

Weinheimer IAS 2017 #MOPEB0352



Ibalizumab (IBA): HIV Entry Inhibitor

- Phase 3
  - Study population: VL>1000, on ART >6 months, 3-class resistance, ≥1 sensitive drug (N=40)
  - Study treatment:
    - continue ART, add IBA 800 mg day 7



Lalezari IDWeek 2016 #LB6

- +OBR day 14, +IBA day 21 and q 2 wks →24 weeks
  - HIV RNA <50 copies/ml in 43% Lewis CROI 2017 #449LB

- 27 continued OBR with IBA → 48 weeks
  - HIV RNA <50 copies/ml in 59% Emu IDWeek 2017 #1686

Ibalizumab (IBA): HIV Entry Inhibitor

- 3/6/2018: FDA approves for heavily rx-experienced adults with MDR HIV-1 infection failing their current antiretroviral regimen
- Dosing: Loading dose of 2g IV, then 800mg IV q2weeks
- Cost: US list price: $118,000/year (not including cost of infusions)

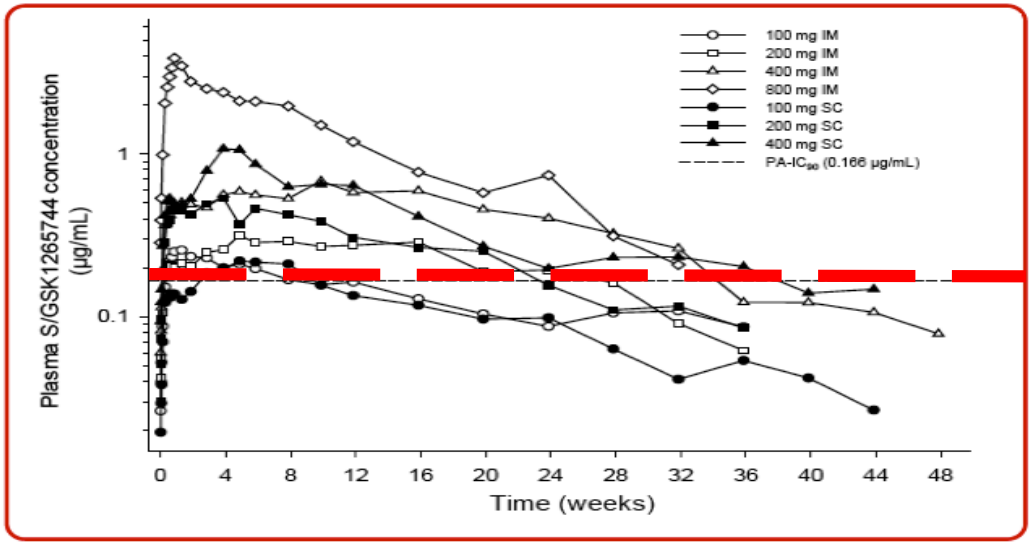
Cabotegravir (CAB, GSK 1265744)

- Integrase inhibitor similar to DTG; similar resistance
- Potent in HIV+ individuals (5, 10, 30, 60 mg oral)
  Spreen HIV Clin Trials 2013;14:192
- Nanotechology formulation; SC + IM injections
- T ½ 21-50 days!
- Supports monthly or quarterly dosing
- Safety:

  injection site reactions (ISR; mild) / nodules with SC dosing

Pharmacokinetics

Figure 4. Mean Plasma S/GSK1265744 Concentration-Time Profiles Following Single Dose LAP Formulation Administration



Spreen JAIDS 2014;67:481

LATTE-2: IM CAB + IM RPV

- Randomized, open-label, phase 2b, non-inferiority study
- Study population: ART-naïve (N=309)
- Study rx: PO CAB + ABC/3TC X 4 wks, then randomized 2:2:1
- Results (HIV RNA <50 at 96 wks)
  - **IM CAB + IM RPV q8 wks – 94%**
  - **IM CAB + IM RPV q4 wks – 87%**
  - **PO CAB + ABC/3TC – 84%**
- Injection site reactions were nearly universal
  - 97%+ were mild or moderate; lasted a median of 3 days
  - 2 pts (<1%) d/c due to ISR
- Conclusions: IM non-inferior (comparable) to PO; well-tolerated
- Phase 3 studies
  - FLAIR (switch from ABC/3TC/DTG; CAB + RPV q4 wks)
  - ATLAS (switch; CAB + RPV q4 wks)
  - ATLAS-2M (switch; CAB + RPV q4 vs. 8 wks)

Eron IAS 2017 #MOAX0205LB
Margolis Lancet 2017;390:1499

Cabotegravir (CAB) – Prevention: HPTN 077

- Phase 2a randomized, double-blind, pbo-controlled
- Study pop: low-risk HIV- participants (N=199); median age 31, 66% women, 34% men
- Study meds: 3:1 to oral CAB X 4 wks then CAB IM 800 mg q12 weeks or 600 mg q8 wks (or PBO)
- Results:
  - ISR more common with CAB (34%) vs. PBO (2%); 1.5% d/c'ed
  - No other differences in safety/tolerability
  - drug troughs lower with CAB 800 q12 wks
- Conclusion: CAB 4 wk oral → 600 mg IM q8wks optimal

Landovitz IAS 2017 #TUAC0106LB

HPTN 083:
PrEP with TDF/FTC oral vs. CAB IM

- Study population: Adult MSM and TGW, at high-risk for HIV acquisition (N=4500)
  - High risk
    - any non-condom receptive anal intercourse (RAI)
    - >5 partners
    - stimulant drug use
    - rectal or urethral STI in past 6 months

- Study regimen: TDF/FTC daily oral vs. CAB q2 month injections
  - double-blind, double-dummy design

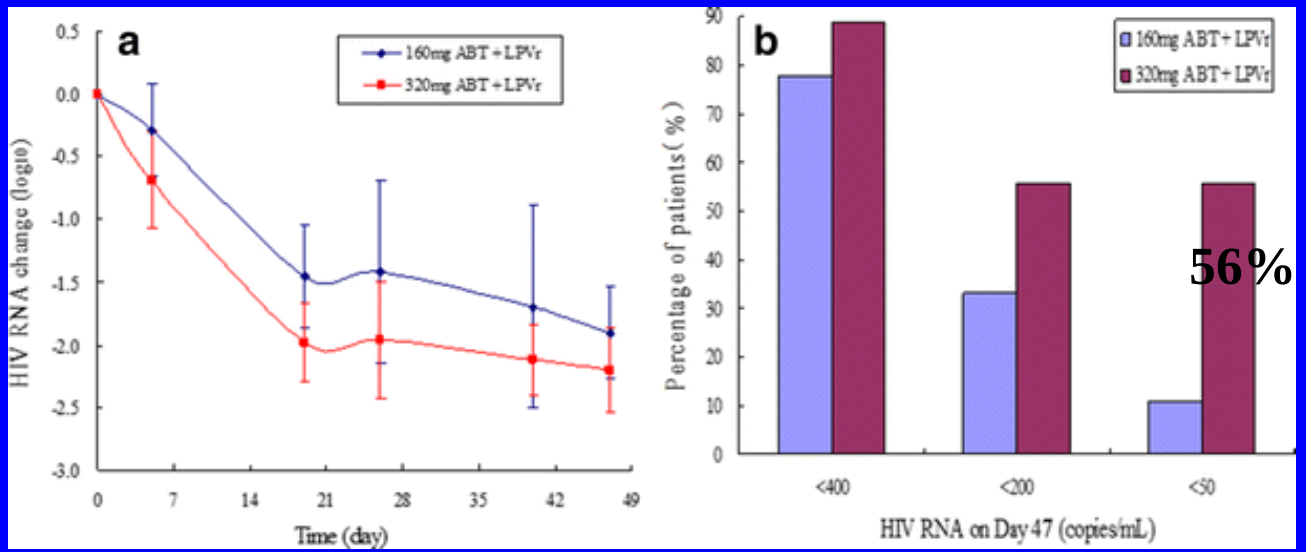
- Design: non-inferiority, efficacy study

- Primary endpoint: HIV seroconversion

- Now enrolling!

Albuvirtide (ABT): HIV Fusion Inhibitor

- 1/2-life = 11-12 d → <u>weekly</u> dosing
- Pilot study:
  - Study pop: ART-naïve, VL 5K-1M, CD4 >350 (N=20)
  - Design: 7 weeks, open-label, randomized
  - Study regimen: ABT (160 or 320 mg/wk) + LPV/r bid



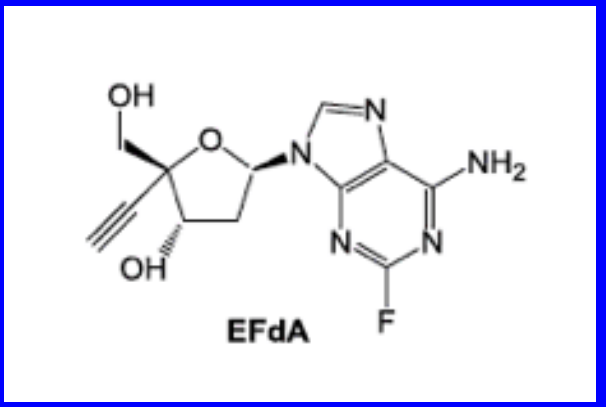
Zhang AIDS Res Ther 2016;13:8

Albuvirtide (ABT): HIV Fusion Inhibitor

- TALENT
  (**T**est **Al**buvirtide in Treatment-**E**xperie**n**ced Pa**t**ients)
  - Phase 3 -- Second-line therapy following VF on a first-line ART regimen (N=389)
  - Study rx; LPV/r bid + [2 NRTI or ABT]
  - Planned Interim analysis; ½ of study participants (n=175) on study X 48 wks:
    - VL <50; 66% (NRTI) vs. 80% (ABT)
    - → non-inferiority
    - In 5 pts on ABT with VL >500 → no resistance

Wu Glasgow 2016 #O335

MK-8591 (EFdA)

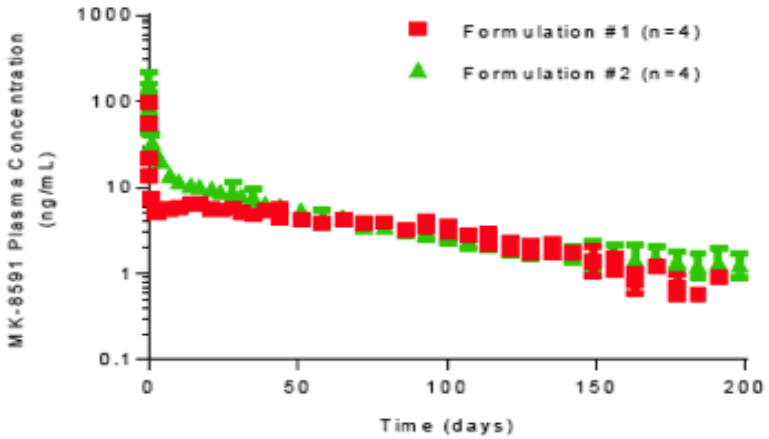


- 4’-ethynyl-2-fluoro-2’-deoxyadenosine; EFdA
- Non-obligate chain terminator
- Inhibits RT by preventing translocation (NRTTI)
- ½ life 150-160 hours(!)
- Potent antiviral activity (PBMC EC50 = 0.2 nM) with broad coverage (HIV-1, HIV-2, MDR strains)
- Accumulates in LN, vagina, rectum (animals)

  Grobler CROI 2017 #435
- Low-dose and parenteral formulations

MK-8591 (EFdA)

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

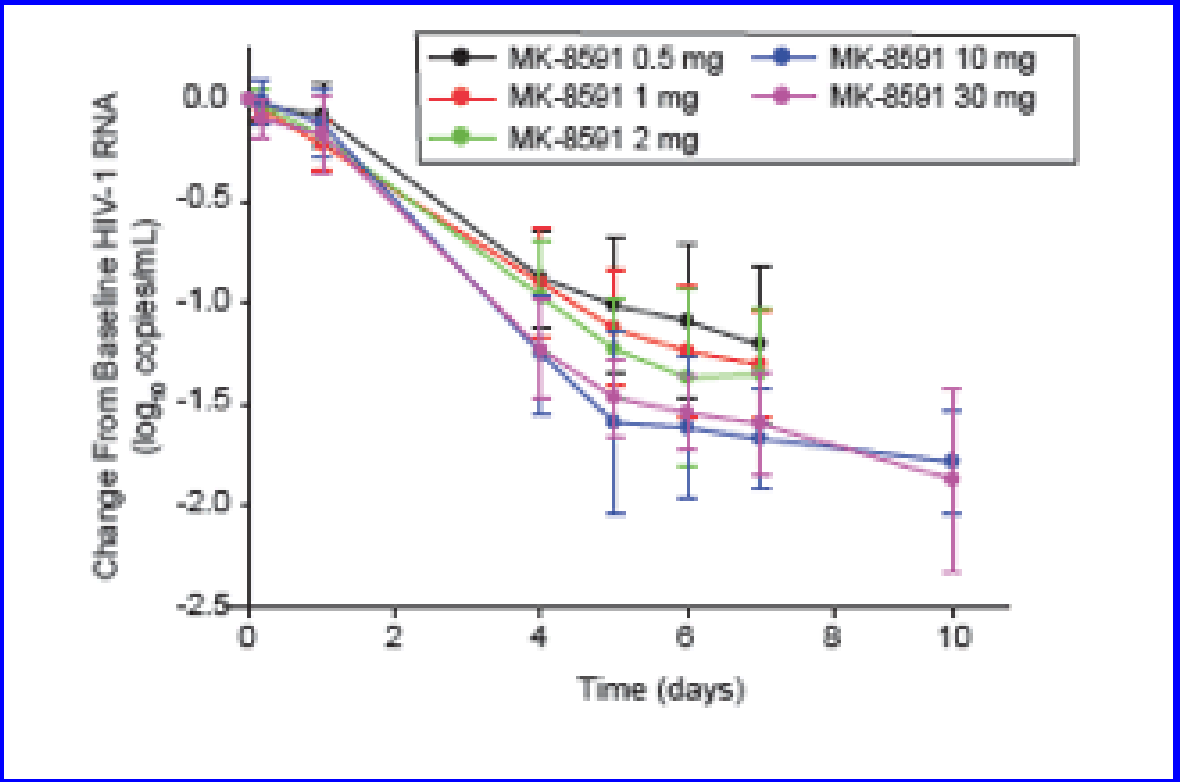


- Low dose amenable to extended-duration parenteral formulation
- >180-day extended release from solid state formulations after a single injection in rat
- Data suggest the potential to provide coverage for durations up to 1 year

Grobler CROI 2016 #98
Friedman CROI 2016 #437LB
Grobler CROI 2017 #435

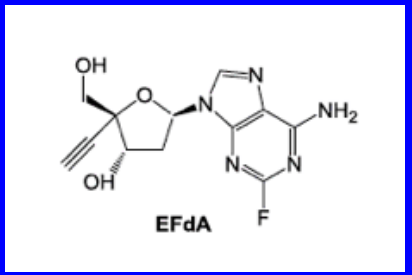
MK-8591 (EFdA)

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



Matthews IAS 2017 #TUPDB0202LB

MK-8591 (EFdA)



- Double-blind, placebo-controlled, 3-panel trial
- HIV- participants
- MK-8591 (or placebo)
  – 5 mg X 6 weeks, 0.75 mg X 4 weeks, 0.25 mg X 4 weeks
- Results:
  - After 2-3 weeks of dosing, MK-8591-TP levels exceeded 1.0 pmol/million cells (similar to 10 mg weekly dosing)
  - Tissue (vaginal, rectal) and PBMC levels adequate
- Conclusion: Low daily doses expected to suppress HIV

Matthews CROI 2018 #22

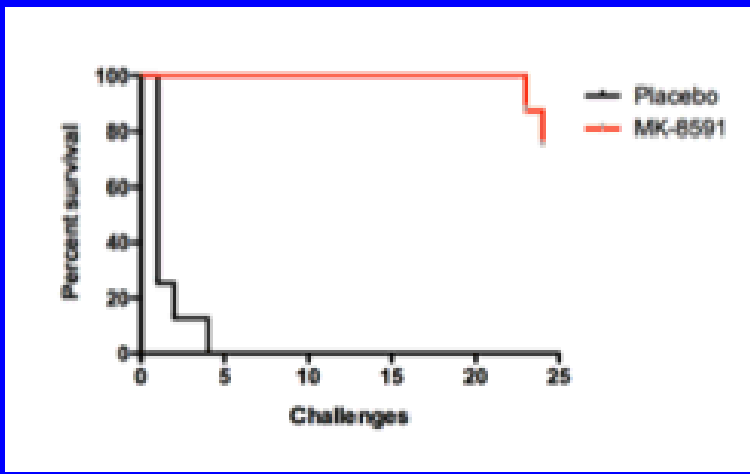
- Phase 2 study of MK-8591 + 3TC + doravirine (DOR) now enrolling

MK-8591 -- Prevention

- MK-8591 3.9 mg/kg (vs. placebo) given to male macaques weekly by oral gavage up to 14 weeks (8/group)
- 6 days after dosing, macaques exposed to intrarectal SHIV (until infection or a total of 12 challenges)
- Results: All 8 control macques infected; all MK-8591 macaques remain (-)

  Markowitz IAS 2017 #MOAX0203LB

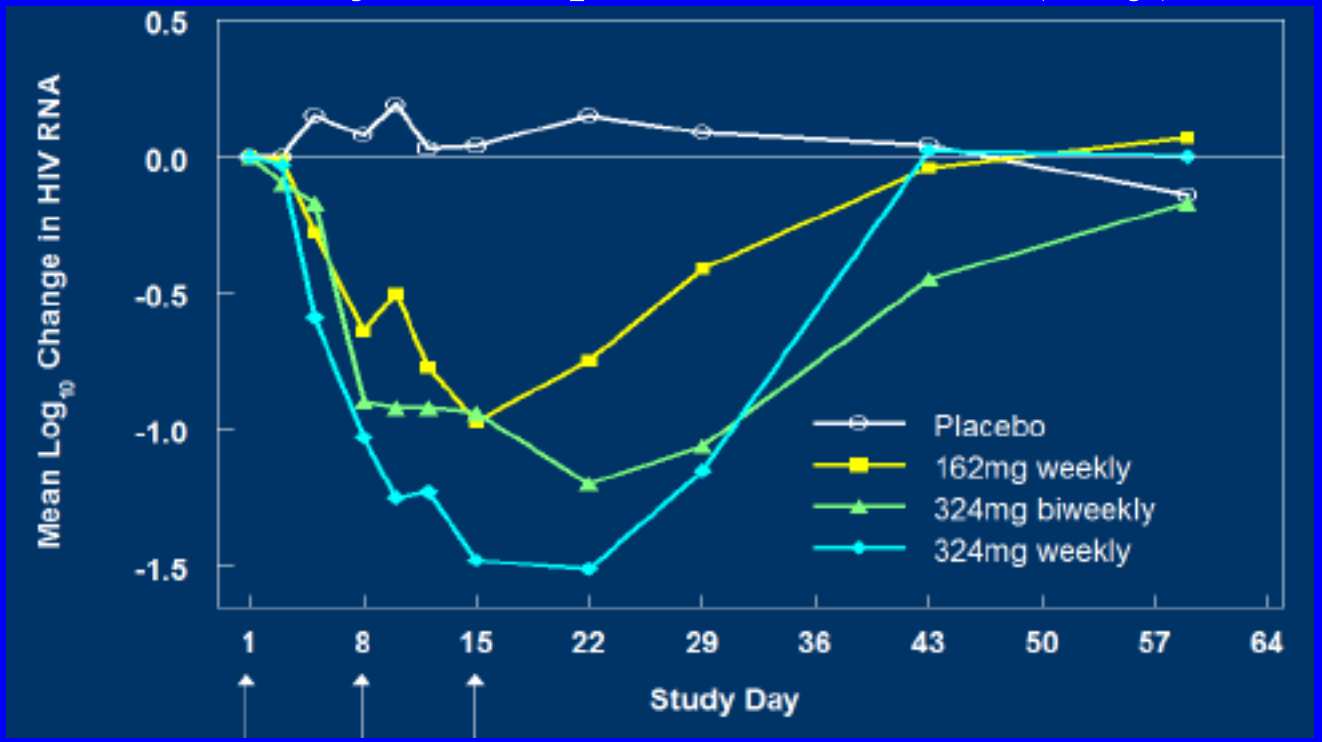
- Follow-up study with lower doses
- MK-8591: 1.3, 0.43, 0.1 mg/kg weekly (8 macaques/group)
- Results
  - 1.3 mg/kg: all 8 remained uninfected
  - 0.43 mg/kg: all 8 remained uninfected
  - 0.1 mg/kg: 2 of 8 became infected
- Conclusions:
  - MK-8591 protective at low doses
  - Equivalent to 250 µg/week or 10 µg/day in humans(!)



Markowitz CROI 2018 #89LB

PRO 140

- Humanized CCR5 monoclonal antibody
- Administered IV or SC; dosed weekly or every 2 weeks
- Proof of concept study of PRO 140 given subcutaneously for 15 days in 44 pts with R5 virus (only):

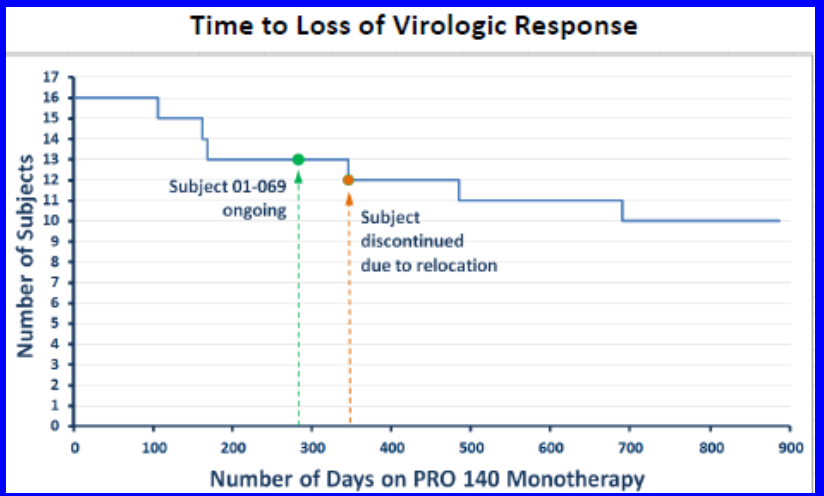


Maximum VL ↓ (log cps/ml)	
162 mg/wk	0.99
324 mg/2 wk	1.37
324 mg/wk	1.65

Jacobson JID 2010;201:1481-7

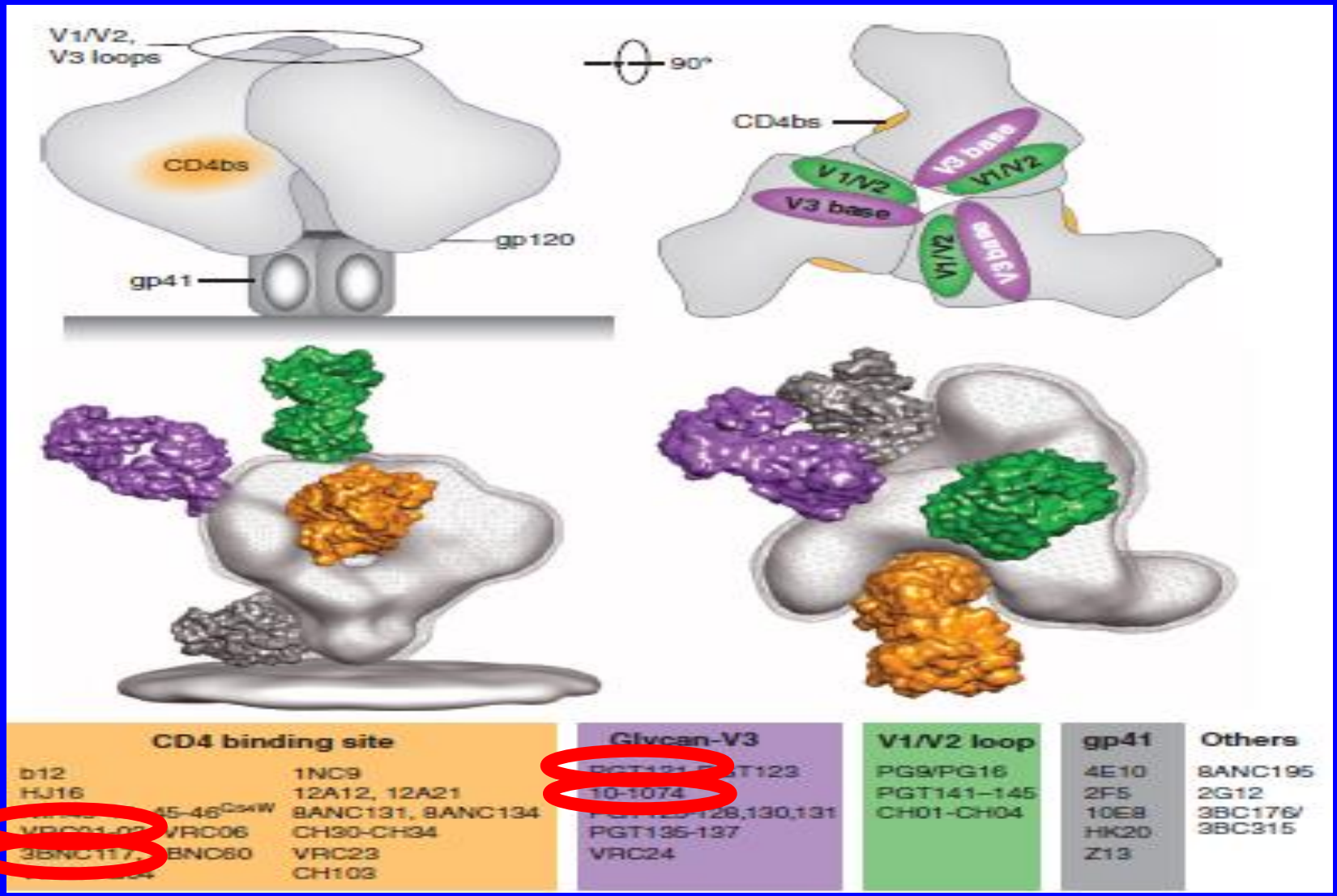
PRO 140

- Phase 2b, open-label single-arm extension study
- Adult pts with R5 virus on ART with HIV RNA <40 c/ml (N=42)
- Changed to maintenance with PRO 140 350 mg SC weekly
- After 13 weeks of virologic suppression, 16 eligible pts started extension with self-administered PRO 140
- Results:
  - 10 pts with virologic suppression up to 2 years
  - 5 pts with viral rebound (mean time 329 days)
  - 1 pt moved
- Conclusion: potential for LA maintenance rx

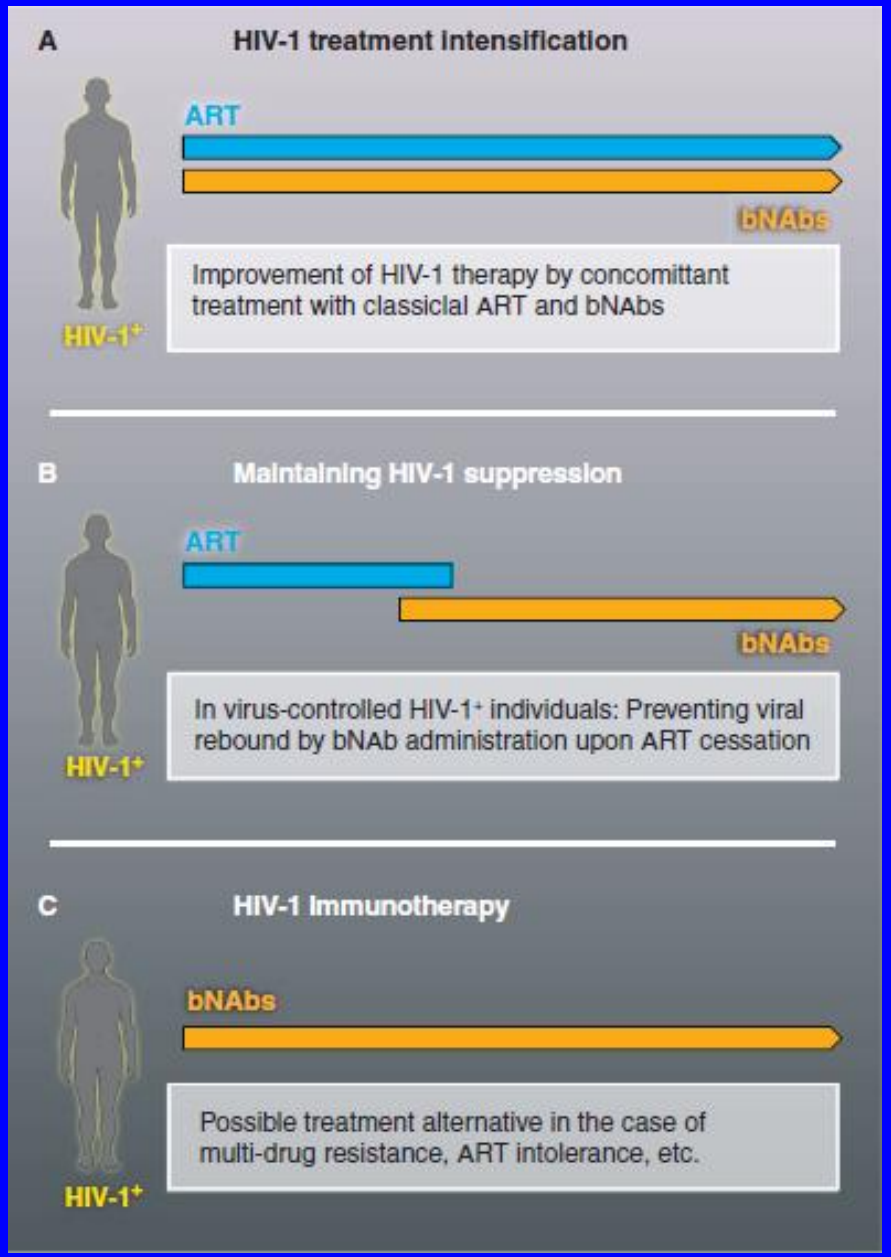


Lalezari CROI 2017 #437

HIV-1 Broadly Neutralizing Antibodies



Klein, Science 2013;341:1199



D HIV Prevention

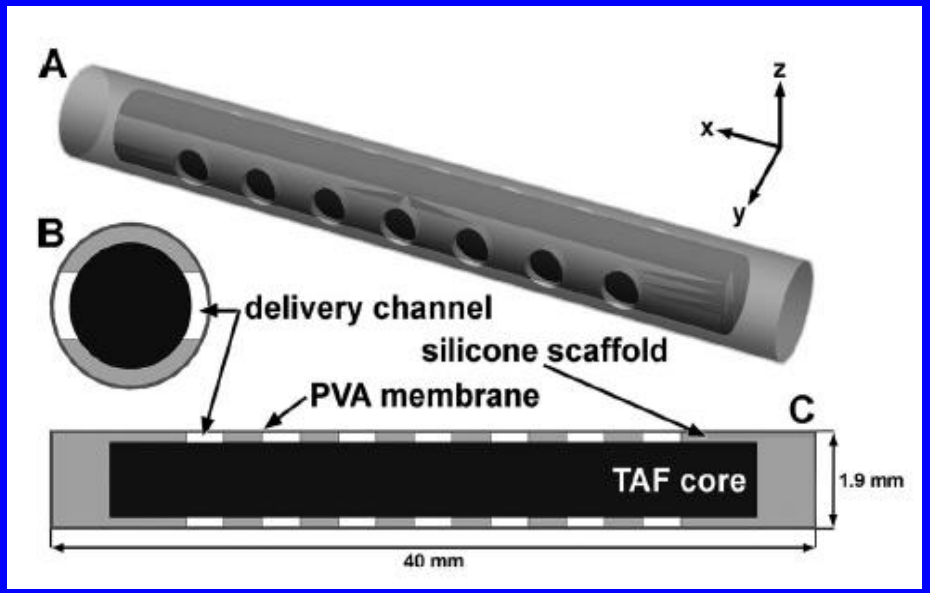
Potential Uses of Broadly Neutralizing HIV Antibodies

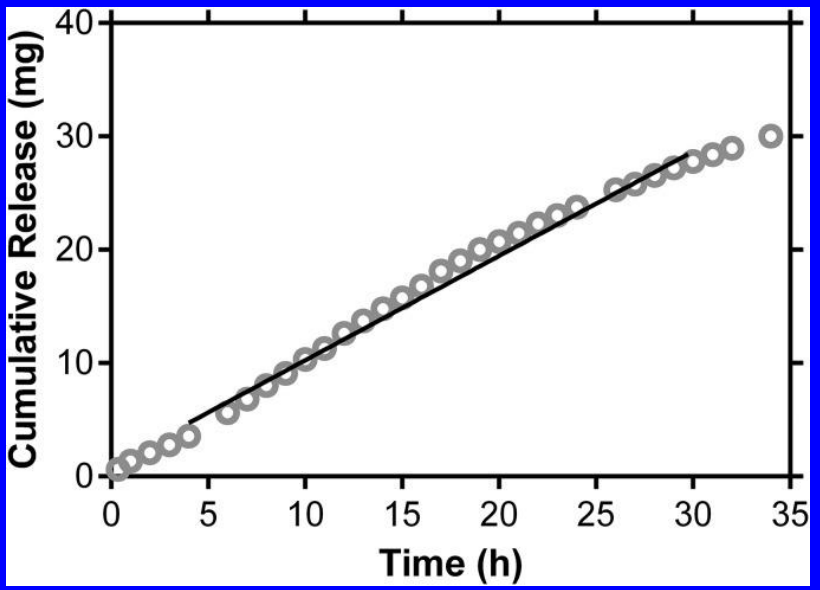
Klein, Science 2013;341:1199

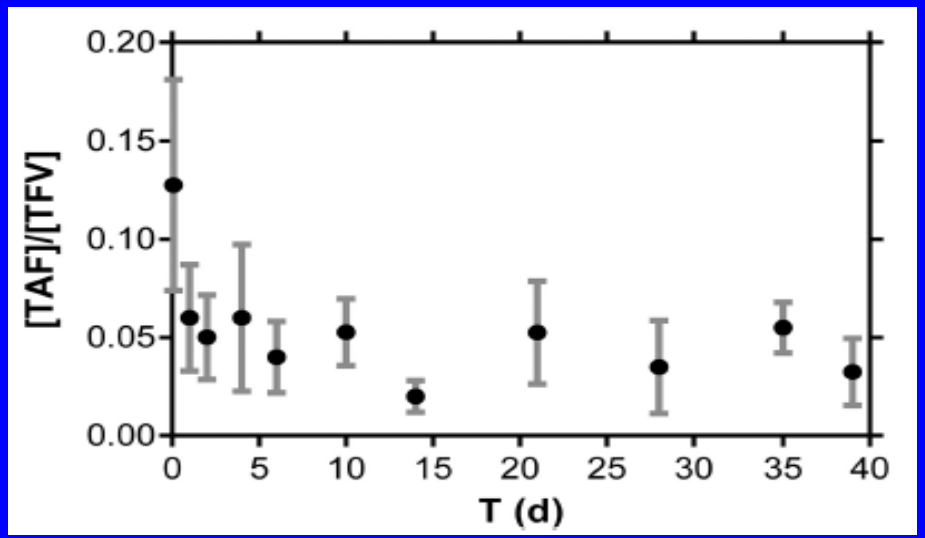
Long-Acting Implants

- Potential advantages over injectables
  - Removable
  - More consistent and predictable drug release
  - PK not dependent on injection site
  - May remain in place for years (inert, non-degradable subcutaneous versions)
- Potential disadvantages over injectables
  - Specialized device required for insertion
  - Minor surgical procedure to remove
  - Regulated as both a drug and a device
  - Difficulty moving to a generic marketplace

Long-Acting Subdermal Implants: Tenofovir Alafenamide (TAF) in Dogs







Gunawardana
AAC 2015;59:3913

Long-Acting ART: Issues

- Injection volumes
- Oral lead-in
- Adverse events and side effects
- Coverage of the long drug concentration “tail”
- Pharmacokinetic variability
- Dosing strategies for:
  - children
  - adolescents
  - pregnant women

Long-Acting ART: Conclusions

- Despite ART one-pill, once-daily regimens there is interest in long-acting ART for HIV treatment and prevention
  - Oral – weekly or biweekly
  - Injectable – every 2, 4, 8, 12 weeks (or longer)
- There are approved (ibalizumab) and investigational agents in advanced (cabotegravir LA, rilpivirine LA) and earlier (albuvirtide, MK-8591, PRO 140, BNAbs) clinical development.
- There are potential benefits as well as potential issues with long-acting ART.
- Further research is required.

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- Division of AIDS, NIAID, NIH
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