Potential Clinical Role of Long- and Longer-Acting ART

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Disclosures

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  - ViiV

Why do we need LA-ART?

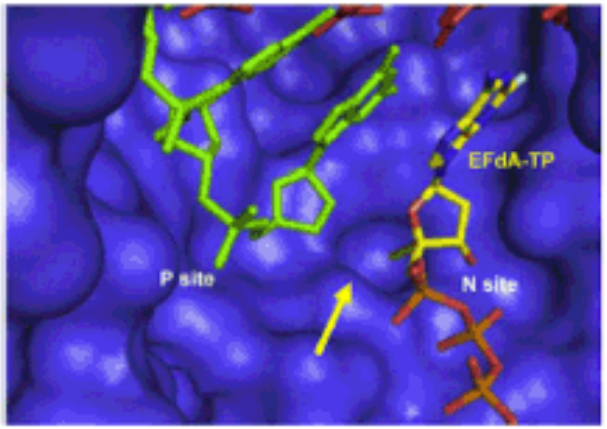
- **Some patients perfectly happy with daily STR**
- **Many patients (N?,%?) might prefer less frequently dosed ART**
  - Greater convenience
  - Less stigma
- **LA-ART could enhance treatment of patients with adherence challenges**
  - Adolescents
  - Patients with substance use disorder, psychiatric disease, chaotic lives
- **Additional options for PrEP**

Approaches to ART

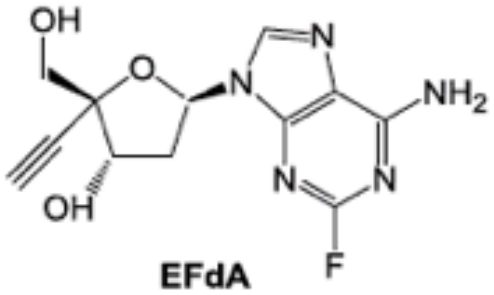
- Weekly oral dosing
- Weekly s.c. injection
- Monthly or bi-monthly i.m. injection
- Monthly or quarterly infusion
- Semi-annual or annual implant

Weekly Oral Therapy

MK-8591 (EFdA)



Michailidis et al (2009) JBC



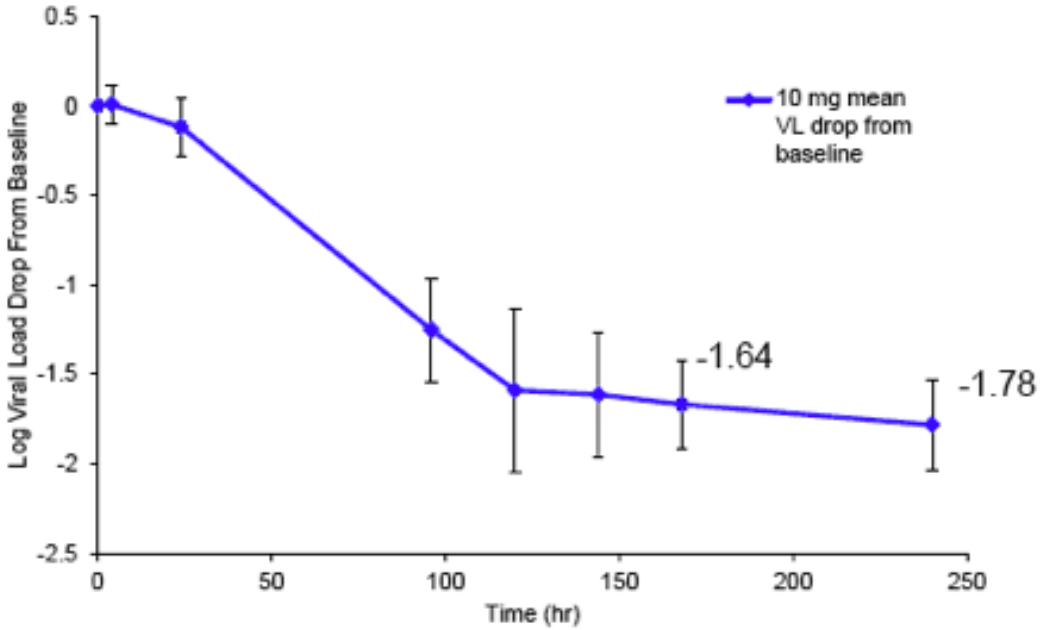
EFdA

- MK-8591 (4'-ethynyl-2-fluoro-2'-deoxyadenosine; EFdA) licensed from Yamasa
- Virologic profile and mechanism of action is extensively described in the literature (Mitsuya, Sarafianos, Parniak)
  - Non-obligate chain terminator
  - Inhibits reverse transcriptase by preventing translocation
  - Potent antiviral activity (PBMC EC_{50} = 0.2 nM) with broad subtype and mutant coverage (HIV-1, HIV-2, MDR strains)

Grobler JA et al CROI 2016

MK-8591: Phase 1b results

Friedman, et al., Poster 437LB



- A single 10 mg oral dose in HIV-infected patients results in 1.6 log decrease in viral load at day 7-10
- Intracellular MK-8591-TP $t_{1/2}$ = 103 hr
- No evidence of resistance out to Day 10

Grobler JA et al CROI 2016

Weekly oral therapy

- MK-8591 (NRTTI) and GS 6207 (capsid inhibitor) are possible candidates
- Is weekly oral therapy sufficiently infrequent to be attractive to most patients?
- Is weekly oral therapy a goal in and of itself or a necessary step on the path towards longer-acting formulations?
- Could these drugs maintain suppression as dual or monotherapy?

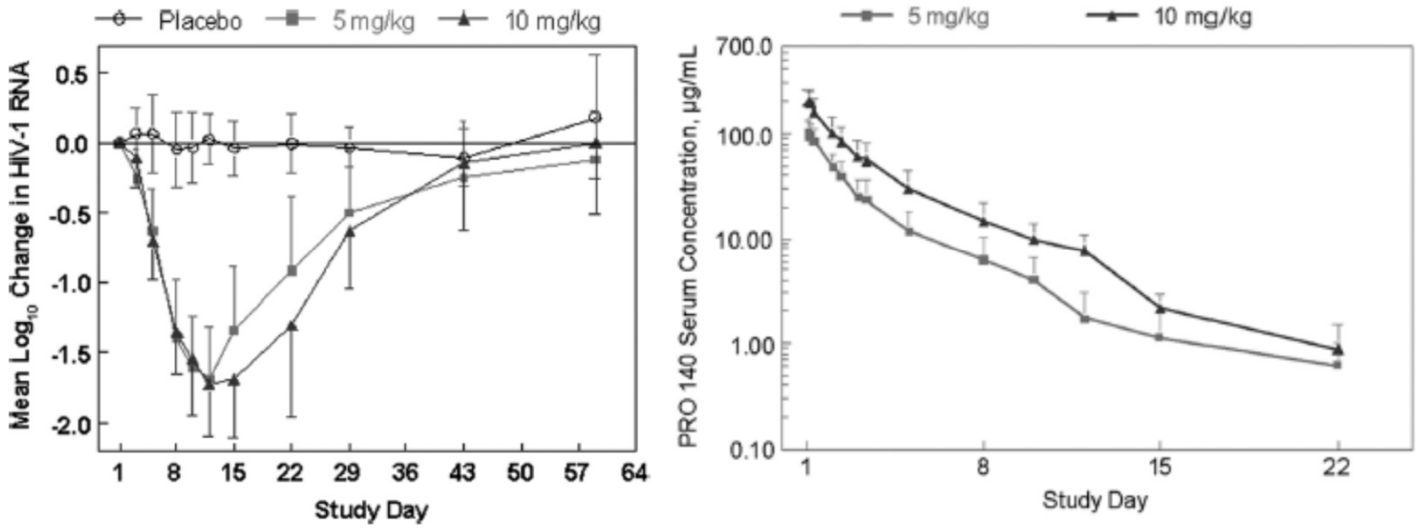
Weekly Subcutaneous Injection

Advantages and disadvantages of weekly s.c. injectable ART

- **Advantages**
  - Less frequent than daily therapy
  - Can be self-administered or administered by a care giver
- **Disadvantages**
  - Not long enough?
  - Need to keep sterile injection equipment at home
  - Need for cold storage or reconstitution of drug

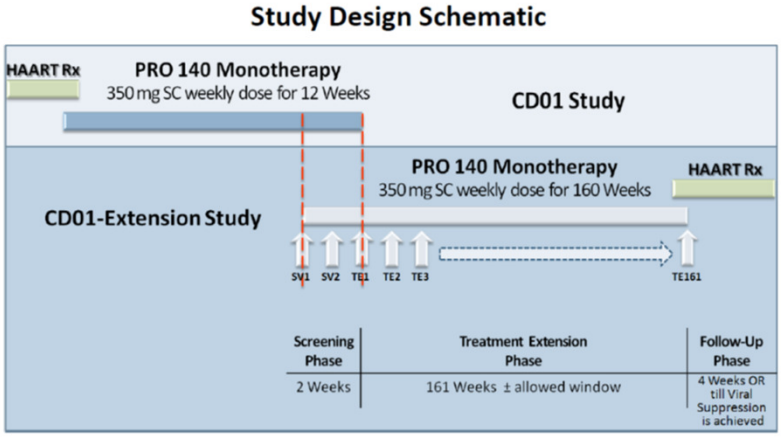
PRO 140

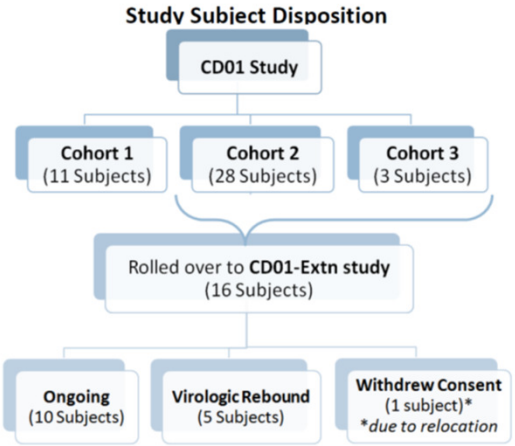
- Humanized IgG4 mAb directed against CCR5
- Inhibits infection by R5 strains of HIV-1
- Can be self-administered by weekly s.c. injection

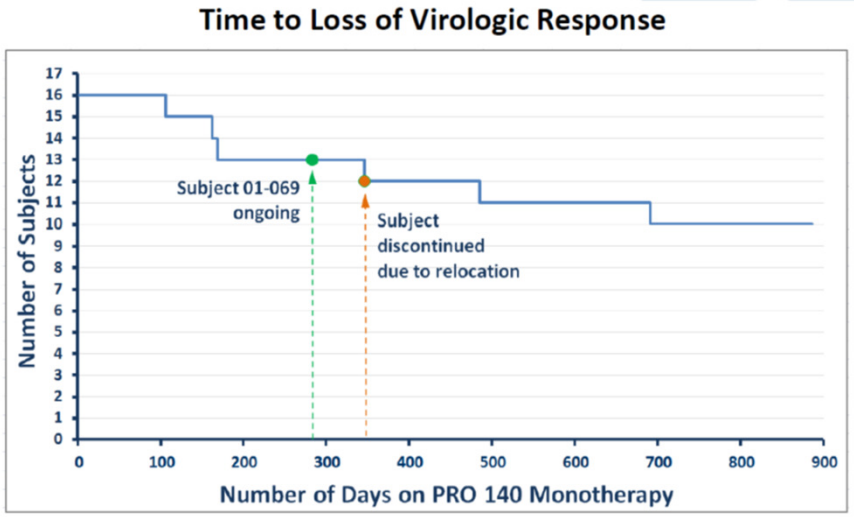


Jacobson JM et al Antimicrob Agents Chemother 2010

Maintenance of viral suppression by weekly PRO 140 monotherapy







Lalezari J et al CROI 2017

Weekly s.c. injection

- **Reasonably convincing data that PRO140 maintains viral suppression with once-weekly self-administered s.c. dosing**
  - Overall success rate difficult to determine (25-50%)
  - No (rare) emergence of CXCR4-using virus or MVC-resistance in participants with virologic failure
- **Uncertain path to approval**
  - RCT comparing weekly s.c. PRO140 unlikely to show non-inferiority compared to continued oral STR
- **Even if approved, cost compared to daily oral STR likely to be prohibitive**

Monthly or bi-monthly injectables

Monthly or bi-monthly injectables

- **Phase 3 trials of cabotegravir and rilpivirine are underway**
  - FLAIR, ATLAS
- **The question remains as to how broadly this regimen will appeal to patients in practice**
- **Need for oral lead-in a major limitation at present**
- **Little rationale for development of additional, similar regimens**

LA injectables: Pros and Cons

- **PRO**
  - Allow monthly dosing
  - Tolerated well to date
  - More convenient
  - Less stigma
  - May promote adherence
  - Potential for DOT?
- **CON**
  - Require i.m. injection
  - Cannot be self-administered
  - Long-term tolerability?
  - Very long terminal ½-life
  - Potential for resistance in non-adherent patients

Infusion therapy

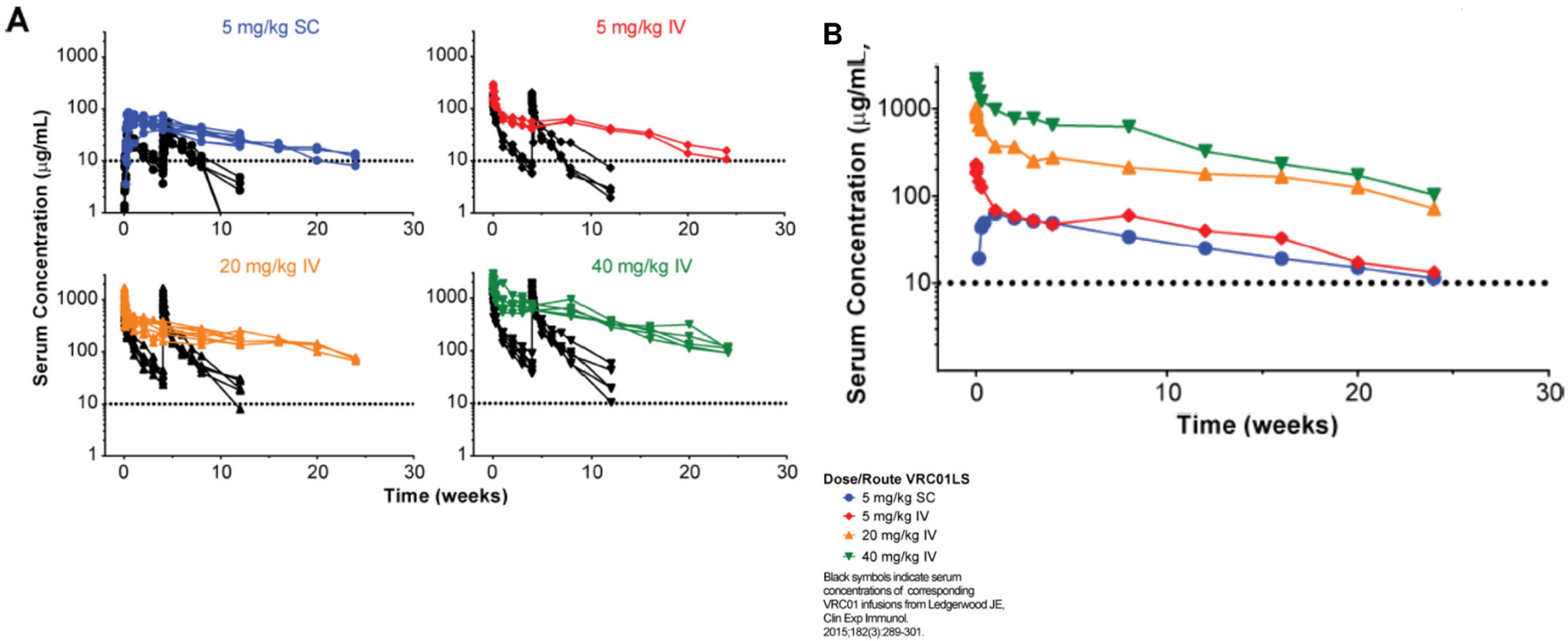
Potential advantages of bNAbs for PrEP or ART

- Infrequent dosing
- No cross-resistance with standard ARVs
- Established paradigms for therapeutic use of mAbs in other disease areas
- Potential for overcoming adherence challenges
- Potential for less stigma
- Potential to enhance HIV-specific immunity

Monthly or quarterly infusions

- Broadly neutralizing antibodies may be useful for maintenance of virologic suppression
- Will require combinations or bi-/tri-specific bNAbs
- All currently require i.v. infusion
- LS modification of Fc domain results in prolonged half-life, allows q 3 month dosing
- Phase 2-3 trials most likely will be switch studies
- Novel delivery systems will be needed to make these approaches practical
- Concerns about durability, emergence of anti-bNab antibodies

LS modification prolongs VRC01 half-life



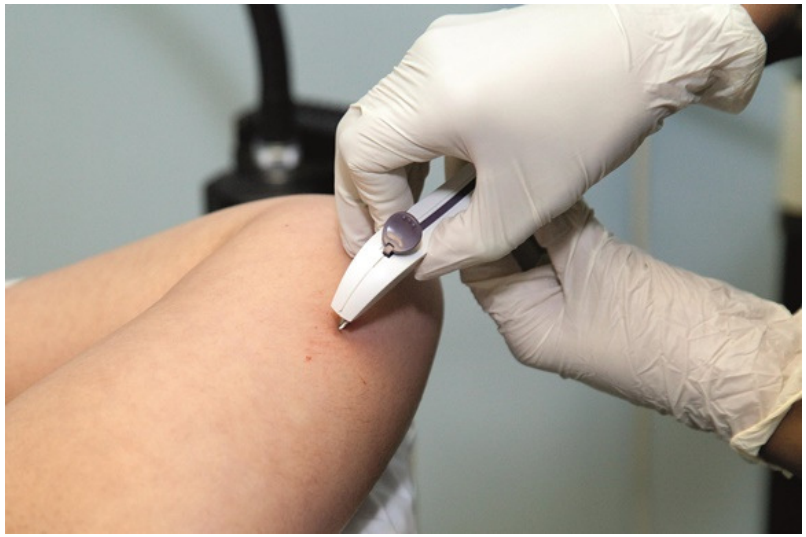
Gaudinski MR et al PLoS Medicine 2018
Gaudinski MR et al CROI 2018 Abstr 1061

Challenges in clinical use of bNAbs

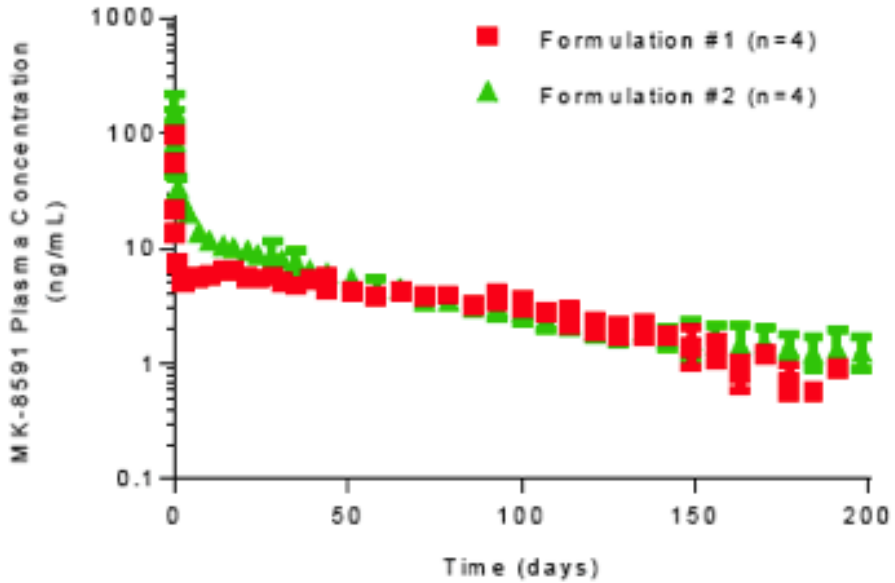
- **Acceptability of infusion or injectable ART/PrEP**
  - IV or SC administration
- **Dosing frequency**
- **Cost**
- **Capacity**
- **Global access**
  - (see also Cost and Capacity, above)

Implantable ART

Implantable etonogestrel



MK-8591: extended release formulation



- 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 JA et al CROI 2016

Semi-annual or annual implantables

- **May be more acceptable than monthly or bi-monthly i.m. injections for many patients**
  - May not be acceptable to some
- **Much depends on whether MK-8591 monotherapy is sufficient for maintenance**
  - If not, need a partner drug, likely requires two implants for administration
- **Ability to remove implants may obviate need for oral lead-in**
- **Clinical trials path similar to oral weekly dosing, monthly i.m. injectables**