

The long-acting wave: perspectives and pipeline



DIVISION OF
CLINICAL
PHARMACOLOGY

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CLINICAL
PHARMACOLOGY

Why do I think LA/ER
antiretrovirals will play
a major role in the future
of HIV treatment
and prevention?

Why I think LA/ER antiretrovirals will play a major role in the future of HIV treatment and prevention

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□ Schizophrenia

Why I think LA/ER antiretrovirals will play a major role in the future of HIV treatment and prevention

- Schizophrenia
- Osteoporosis

Why I think LA/ER antiretrovirals will play a major role in the future of HIV treatment and prevention

- Schizophrenia
- Osteoporosis
- Contraception

Why I think LA/ER antiretrovirals will play a major role in the future of HIV treatment and prevention

- Schizophrenia -- *adherence*
- Osteoporosis -- *convenience*
- Contraception -- *choice*

LA/ER anti-infectives:
What can we learn
from other disease areas?

Long-acting drugs: A new era in medicine?

HEALTH CARE >

Posted May 17 | Updated May 17

INCREASE FONT SIZE 

FDA approves long-acting drug to prevent migraines

Aimovig, taken in a monthly shot, is the first in a new class of migraine drugs to win approval. It will cost \$6,900 a year, without insurance.

New \$1,600 a month heroin-fighting medicine a 'game changer'

POSTED 10:26 PM, JULY 24, 2018, BY CHRIS HAYES, UPDATED AT 03:02PM, JULY 24, 2018

Tezepelumab, a First-in-Class Injectable Asthma Drug, Shows Promise in Trial

New AstraZeneca, Amgen drug reduces exacerbations by up to 71%

Tezepelumab (AstraZeneca/Amgen), a new kind of injectable biotech treatment for severe asthma, may help a much broader range of patients than existing medicines, findings from a mid-stage clinical trial show.

RESEARCH ARTICLE | APPLIED SCIENCES AND ENGINEERING

3D printing of a wearable personalized oral delivery device: A first-in-human study

Kun Liang[†], Simone Carmone, Davide Brambilla[†] and Jean-Christophe Leroux[‡]

+ See a

Aequus Announces Expansion of Market Opportunity for its Long Acting Anti-Nausea Transdermal Patch

Published: July 19, 2018 8:45 a.m. ET

Top Stocks Set to Disrupt the Diabetes Market

Revolutionary new drugs and medical devices could make these companies smart additions to your portfolio



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Extended-Release Injection for Schizophrenia Receives FDA Approval

JULY 30, 2018

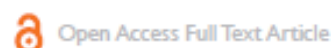
Cecilia Pessoa Gingerich

@CeciliaKPG



1
Intro

 Unitaid



Impact of long-acting injectable antipsychotics on medication adherence and clinical, functional, and economic outcomes of schizophrenia

This article was published in the following Dove Press journal:

Patient Preference and Adherence

12 November 2013

[Number of times this article has been viewed](#)

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Abstract: Schizophrenia is a debilitating chronic disease that requires lifelong medical care and supervision. Even with treatment, the majority of patients relapse within 5 years, and suicide may occur in up to 10% of patients. Poor adherence to oral antipsychotics is the most common cause of relapse. The discontinuation rate for oral antipsychotics in schizophrenia ranges from 26% to 44%, and as many as two-thirds of patients are at least partially non-adherent, resulting in increased risk of hospitalization. A very helpful approach to improve adherence in schizophrenia is the use of long-acting injectable (LAI) antipsychotics, although only a minority of patients receive these. Reasons for underutilization may include negative attitudes, perceptions, and beliefs of both patients and health care professionals. Research shows, however, significant improvements in adherence with LAIs compared with oral drugs, and this is accompanied by lower rates of discontinuation, relapse, and hospitalization. In addition,

Use of LAIs in Chronic Schizophrenia

- The majority of patients with schizophrenia relapse after 5 years and poor adherence is the most common cause.
- The discontinuation rate for oral antipsychotics is 26%-44%.
- Up to a third of patients are at least partially non-adherent.
- Non-adherence is associated with increased relapse, hospitalization and suicide.
- Long-acting injectable treatment is associated with lower rates of relapse, discontinuation and hospitalization versus oral anti-psychotics, and increased cost-effectiveness, functionality, quality of life and patient satisfaction.
- Improved quality of life reported with less frequent injections.



Ther Adv Musculoskel Dis

(2013) 5(4) 182–198

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Clinical experience with intravenous zoledronic acid in the treatment of male osteoporosis: evidence and opinions

Ieva Ruza, Sasan Mirfakhraee, Eric Orwoll and Ugis Gruntmanis

Abstract: Osteoporosis frequently remains underrecognized and undertreated in men. Most osteoporosis-related fractures could be prevented if men at risk would be diagnosed, treated, and remained compliant with therapy. Bisphosphonates, the mainstay of osteoporosis treatment, are potent antiresorptive agents that inhibit osteoclast activity, suppress *in vivo* markers of bone turnover, increase bone mineral density, decrease fractures, and likely improve survival in men with osteoporosis. The focus of the article is on intravenous zoledronic acid, which may be a preferable alternative to oral bisphosphonate therapy in patients with cognitive dysfunction, the inability to sit upright, polypharmacy, significant gastrointestinal pathology or suspected medication noncompliance. Zoledronic acid is approved in the United States (US) and European Union (EU) as an annual 5 mg intravenous infusion to treat osteoporosis in men. The zoledronic acid 4 mg intravenous dose has been studied in the prevention of bone loss associated with androgen deprivation therapy. This article reviews the evidence for zoledronic acid, currently the most potent bisphosphonate available for clinical use, and its therapeutic effects in the treatment of men with osteoporosis.

Use of LAIs in Osteoporosis

- ❑ Adherence to oral bisphosphonates for the treatment of osteoporosis is low.
- ❑ At least one-third of patients do not consistently take oral bisphosphonates as prescribed.
- ❑ Rates of adherence to oral tablets decrease over time.
- ❑ Patients overwhelmingly prefer a once-yearly injectable product (IV zoledronic acid).
- ❑ Once-yearly injectable treatment improves adherence and drug persistence and may be especially suitable for people who do not tolerate or adhere to oral drugs (e.g., people with cognitive dysfunction, polypharmacy, physical limitations).

ORIGINAL ARTICLE

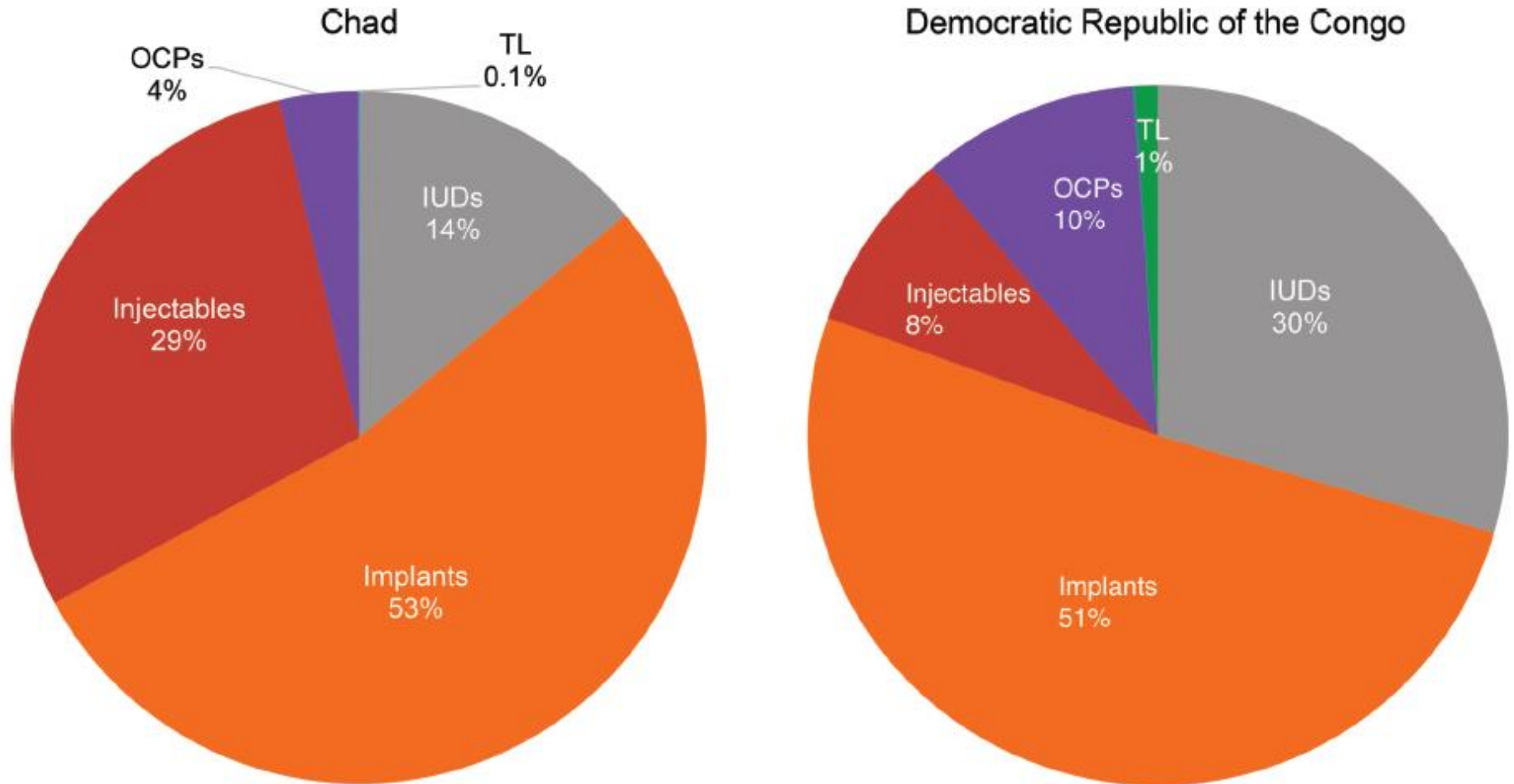
Rapid Contraceptive Uptake and Changing Method Mix With High Use of Long-Acting Reversible Contraceptives in Crisis-Affected Populations in Chad and the Democratic Republic of the Congo

Jesse Rattan,^a Elizabeth Noznesky,^a Dora Ward Curry,^a Christine Galavotti,^a Shuyuan Hwang,^b Mariela Rodriguez^a

Offering a broad choice of contraceptives can rapidly expand use in crisis-affected settings, particularly when the choice includes long-acting reversible contraceptives (LARCs). Over 5 years, the governments of Chad and the Democratic Republic of the Congo, with support from an NGO, provided nearly 85,000 new clients with contraceptives. LARC users, which included an increasing number of IUD users, accounted for 73% of the new clients.

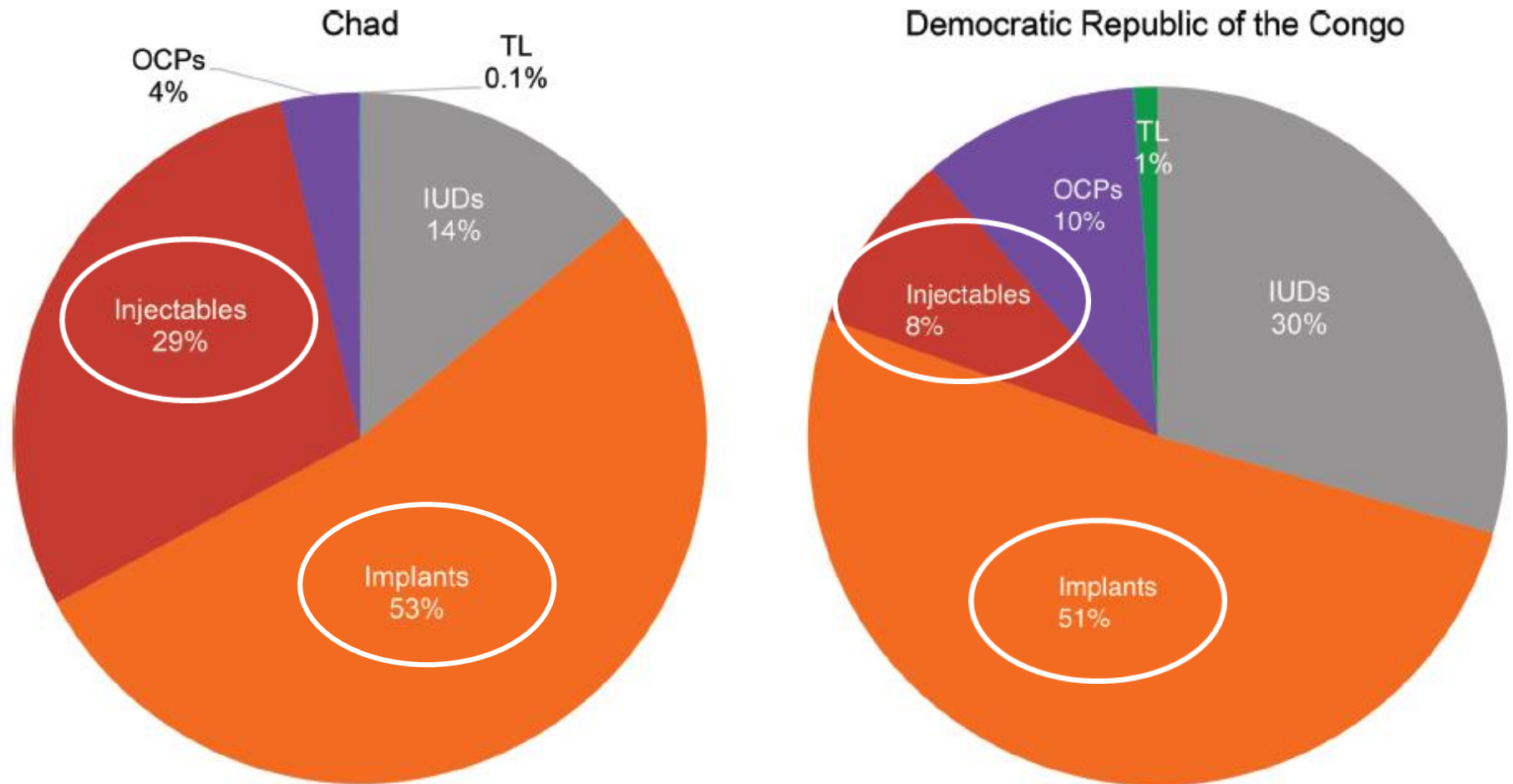
Uptake of contraceptive implants in SSA

FIGURE 1. Contraceptive Method Mix Among New Family Planning Users in Program Areas in Chad^a and DRC, June 2011 to November 2015



Uptake of contraceptive implants in SSA

FIGURE 1. Contraceptive Method Mix Among New Family Planning Users in Program Areas in Chad^a and DRC, June 2011 to November 2015



Use of LAIs in Hormonal Contraception

- Over 40 million women worldwide use injectable contraception, and nearly half (47%) of modern contraception users in sub-Saharan Africa rely on injectable or implantable contraceptives to prevent pregnancy.
- Returning to a health care provider for an injection every 2-3 months is considered a disadvantage of DMPA. Discontinuation rates of injectable contraceptives in sub-Saharan Africa are high, contributing to the growing popularity of longer-acting implants.
- Norplant-2 (levonorgestrel; Jadelle™, Levoplant, Sinoplant – 2 rods, 5-year duration) is now used by millions of women in SSA. Cost per generic implant is less than \$15 USD (~\$3 pppy for effective hormonal contraception).

Long Acting ARV's in Clinical Development

□ Approved

- Ibalizumab (in U.S.)
- Albuvirtide (in China)

□ Phase 3

- Cabotegravir-LA
- Rilpivirine-LA

□ Phase 2+

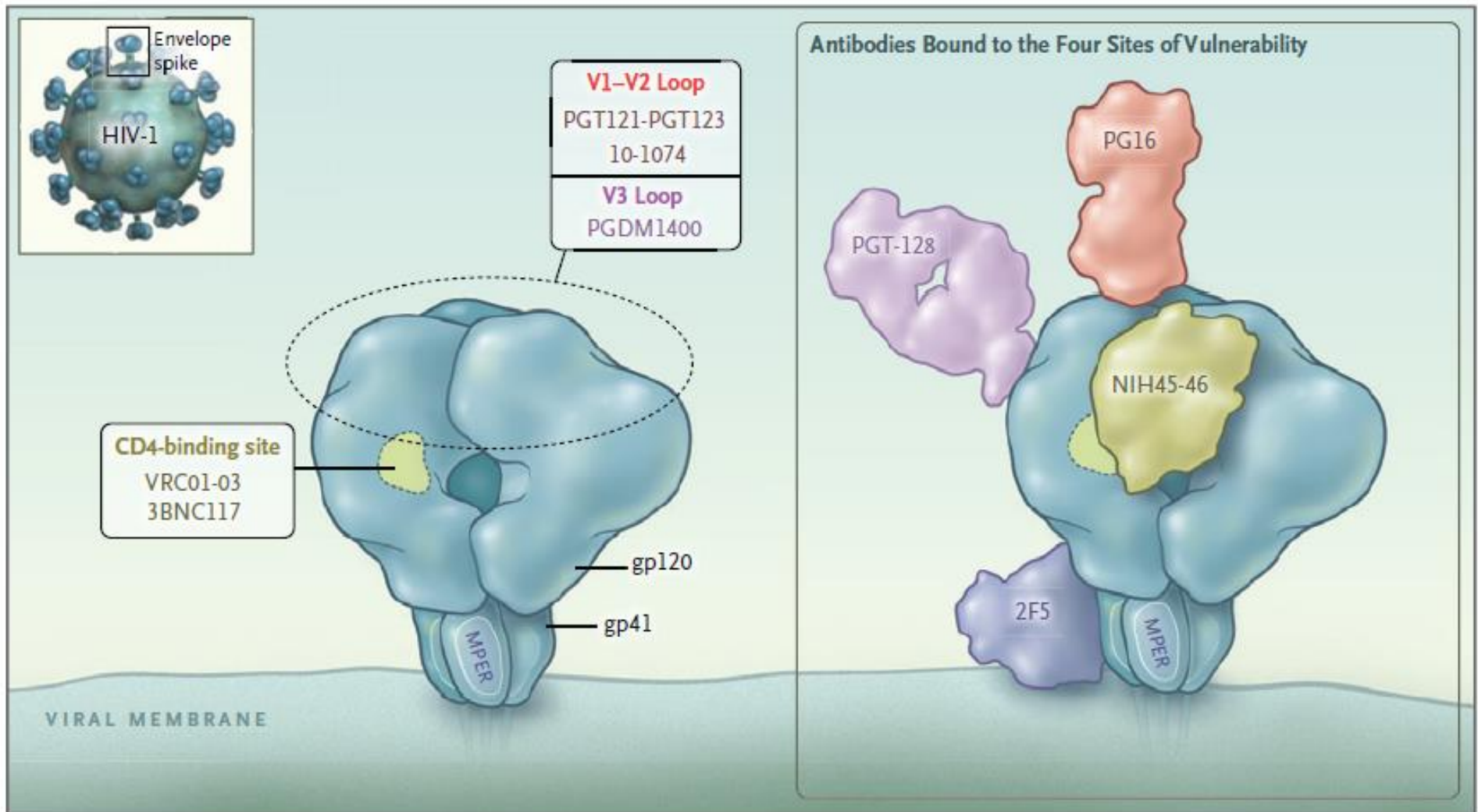
- PRO-140
- Broadly-neutralizing monoclonal antibodies
 - VRC01 and -LS; 3BNC117 and -LS; 10-1074 and -LS, etc.

□ Phase 1+

- EFdA; MK8591
- GS-CA1 capsid inhibitor

Future LA/ER technologies:
What's in the pipeline?

LA/ER Drugs:
Broadly-neutralizing
monoclonal antibodies



HIV-1 Spike Protein, Showing Sites Targeted by Broadly Neutralizing Monoclonal Antibodies.

The inset shows the virus with its surface spikes. The left panel shows target sites of monoclonal antibodies in clinical development. The right panel illustrates the binding of four different broadly neutralizing antibodies.

U.S. AIDS Clinical Trials Group (ACTG)

bnAb Clinical Trials - 2019

□ Currently open/completed trials

- A5342 (completed. Published JID) effects of a single bNAb, VRC01, on HIV reservoir
- A5240 (completed. Published in NEJM and JCI) Does a single antibody, VRC01, prevent viral rebound and effects of ATI on reservoir?
- A5357 Combination of VRC01LS with cabotegravir as maintenance Q4 2018
- A5377 Phase 1 Tri-specific antibodies (collaboration with Sanofi) Q4 2018;
- A5378 Phase 1 antiviral activity of VRC01LS and VRC507LS Q3 2018

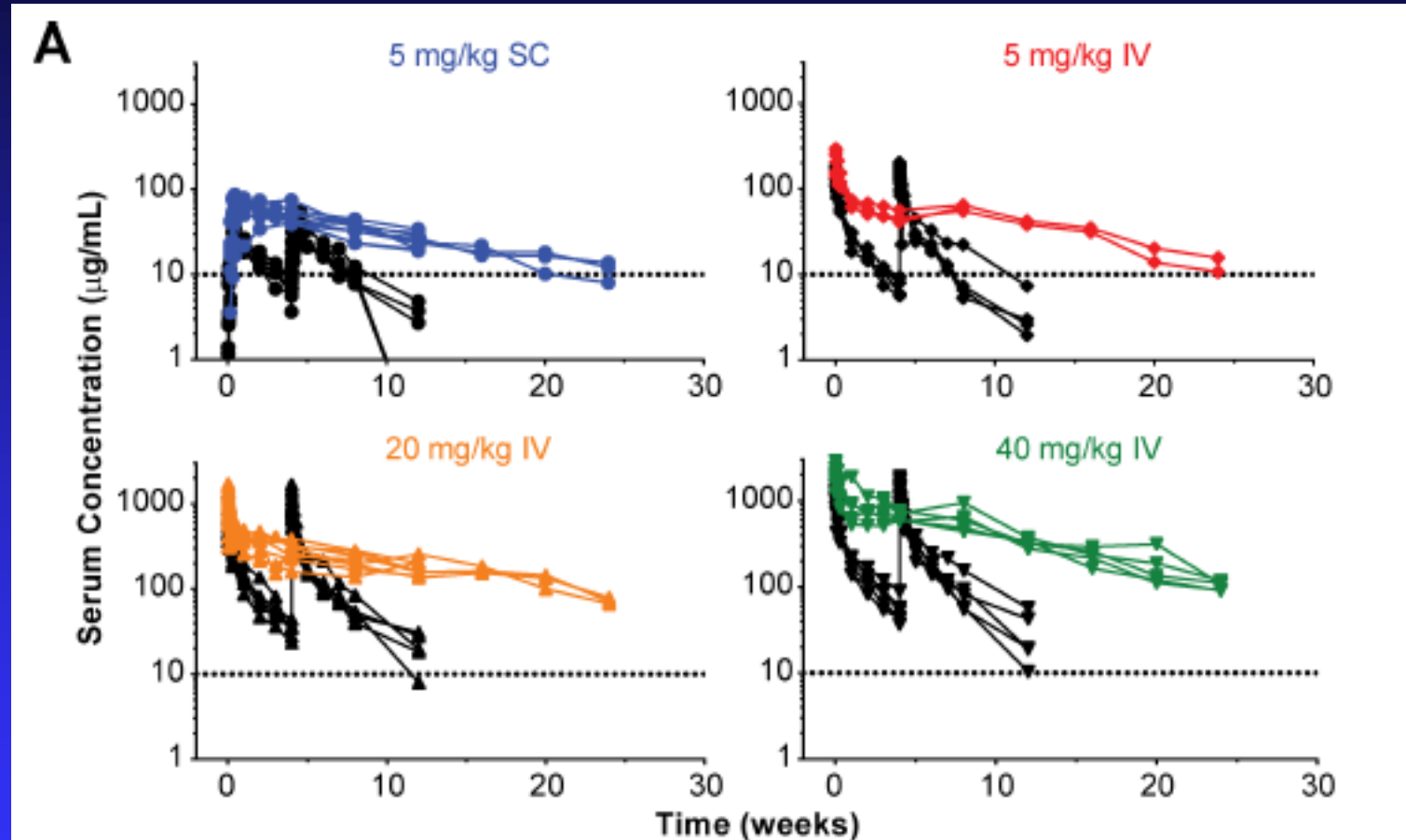
□ In development

- A5364 Combination of two long acting bNAbs to maintain suppression –and effects on the reservoir Q1 2019

□ Under review (Partnerships with Delaney Collaboratories)

- Effect on reservoir of 3 bNAbs in acutely treated and pts treated during chronic infn; Q2 2019
- ART plus combination of 3 bNAbs (or not) in acutely treated infection Q2 2019
- Combination of bNAbs plus a LRA (N-803) in acute and chronic infection Q2 2019

PK profile of VRC01-LS



Broadly-neutralizing monoclonal antibodies

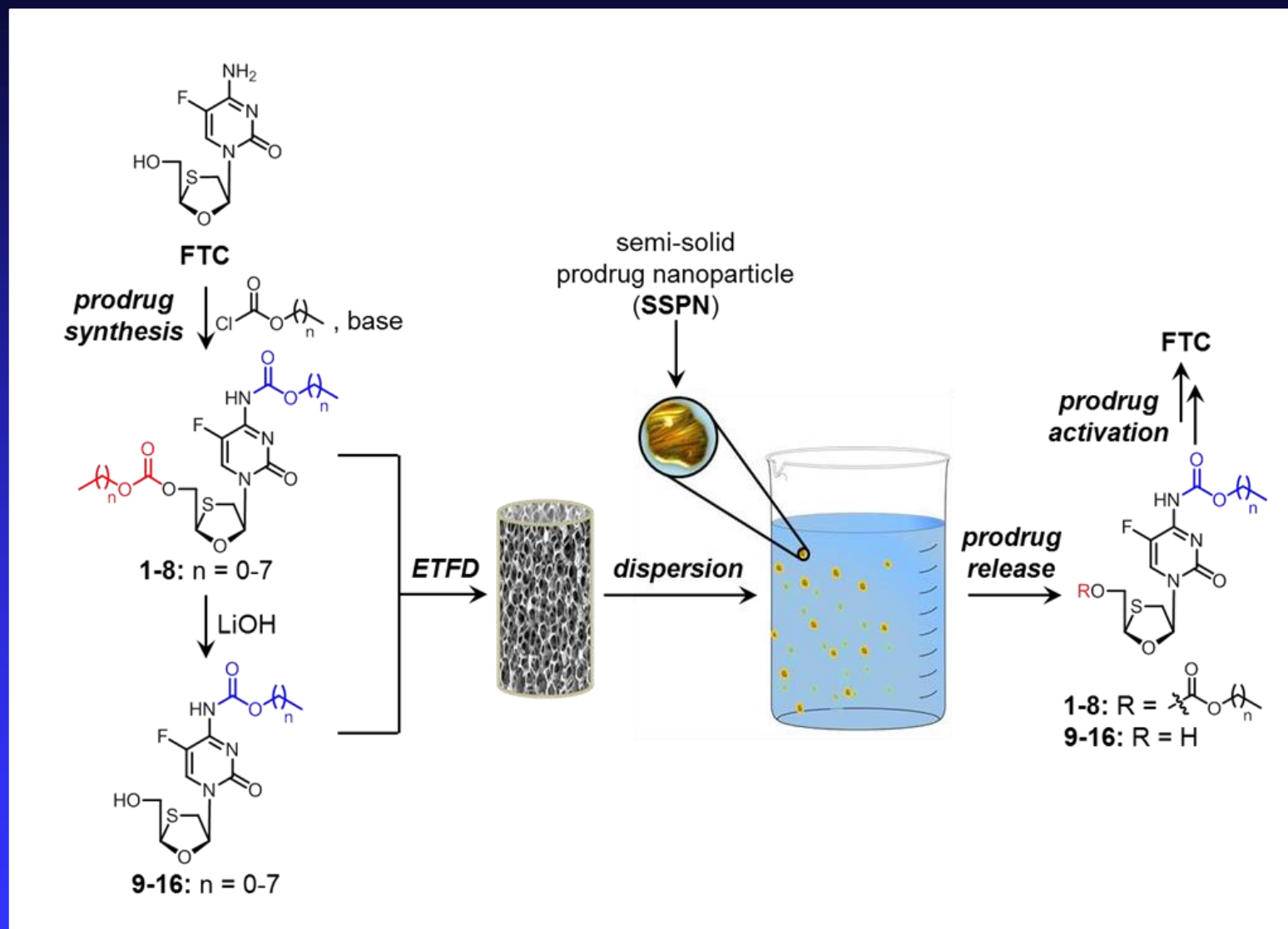
- Questions for the future:
 - How many bnAbs?
 - Breadth versus depth?
 - Can bnAbs be given by alternative routes of administration?
 - Subcutaneous
 - Intramuscular
 - Does it matter?
 - How can bnAbs be combined with small molecule LA formulations?
 - ACTG VRC01 plus CBT maintenance study in development
 - Can bnAbs be delivered by device?
 - Implantable “pumps,” microneedles, etc.
 - Will bnAbs ever be affordable in LMICs?

Novel LA/ER technologies: LA/ER NRTIs

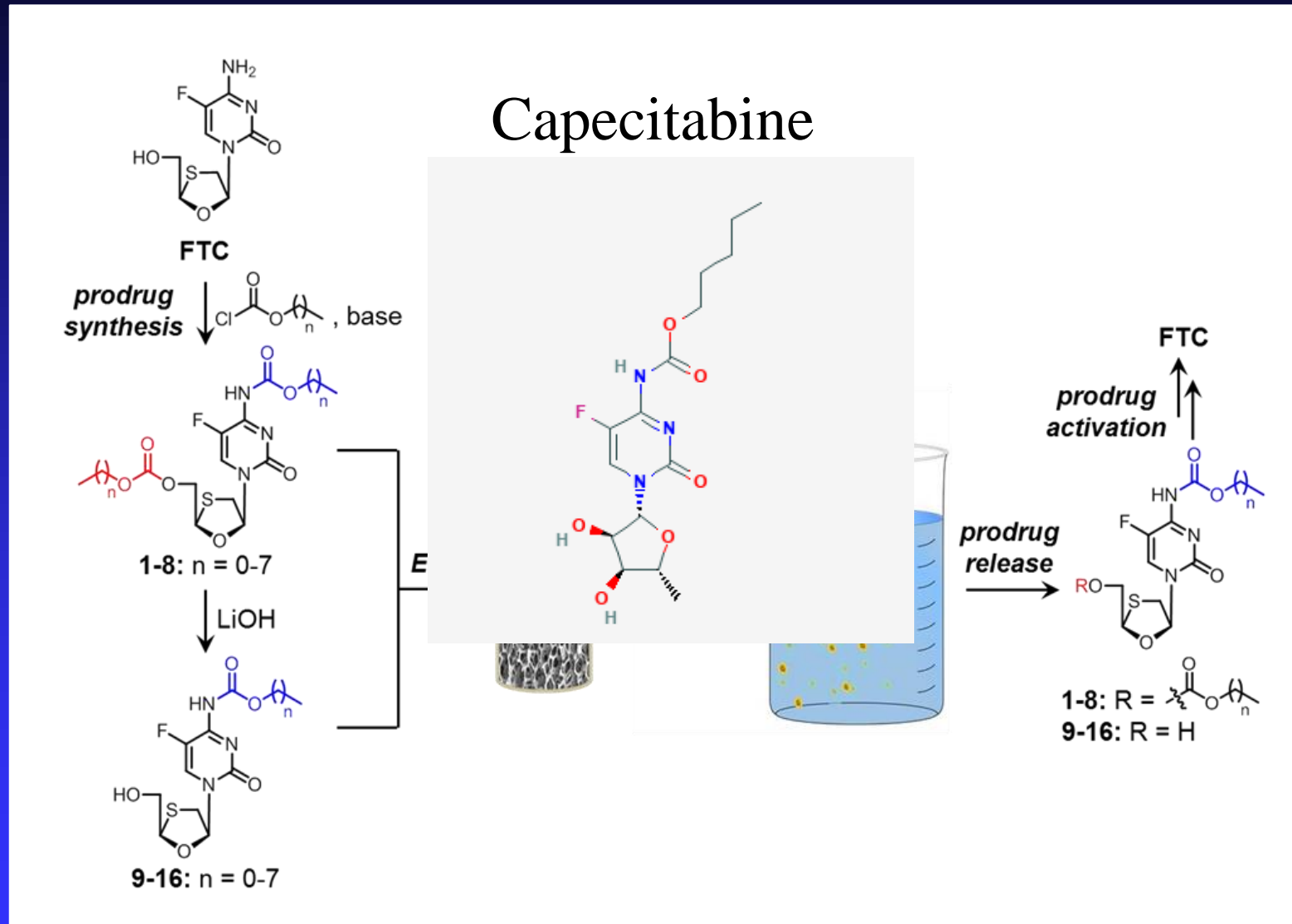
Why long acting NRTI's?

- Need something to pair with other LA ARV formulations in treatment regimens.
 - CBT
 - RPV
 - bnAb's, etc.
- Value of having a nucleoside “backbone” for combination LA ARV regimens.
- Need LA ARV formulations with activity against HBV.
 - More relevant for treatment than prevention

“Extendification” of existing NRTI’s

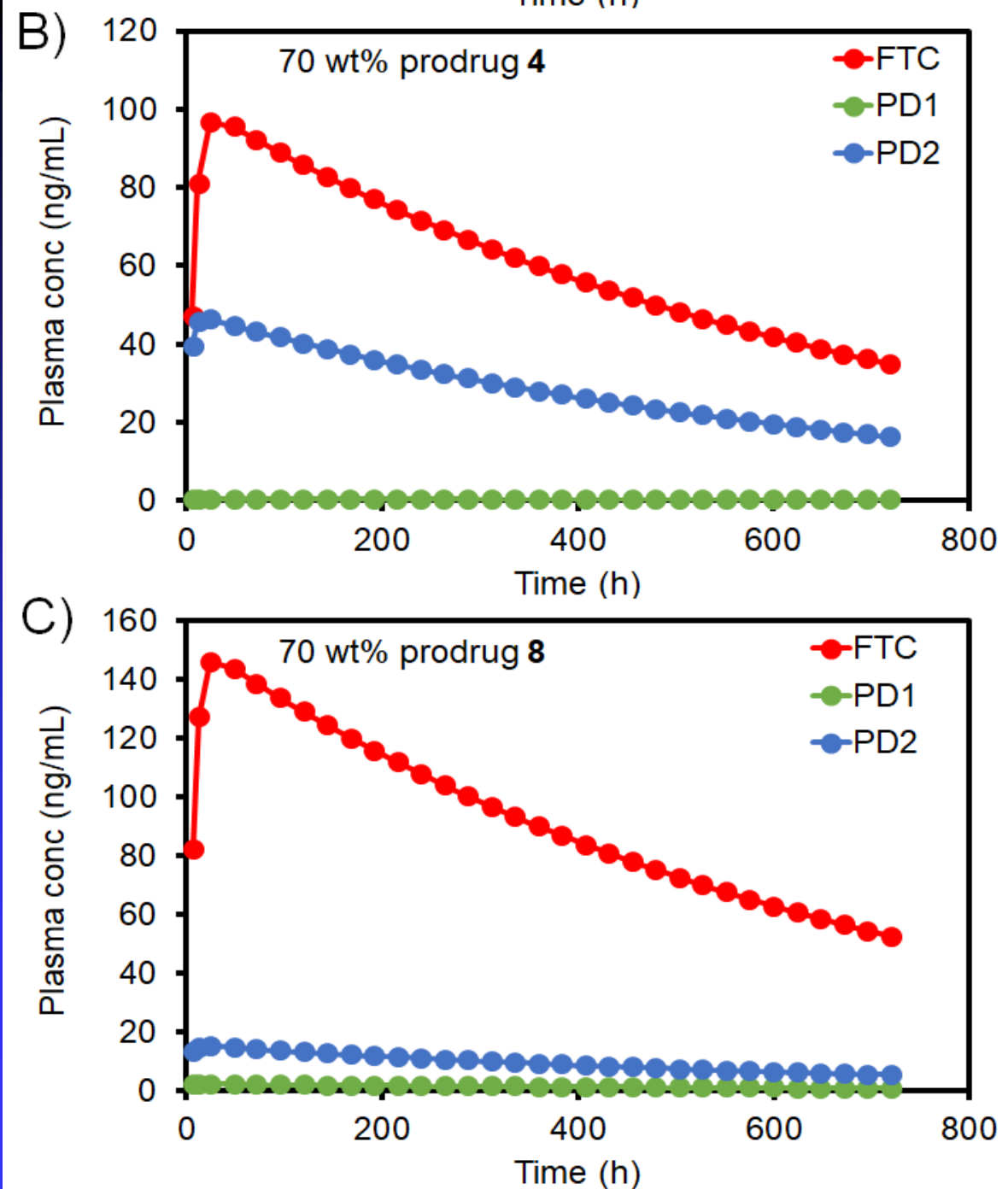


“Extendification” of existing NRTI’s



Estimated plasma concentrations of FTC after administration of prodrug SDN's

- Hobson et al., *CROI 2018*

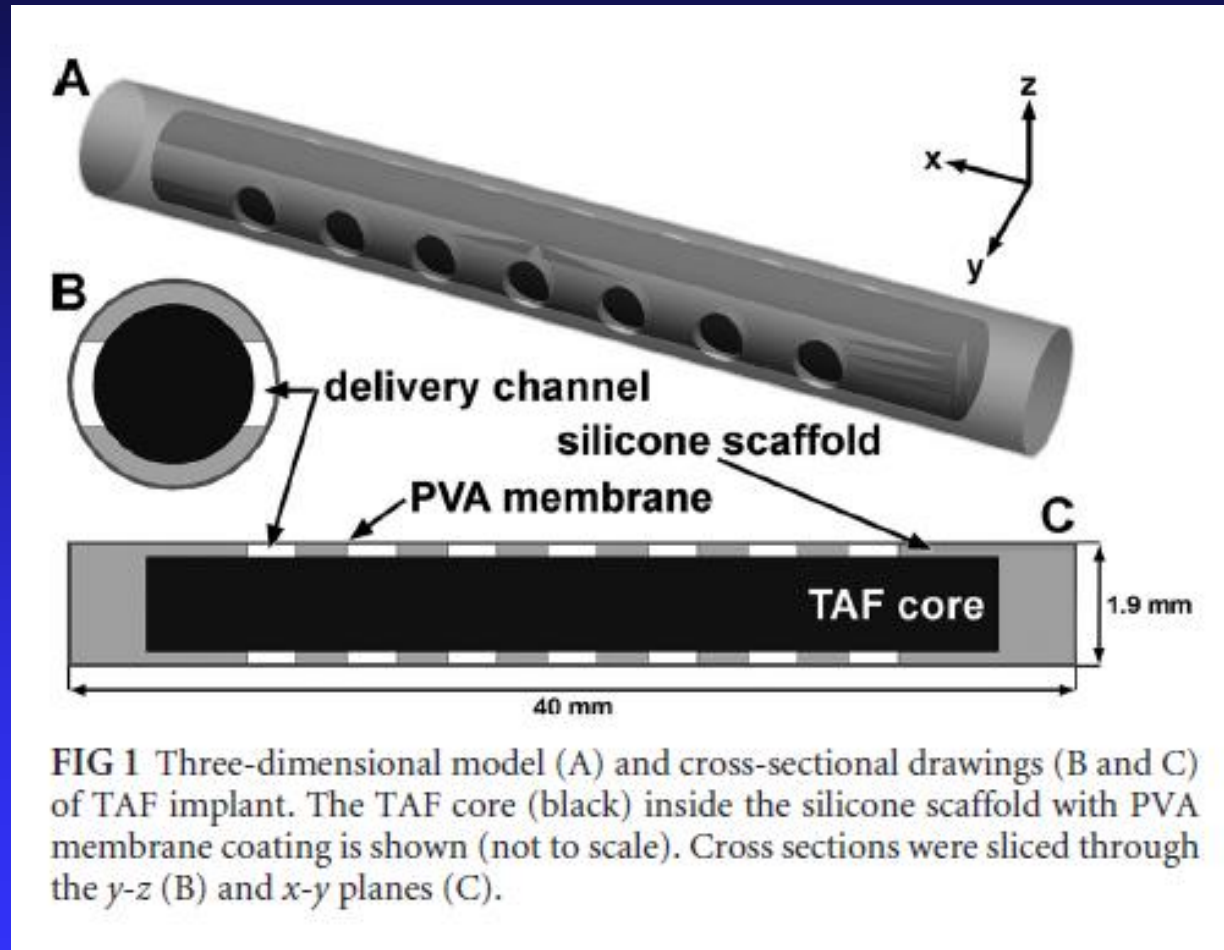


Novel LA/ER technologies: Implants

Long Acting ARV 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

LA ARV Implants – Tenofovir Alafenamide



M Gunawardana et al., *Antimicrob Agents Chemother* 2015; 59: 3913

LA ARV Implants – Tenofovir Alafenamide

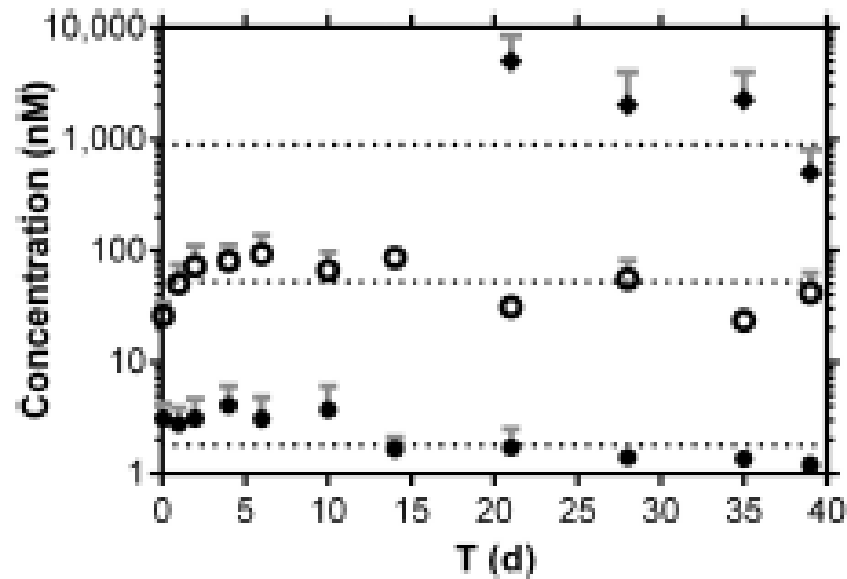


FIG 3 Subdermal implantation of TAF LA prototype device in beagle dogs maintains sustained drug levels with low systemic exposure to TAF and TFV with concomitant, efficient PBMC loading with TFV-DP. Pharmacokinetic profiles of plasma TAF (closed circles) and TFV (open circles) and PBMC TFV-DP (closed diamonds). Each data point represents the means \pm standard deviations from four beagle dogs, and dotted lines correspond to the median concentrations for each analyte over the 40-day study. Note that TFV-DP levels were measured only after day 20.

M Gunawardana et al., *Antimicrob Agents Chemother* 2015; 59: 3913

Chemical structure of MK-8591 (EFdA)

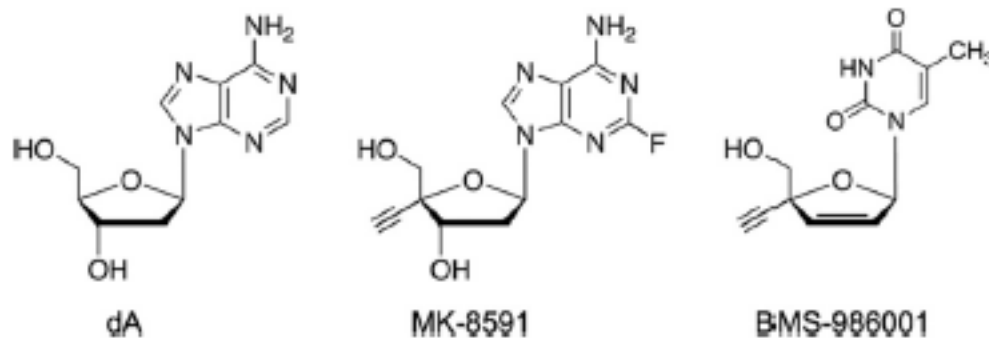


FIG 1 Chemical structures of 2'-deoxyadenosine (dA), MK-8591 (4'-ethynyl-2-fluoro-2'-deoxyadenosine [EFdA]), and BMS-986001 (2',3'-didehydro-3'-deoxy-4'-ethynyl-thymidine; also known as festinavir, cenvavudine, 4'-ethynyl stavudine, 4'-ethynyl-d4T, and OBP-601).

MK-8591 (EFdA) Implant Formulations Release Effective Drug Levels for >180 days

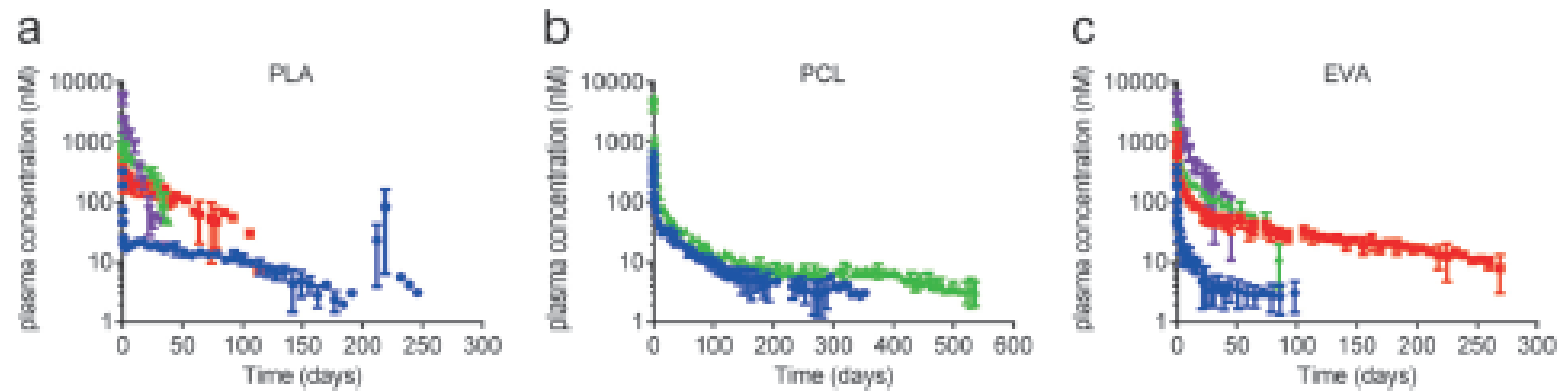


FIG 5 *In vivo* MK-8591 plasma concentration-versus-time profiles in male Wistar Han rats from a series of bioerodible, PLA (a) and PCL (b), and nonerodible EVA (c) implants. Data represent mean \pm standard deviation (SD) of $n = 4$ subjects for all studies. Blue circles, 40 wt% MK-8591 plus 60 wt% polymer; red squares, 50 wt% MK-8591 plus 50 wt% polymer; green triangles, 60 wt% MK-8591 plus 40 wt% polymer; purple inverted triangles, 80 wt% MK-8591 plus 20 wt% polymer.

- >180-day extended release from solid state formulations after a single injection in rats.
- Data suggest the potential to provide coverage for durations up to 1 year.

- Barrett SE et al. *Antimicrob Agents Chemother* 2018; DOI: 10.1128/AAC.01058-18

Novel LA/ER technologies:
Transdermal drug delivery?
Microneedles

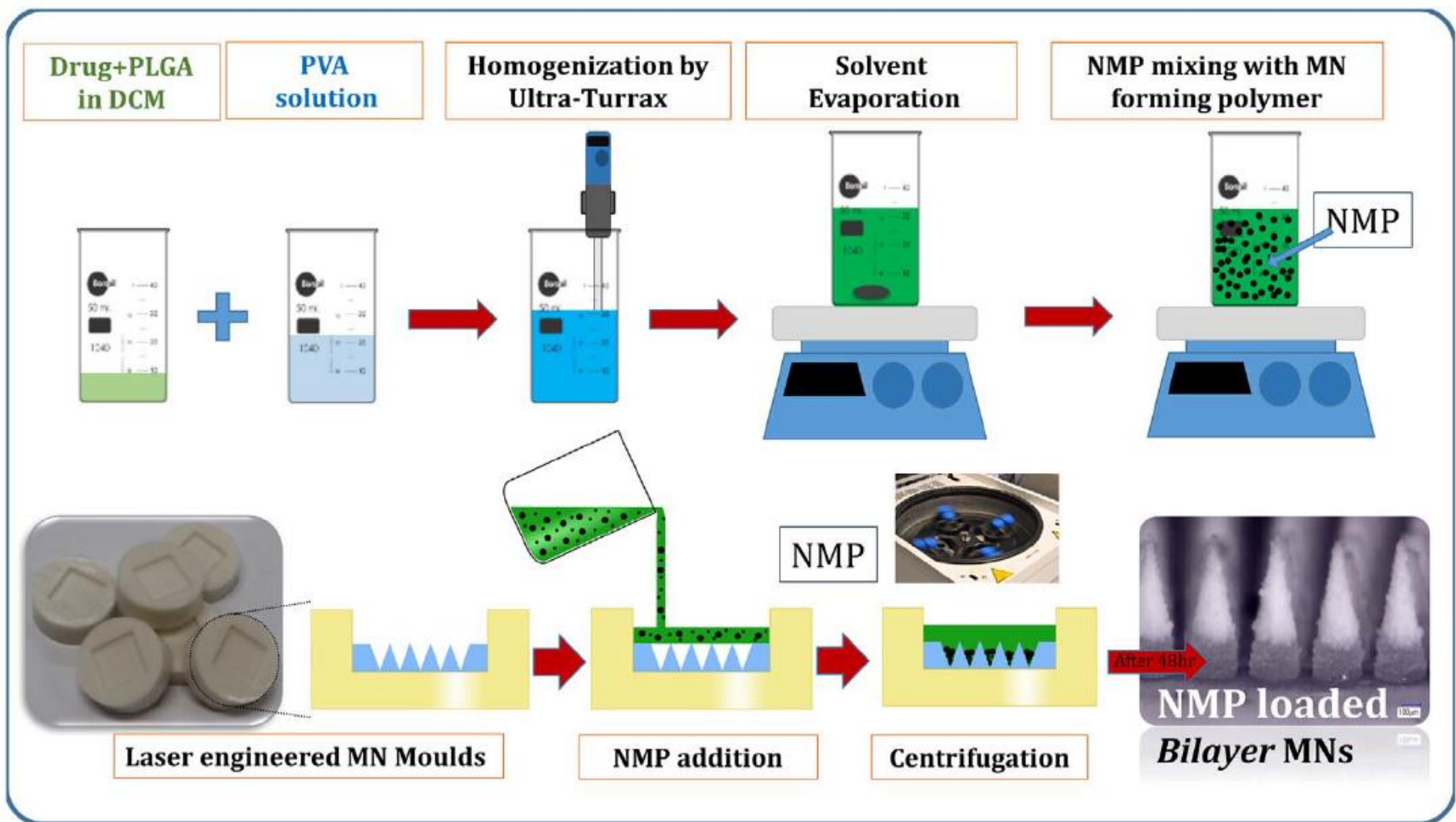


Fig. 1. Schematic representation of fabrication of PLGA nano-microparticle-loaded bilayer microneedle arrays.

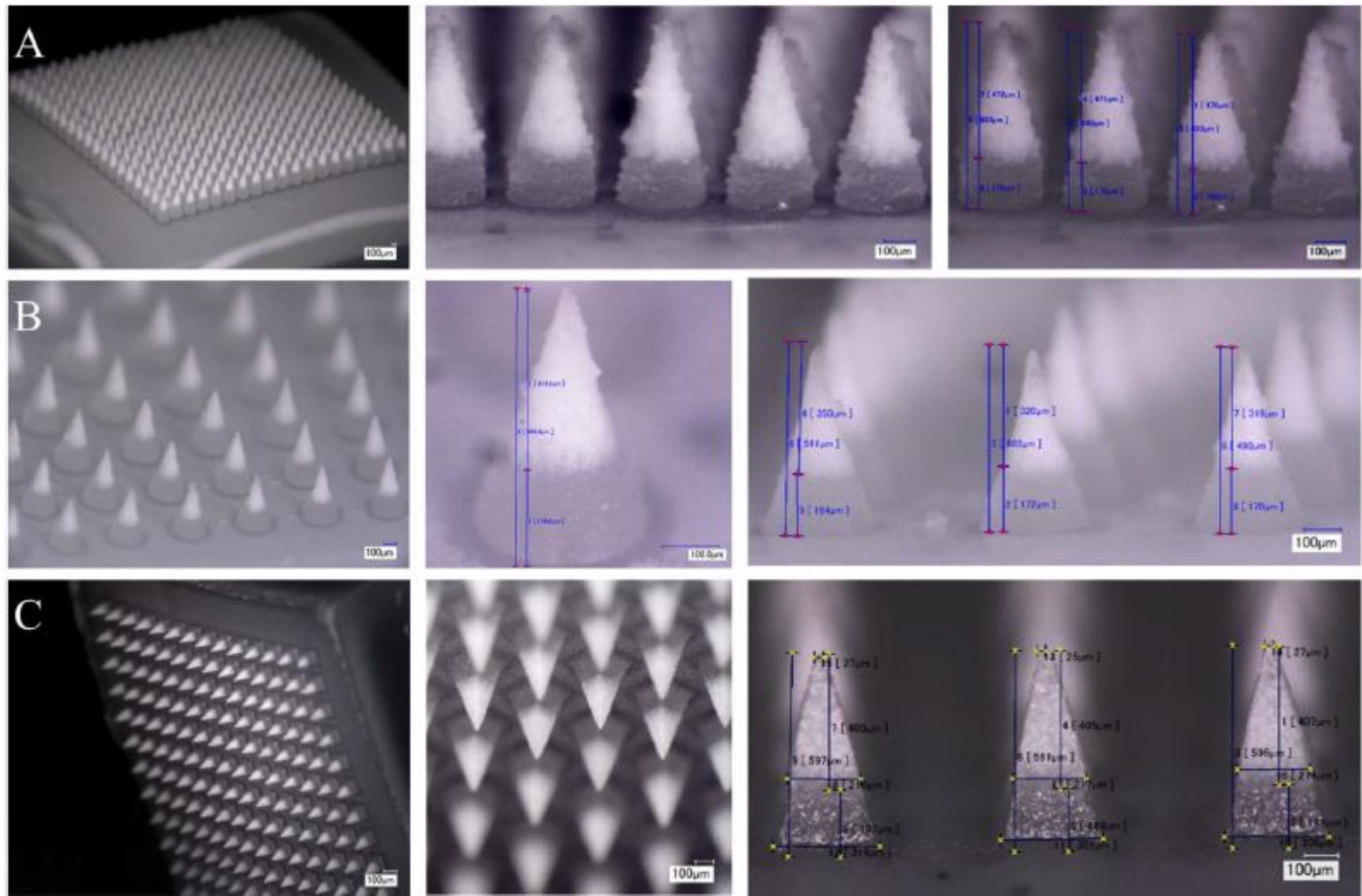


Fig. 4. Digital microscopic images of PLGA NMP-loaded bilayer microneedles. (A) Conical MN arrays (19 × 19). (B) Conical arrays (12 × 12). (C) Pyramidal (14 × 14) arrays.

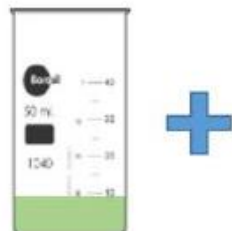
Drug+PLGA
in DCM

PVA
solution

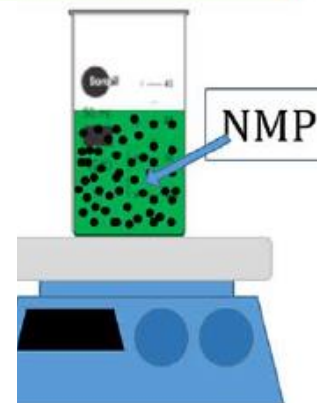
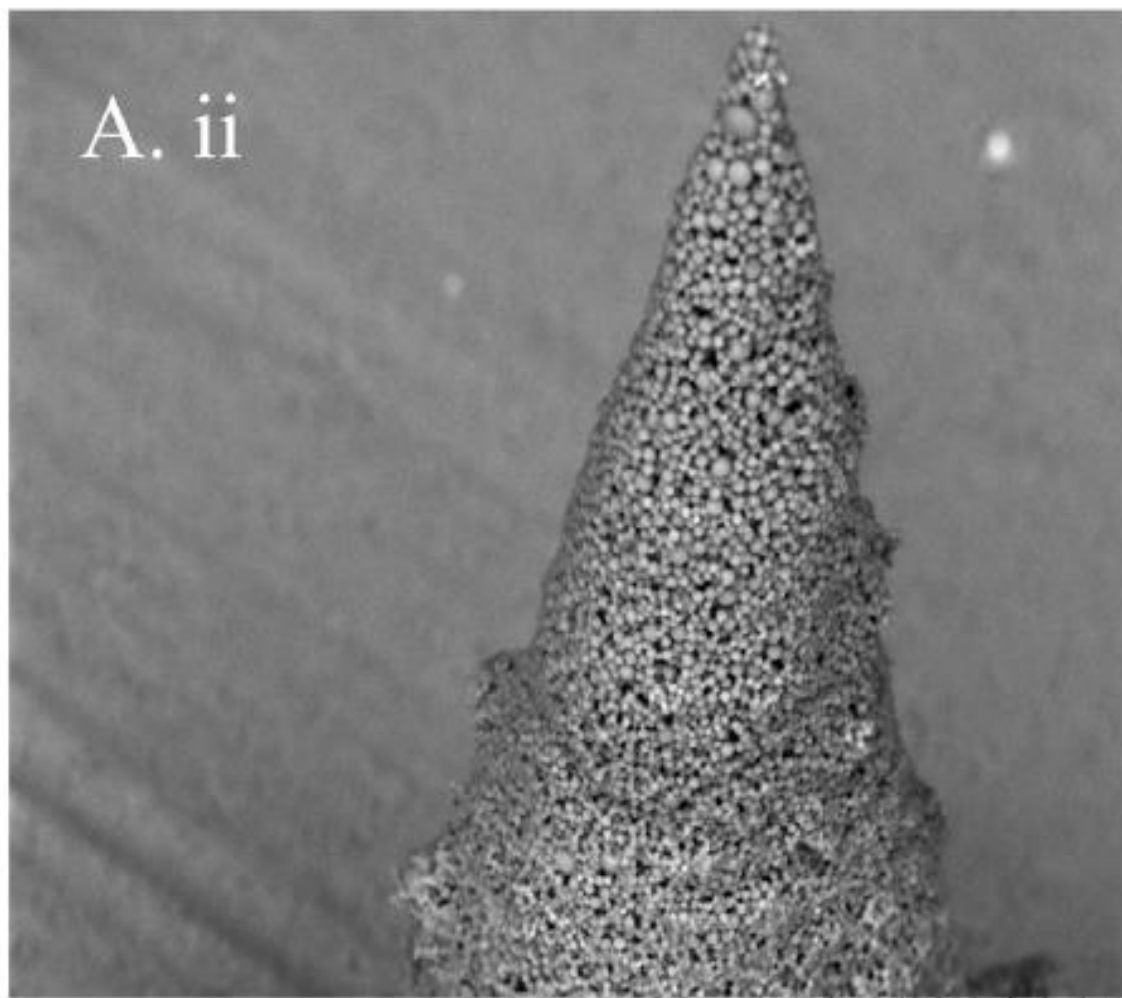
Homogenization by
Ultra-Turrax

Solvent
Evaporation

NMP mixing with MN
forming polymer



Laser engi



needle arrays.

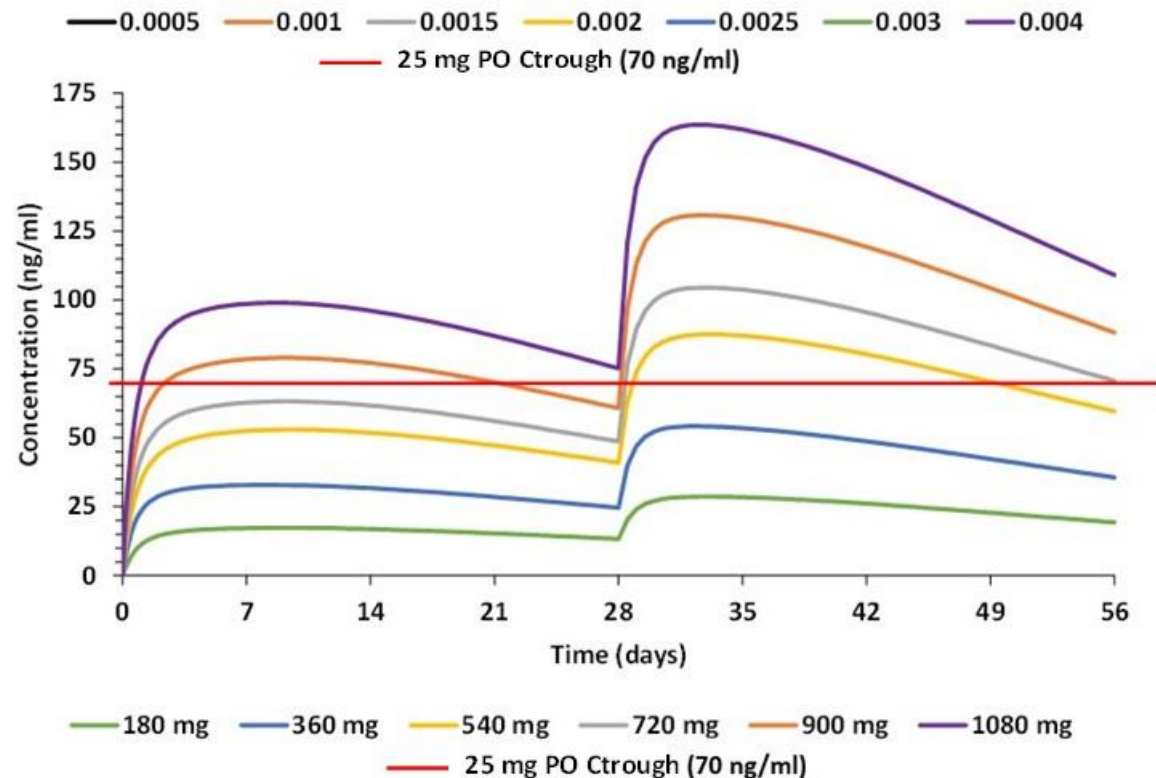
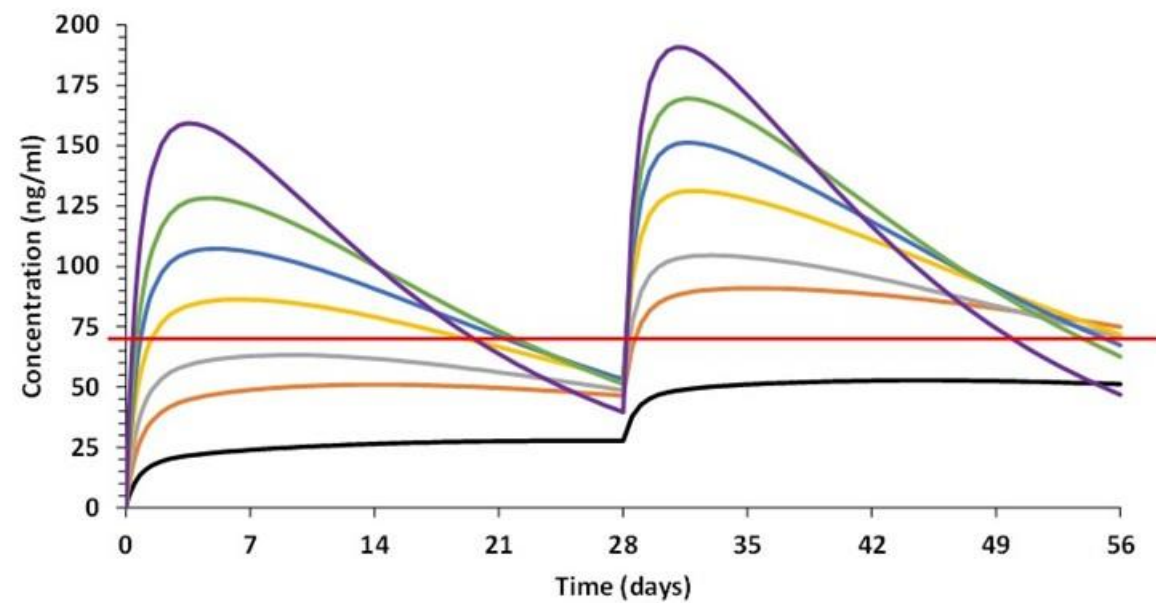
Fig. 1. Sc

What is it like
to wear a
microneedle
patch?



Estimated cabotegravir concentrations after applying a 30-60 cm² microneedle patch (adults)

- Rajoli et al. *CROI 2018*



The Long-Acting Wave: Big Questions for the Future!



- How big is the market, really?
- Affordability for low income countries?
- Will future Rx regimens need to cover HBV?
- What will be the role for broadly neutralizing antibodies?
- Can bnAbs be combined with LA small molecules?
- Will implants have broad acceptability?
- What about missed doses and fear of resistance?
- Will LA be used mainly for prevention and not treatment?

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