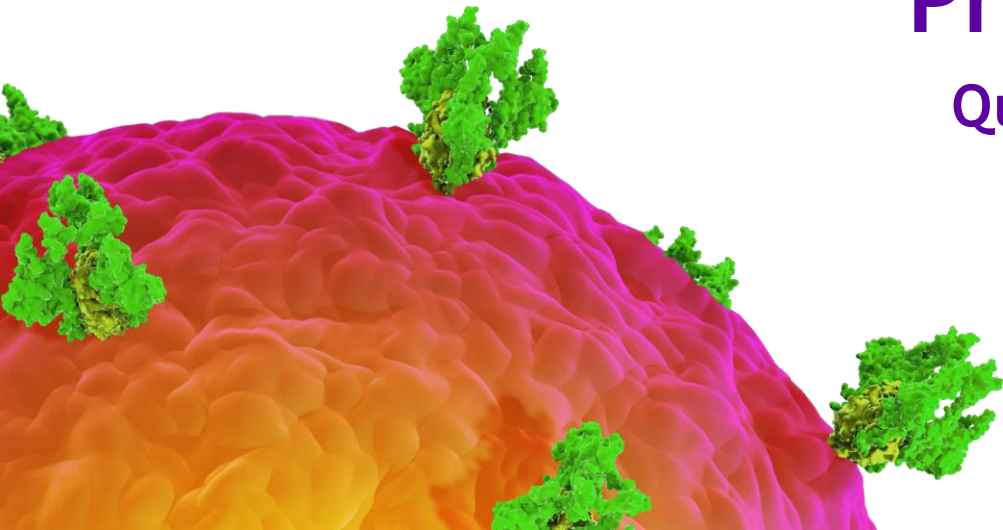
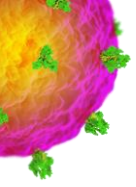


Long-Acting Antiretroviral Treatment in relation to the 3rd 90

Professor Chloe Orkin

Queen Mary University of London
Barts Health NHS Trust





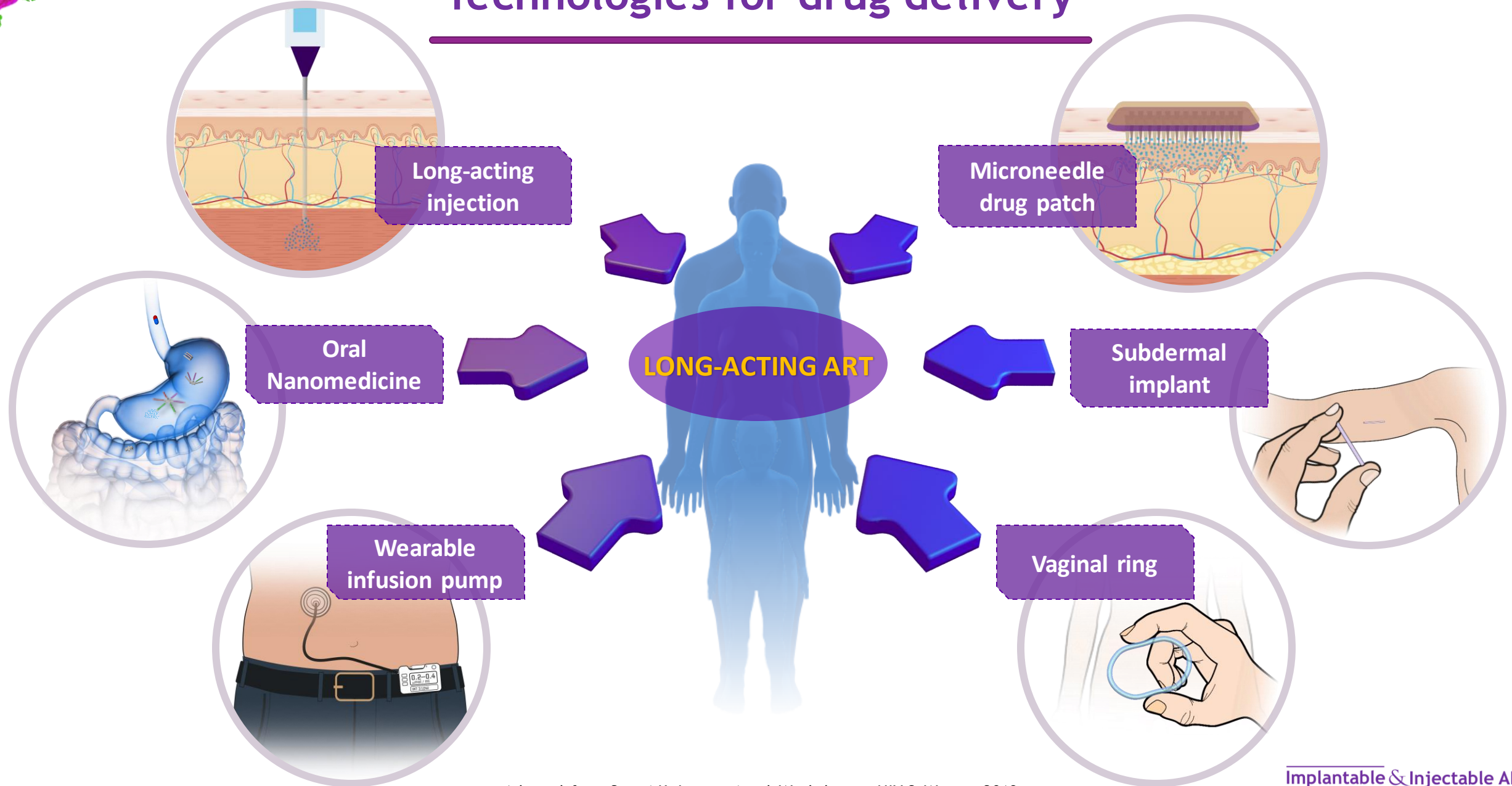
Disclosures

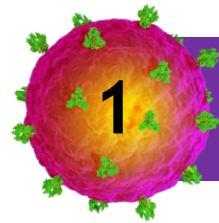
I have received:

- Honoraria for lectures and advisory boards
- Travel grants
- Research grants to my institution

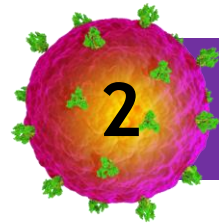
From Gilead Sciences, Janssen, MSD and Viiv Healthcare

Technologies for drug delivery

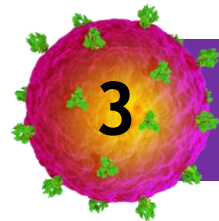




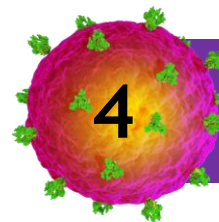
Lessons from other specialties



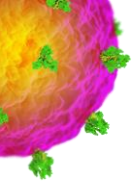
Long-acting injectable ART



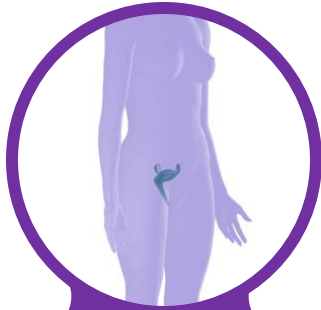
Long-acting implantable ART



Horizon scanning



What have implantable and injectable drugs done for other specialties?



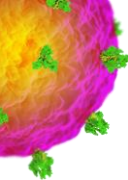
CONTRACEPTION



PSYCHIATRY



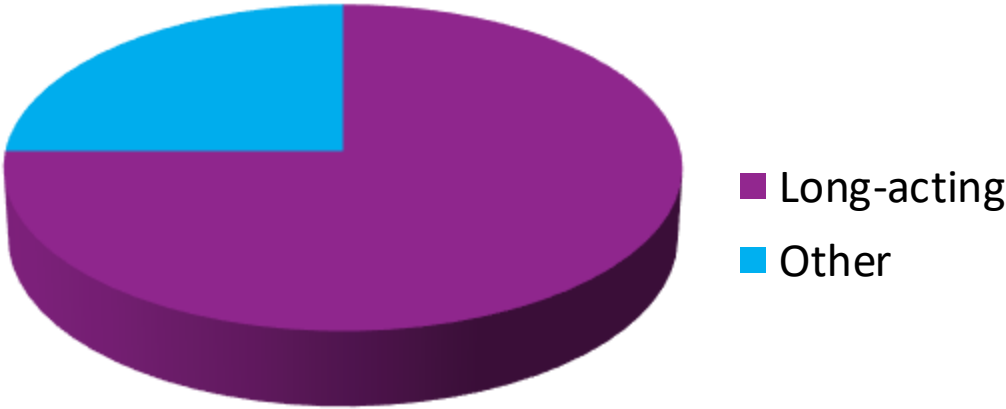
OSTEOPOROSIS



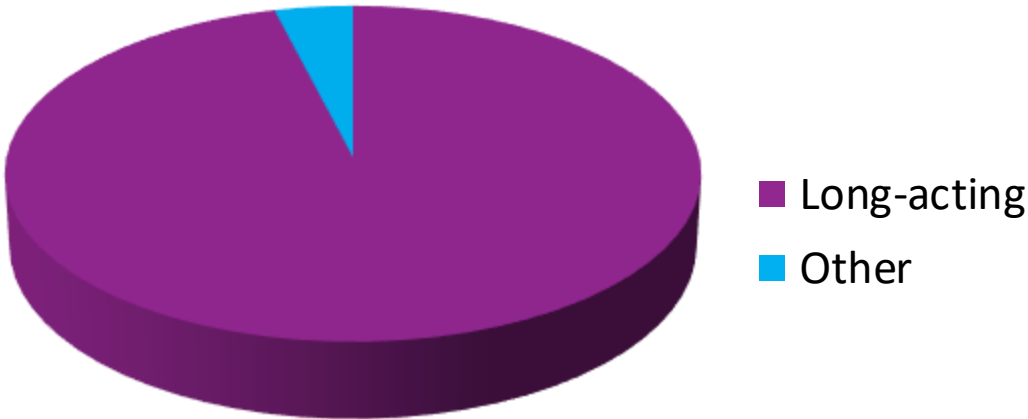
Women prefer long-acting reversible contraception (LARC)

Uptake of contraceptive methods

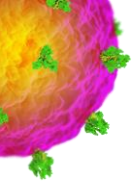
US: Contraception method



Chad: Contraception method



ECHO trial : LARC led to low pregnancy rates. Strong justification to improve access



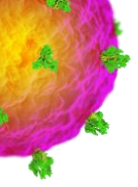
What have implantable and injectable drugs done for other specialties?



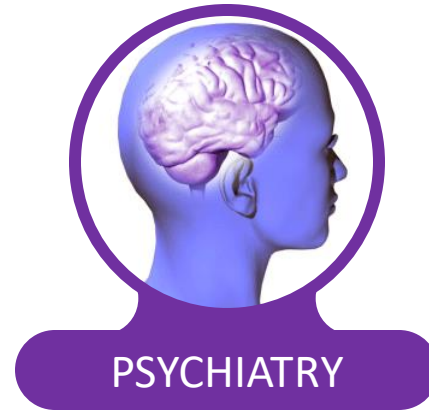
Adherence to oral bisphosphonates is low and decreases over time

Once-yearly infusion improves adherence

Helpful for cognitive impairment, polypharmacy, immobility



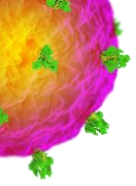
What have implantable and injectable drugs done for other specialties?



Reduces relapse rate and hospitalizations

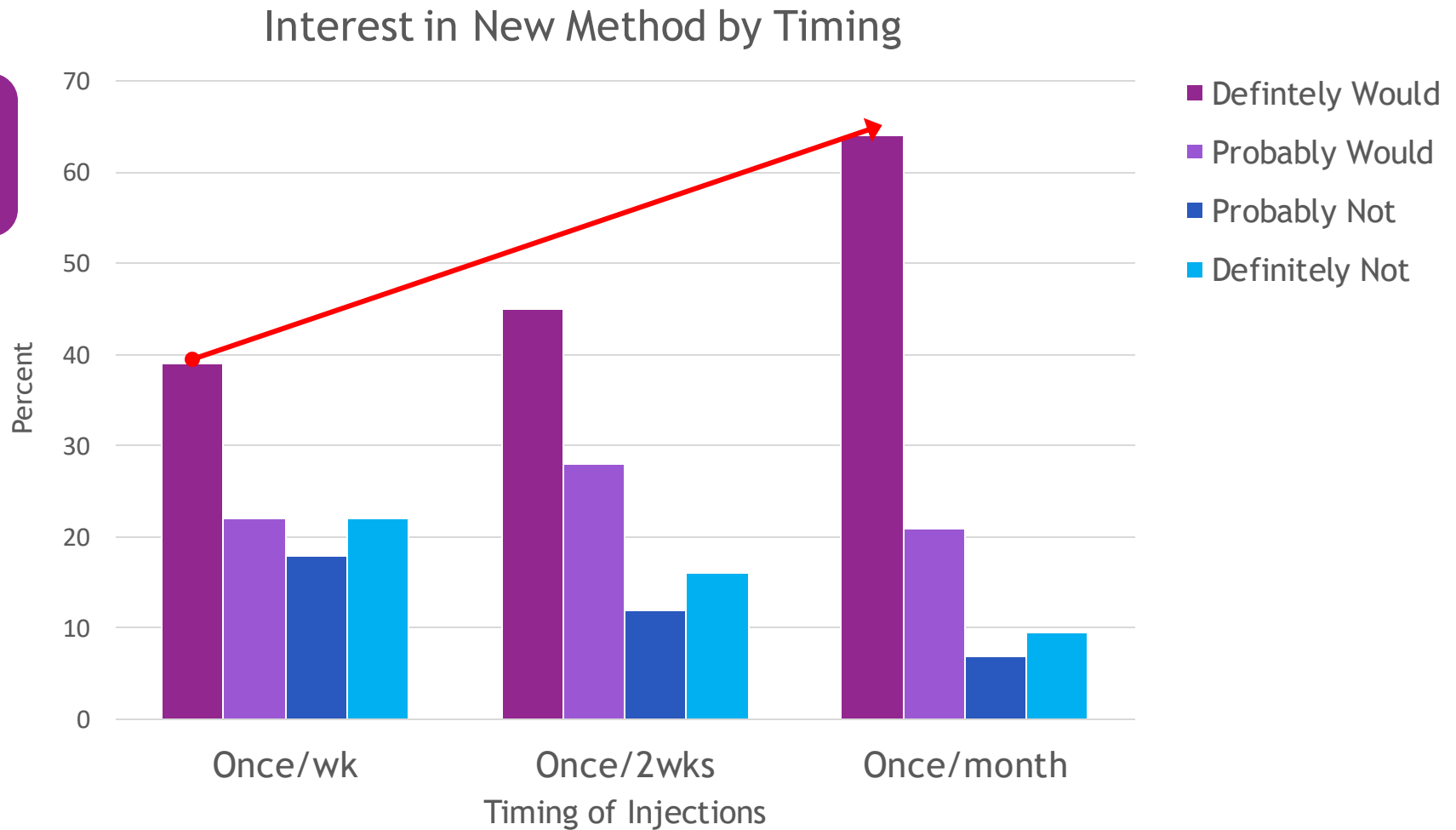
Improves patient satisfaction

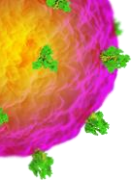
Avoids first pass metabolism, reduces DDIs



Demand for long-acting ART in HIV?

>60% interested
in once/month

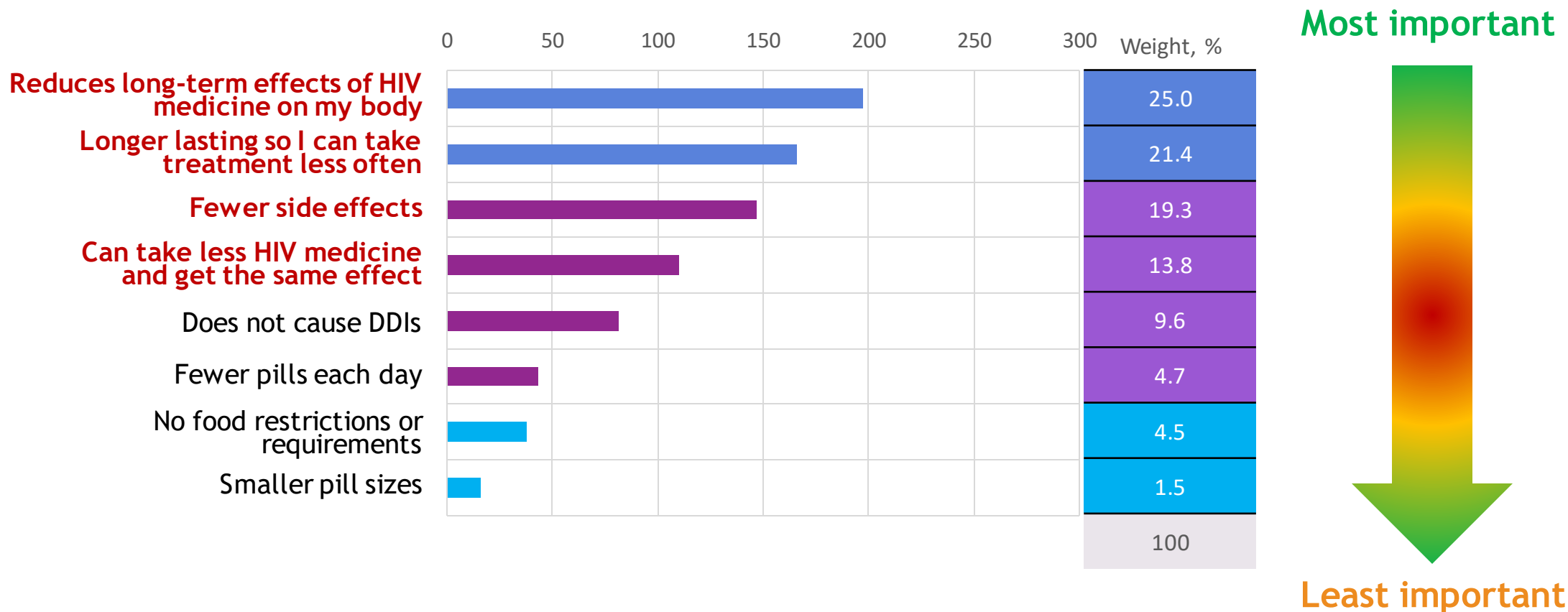


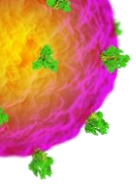


Patient survey

Reducing long-term effects and longer treatment intervals important

Score (100 = average importance)



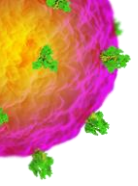


Do we really need 3 drugs for 50 years?



Age 30

Age 80



Yearly intake of ARV by regimen over 50 years

Once daily single tablet = **17kg**



2 monthly injection = **600g**



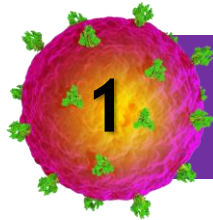
Age 30

Age 80

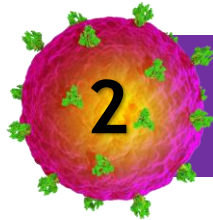
Implantable & Injectable ART



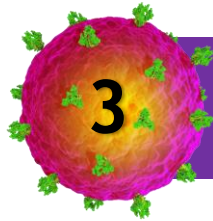
What does LA injectable ART involve?



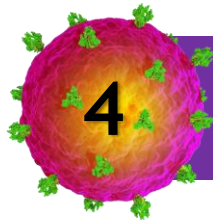
What ATLAS and FLAIR phase III trials show



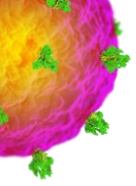
Patient Reported Outcomes



What else do we need to know?



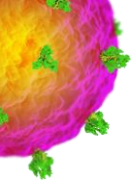
Planned studies for CAB/RPV



Long-Acting Injectable (LA) ART : Cabotegravir (CAB) + Rilpivirine (RPV)

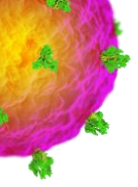
- LA : slow release of the active drug or continued absorption the drug over an extended time





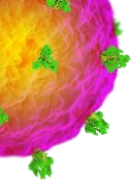
Long Acting injectables - What's the attraction?

- Infrequent dosing
- Lower overall drug dose
- Prevents poor pill-taking, helps pill fatigue
- Potential for directly observed therapy
- Protects health privacy and treatment related stigma
- Can avoid certain drug interactions eg with mineral supplements like iron, antacids , acid lowering drugs
- **Children:** NO fixed dose oral combinations for children under 25 kg



Long Acting injectables - some key issues

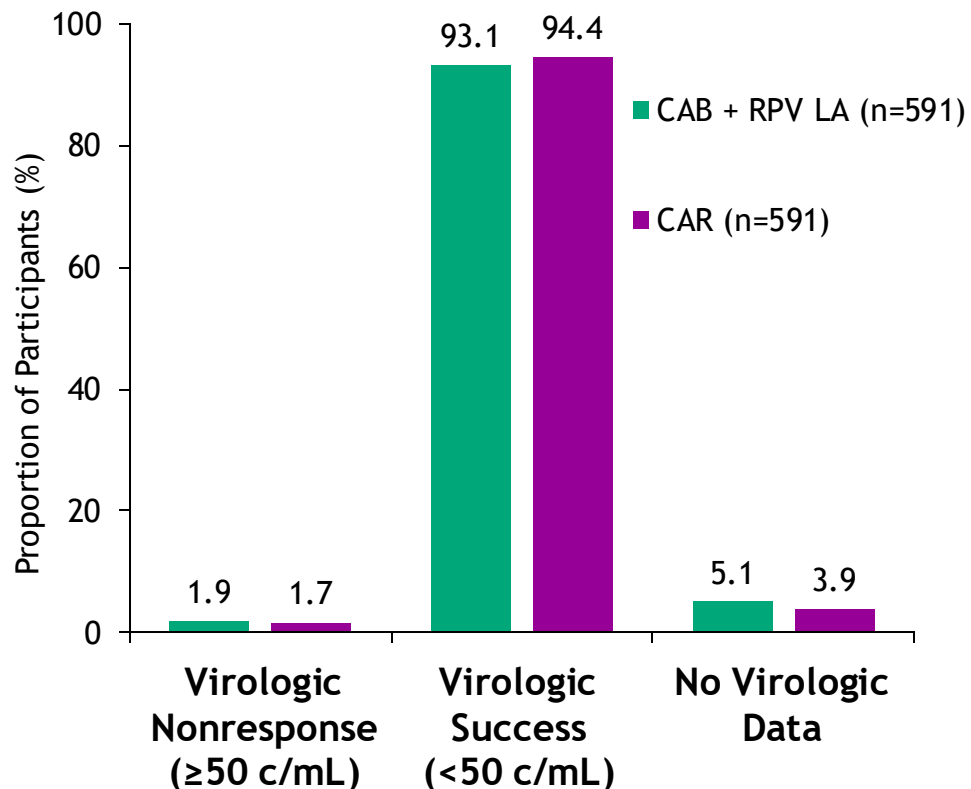
- Not all drugs can be combined
- Must be compatible with small injection volume
- Injection volume is 2ml for each drug
- Must be injected into the buttocks
- Rilpivirine has a cold chain (needs to be stored at -4C)
- What to do about mixed doses
- Long term drug levels at end of dosing interval
- Side effect management as drug cant be removed



Pooled analysis ATLAS and FLAIR studies (wk 48)

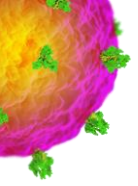
No differences in efficacy between oral and injectable ART

Virologic outcomes



*Adjusted for sex and baseline third agent class.

CAB, cabotegravir; CAR, current antiretroviral; CI, confidence interval; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority; RPV, rilpivirine.

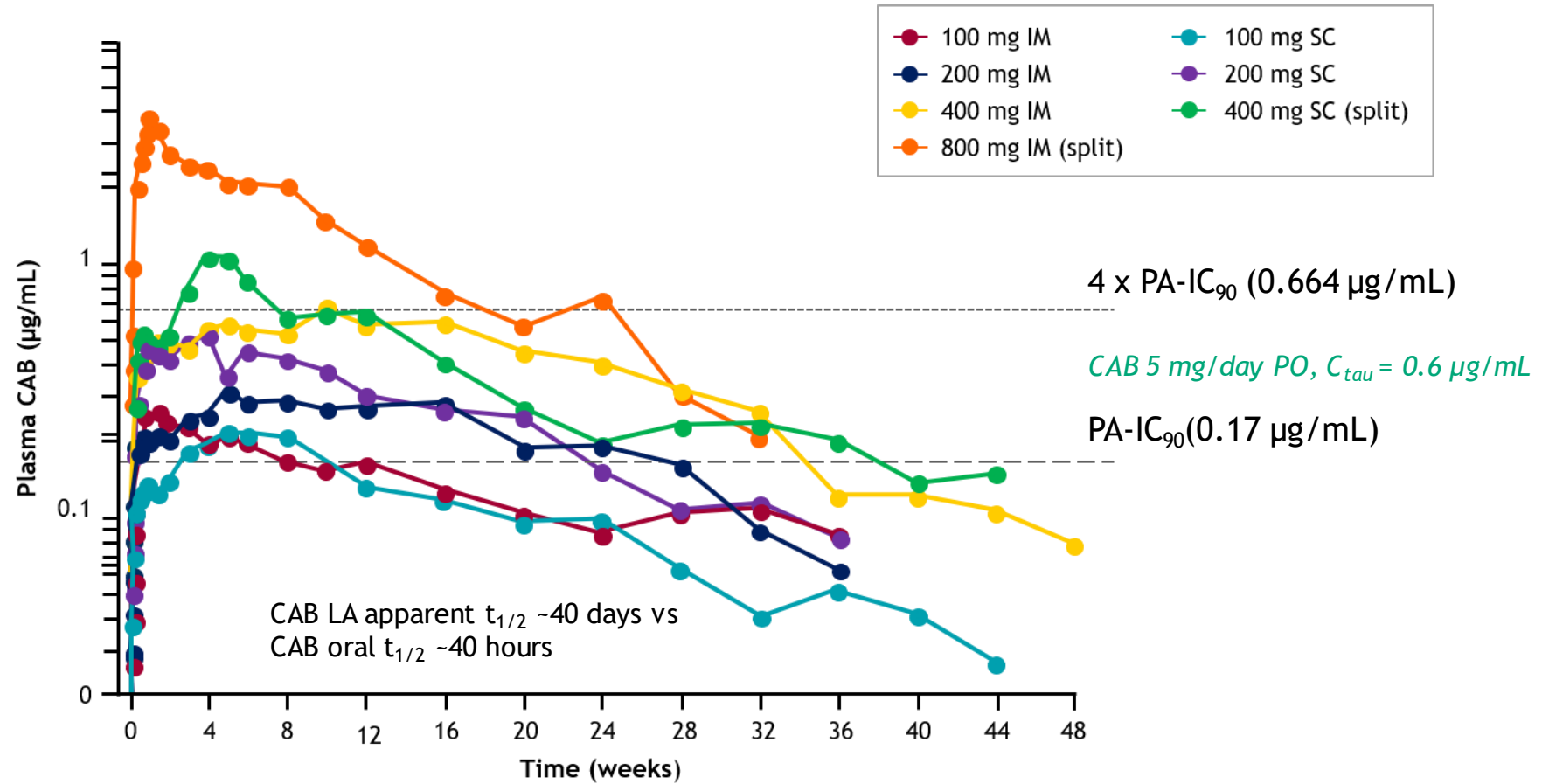


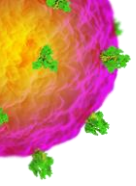
Participant Reported Outcomes: Patients preferred LA (ATLAS)

- Several different PRO scores evaluated
- **ACCEPT score** significantly better after switch to CAB/RPV (all time points)
- **Acceptability of ISR's and pain** scored 'totally/very acceptable' by 90% and 86%
- **Withdrawals due to ISR's** :4 (1%)
- **HIVTSQ score** improvements from baseline were significant at week 24 and 44 and met the threshold for the minimally clinically important difference (MCID)
- **Preference question:** 97% (266/273) of responding participants preferred CAB/RPV*

* ITT group 273/308 had a recorded response to the preference question at week 48; 266/308 86% preferred CAB/RPV.

Long tail: IM CAB drug detectable 48 weeks after single injection



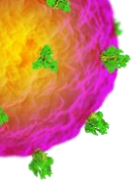


Long Tail: IM RPV detectable 12-24 months post single injection

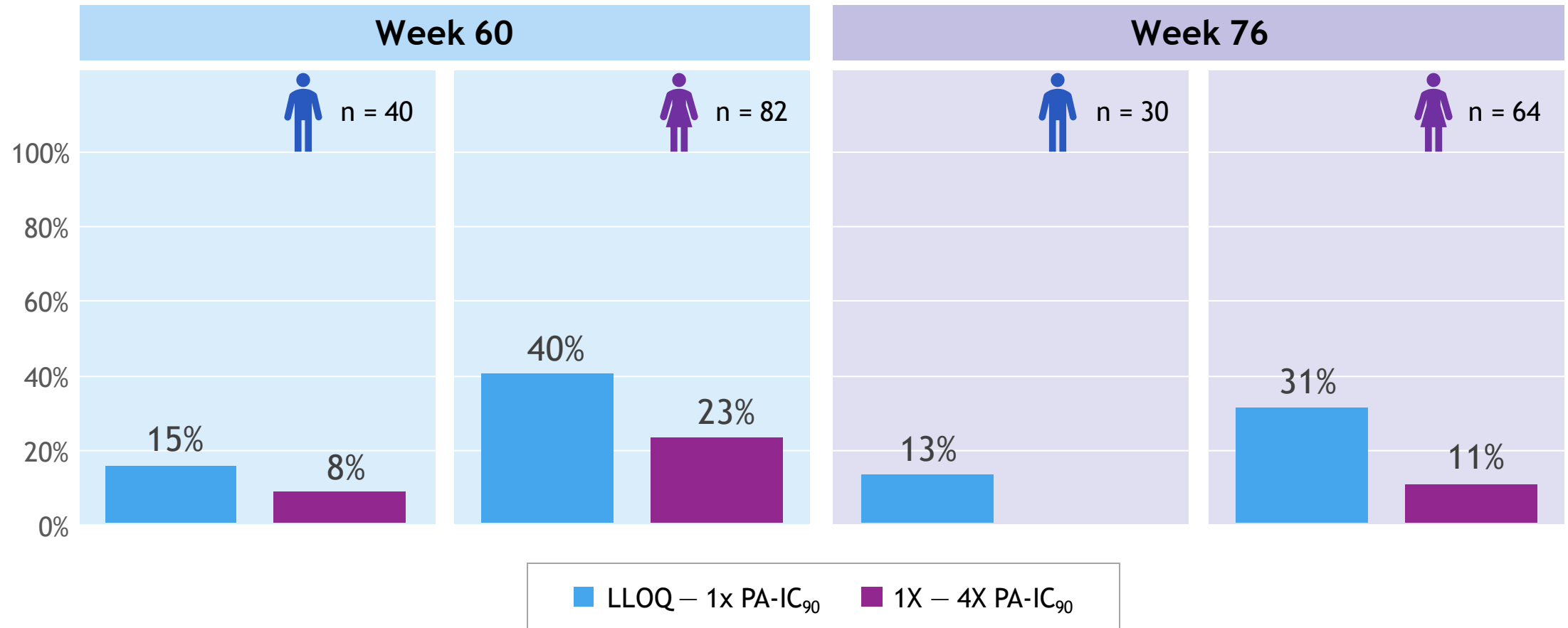
RPV found in plasma and genital fluid 12-24 months post SD LA

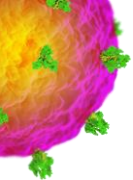
Subject number	Time since Injection (days)	Rilpivirine concentration* (ng/ml)
1	400	7.5
2	450	7.0
3	480	6.0
4	490	2.0
5	500	4.7
6	580	1.5
7	590	2.9
8	700	0.3
9	830	1.6

*RPV target concentration is 12.2ng/ml



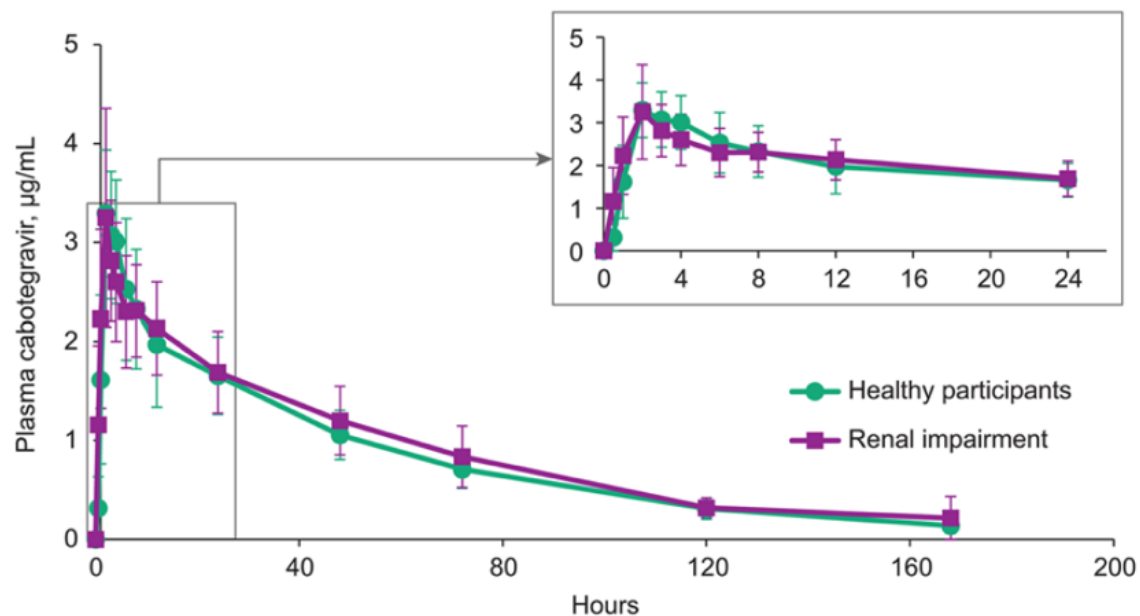
CAB LA tail – women have detectable levels longer than men





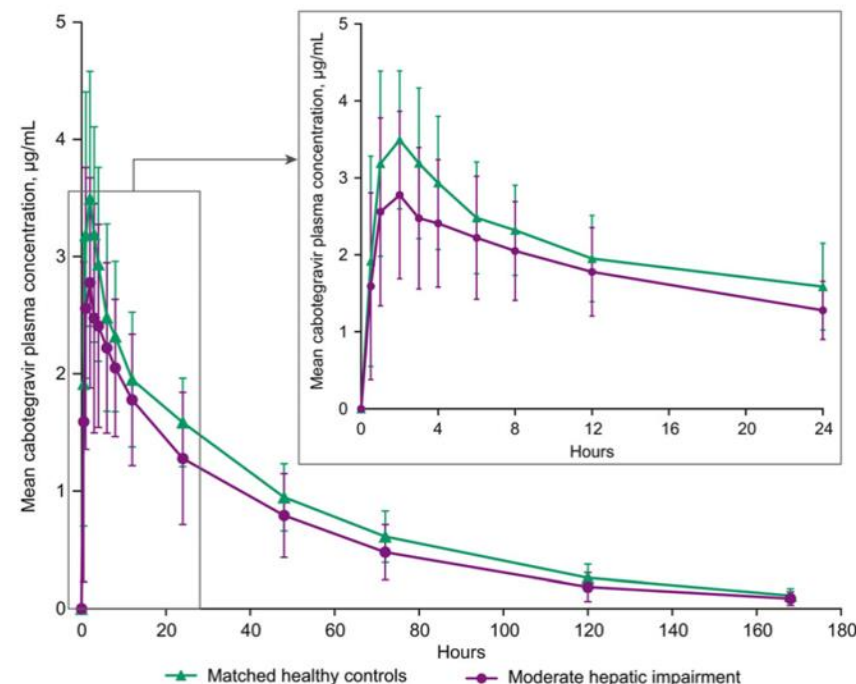
Can be given in severe renal impairment and moderate hepatic impairment

Severe renal impairment

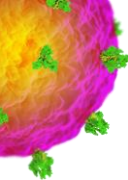


Parasrampur R et al. Clin Pharmacol Drug Dev 2019; Feb 27

Moderate hepatic impairment

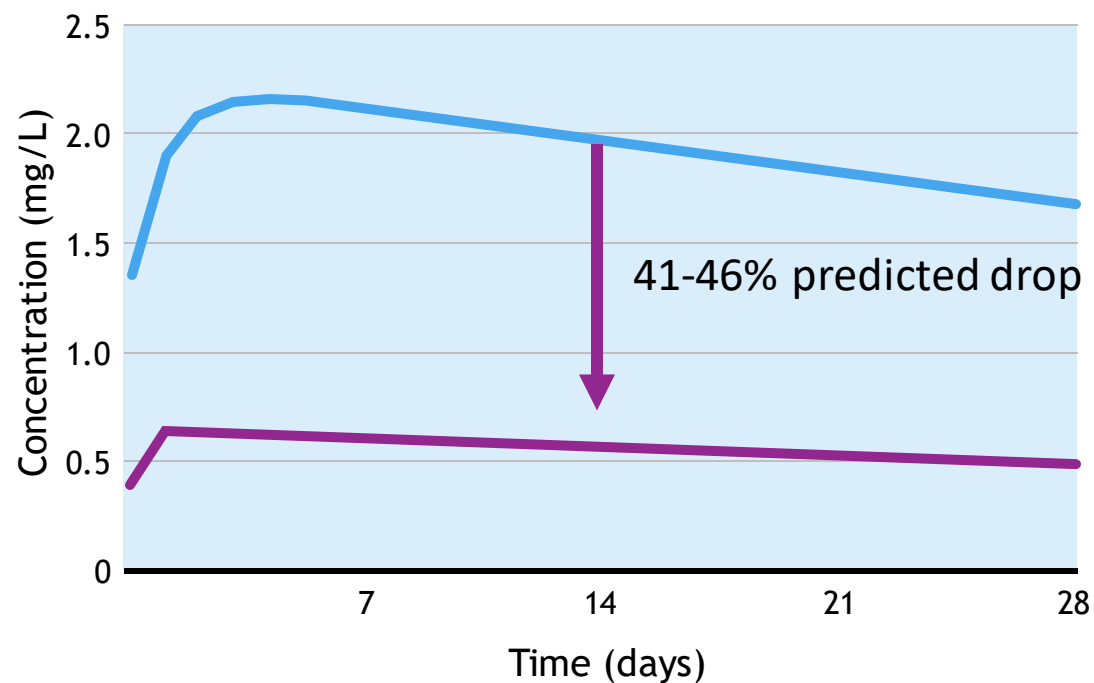


Shaik JSB et al. Clin Pharmacol Drug Dev 2019

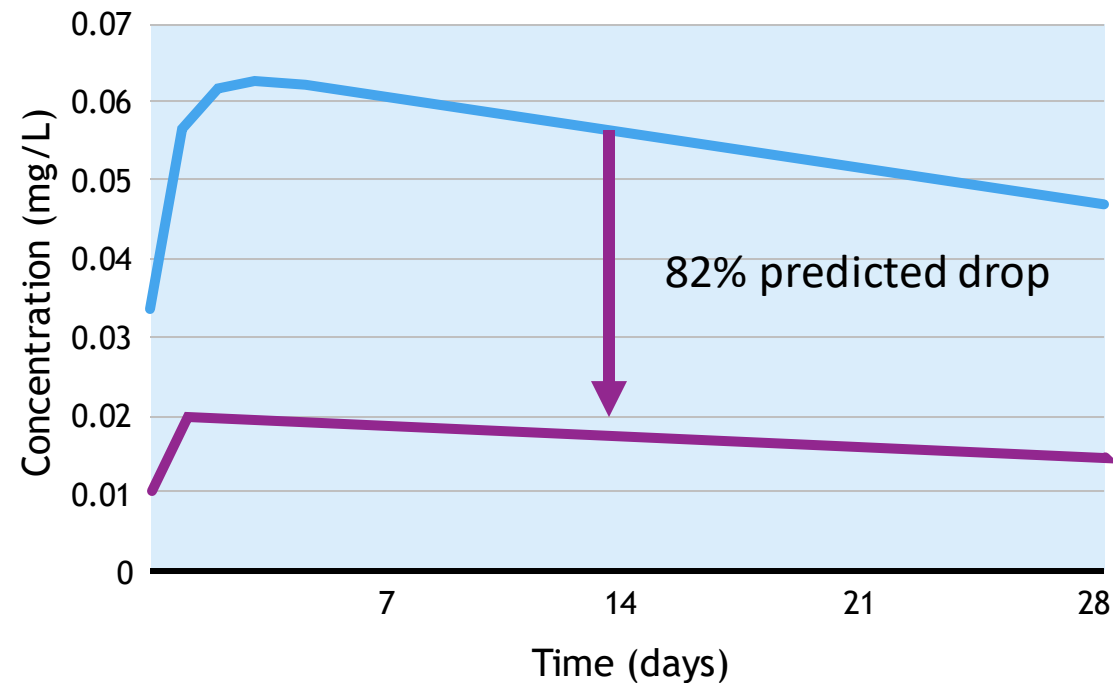


TB: LA CAB / RPV cant be given with rifampicin

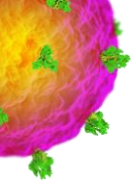
RIFAMPICIN 600 QD CAB 400 Q4



RIFAMPICIN 600 QD RPV 600 Q4



— CAB Alone — CAB + 600 mg RIF



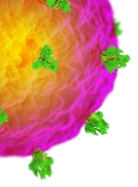
TB: CAB can be given with rifabutin

No significant effects on PK predicted

Oral CAB 30mg QD plus Rifabutin 300 mg QD.

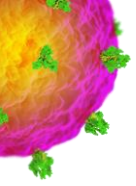
CAB AUC	CAB C _{max}	CAB C _{trough}
0.79 (0.74, 0.83)	0.83 (0.76, 0.90)	0.74 (0.70, 0.78)

Geometric least squares values of CAB+RBT vs. CAB alone.

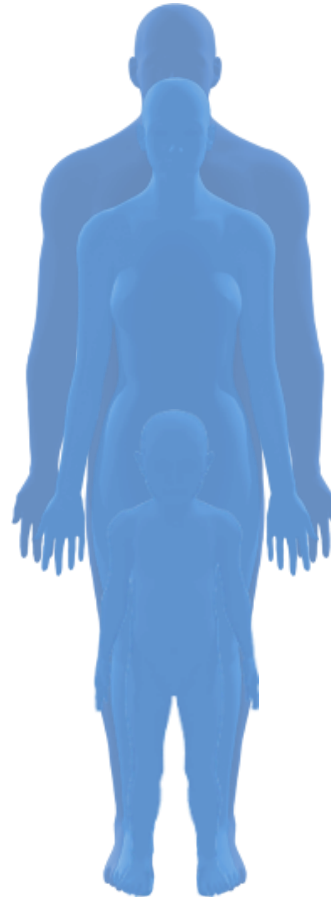


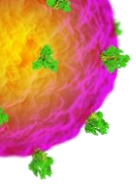
Advantages vs disadvantages to LA injectables?





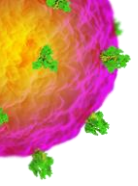
‘Who is the ideal patient for LA CAB/RPV?’





Long-acting Injectables - the logistics

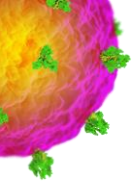
- Monthly or every other month administration: effect on clinic staffing.
- Injection administration: training in Z-track technique; privacy (not like a shot in the arm).
- Clinic visit non-adherence: what steps (proactive or after-the-fact) do you take?
- Costs
 - What is the cost of the drugs?
 - Who pays for the drug?
 - Who provides the drug, and inventory implications?
 - Insurance, administration location and patient co-pays?
- Alternative delivery approaches: pharmacy, home health, mobile units?
- *The need is to have a delivery approach that is as convenient as the long-acting injectable.*



Upcoming/ongoing CAB/RPV studies for HIV treatment

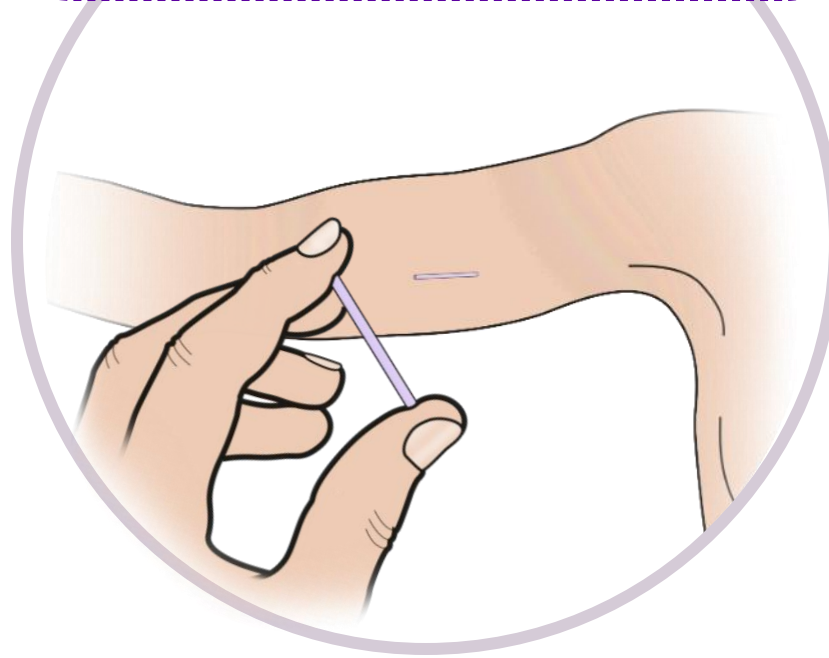
CAB + RPV

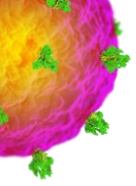
- 2 monthly IM: ATLAS 2M (n=1200)
- Children/Adolescents: MOCHA 12-18 (n=150)
- Poor Adherers ACTG 5359
- Implementation study (US): CUSTOMIZE
 - N=135
 - one year single arm study



Implantable devices

Subdermal implant





Implant advantages and disadvantages

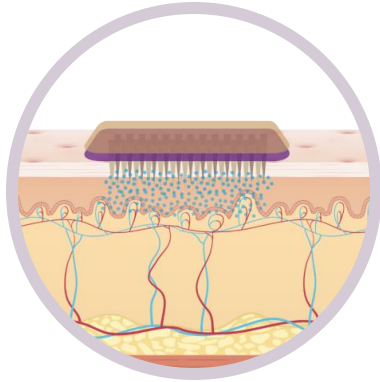
Advantages

- Removable at end of treatment and for adverse effects
- Potential to provide therapy for years with a single insertion
 - Inert, non-degradable options available or biodegradable options in development
- Potentially improved and more stable pharmacokinetics
- Palpable under skin indicates receipt of drug

Disadvantages

- Minor sterile medical procedure required for insertion (and removal)
- Palpation will not determine duration of use
- Complicated regulatory environment
- Generic marketplace

Patches and oral nano-formulations



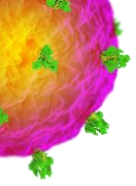
- LA microarray patches
- Monthly CAB, weekly RPV
- 30cm²



- Oral once/wk drug delivery system
 - Testing in swine models
 - Drugs DTG CBV RPV

From lab bench..... to the bed side





The future, for everyone!

THE LANCET HIV

Long-acting or extended-release antiretroviral products for HIV treatment and prevention in infants, children, adolescents, and pregnant and breastfeeding women: knowledge gaps and research priorities

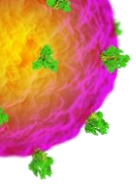
[Prof Sharon Nachman, MD](#)   • [Claire L Townsend, PhD](#) • [Prof Elaine J Abrams, MD](#) •

[Moherndren Archary, MBCHB](#) • [Prof Edmund Capparelli, PhD](#) • [Polly Clayden](#) • et al. [Show all authors](#)

Published: July 12, 2019 • DOI: [https://doi.org/10.1016/S2352-3018\(19\)30147-X](https://doi.org/10.1016/S2352-3018(19)30147-X) •

The future , everywhere!

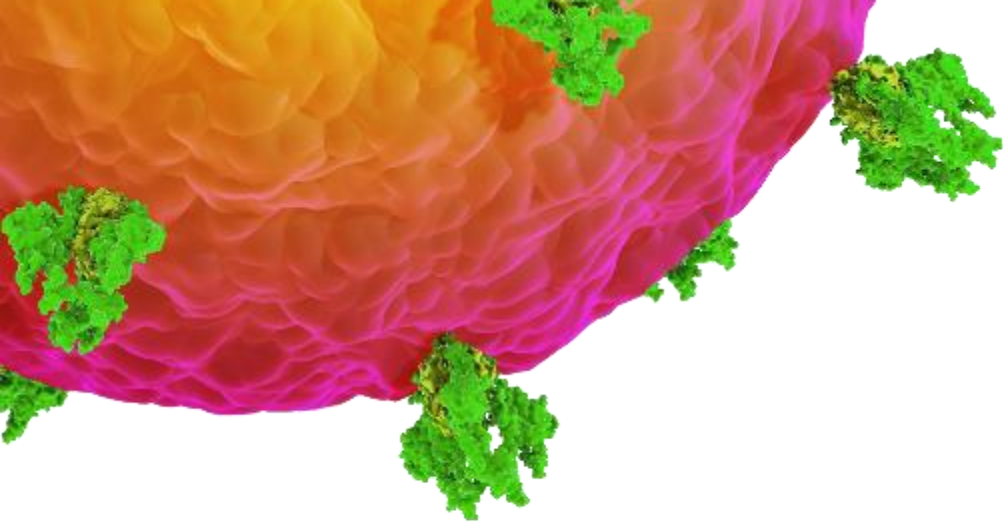




Thank you

- David Back
- Stephanie Barrett
- Diana Brainard
- Courtney Fletcher
- Carey Hwang
- Joseph Polli
- Mark Shaefer
- William Spreen
- John Wong

Emerging information on long acting formulations: www.leapresources.org



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[@profchloeorkin](https://twitter.com/profchloeorkin)