Long-acting ARV Formulations – knocking on the door

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Audience Response Question #1

- What is your greatest concern about the use of long-acting injectable antiretroviral agents in your patients?
  - Patients won't come back for clinic visits.
  - Identifying who the ideal patient is for long-acting injectable therapy.
  - Logistics of administration.

Audience Response Question #2

- Which of the following is true concerning drug-drug interactions with long-acting antiretrovirals?
  - Drug interactions and management will be the same as for the oral agent.
  - Injectable therapy will overcome/prevent any drug-drug interactions.
  - Interactions with drugs that induce hepatic metabolism are likely to still be clinically significant.

Why Long-Acting Injectables (LAIs)

Because of - -	*Example*
Adherence	Schizophrenia
Convenience	Osteoporosis
Choice	Contraception

Slide Courtesy of Charles Flexner, M.D.

Long-Acting Injectables 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.

Kaplan G. et al. Patient Preference and Adherence; 2013.

Slide Courtesy of Charles Flexner, M.D.

Long-Acting Injectables 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 decreases over time.
- **Patients overwhelmingly preferred a once-yearly injectable product (IV zoledronic acid).**
- **Once-yearly injectable treatment improves adherence and drug persistence and my be especially suitable for people who do not tolerate or adhere to oral drugs (e.g., people with cognitive dysfunction, polypharmacy, physical limitations).**

Fobela Lozano M and Sanchez-Fidalgo S. Eur J Hosp Pharm 2019;26:4-9.

Slide Courtesy of Charles Flexner, M.D.

Long-Acting Injectables for Hormonal Contraception

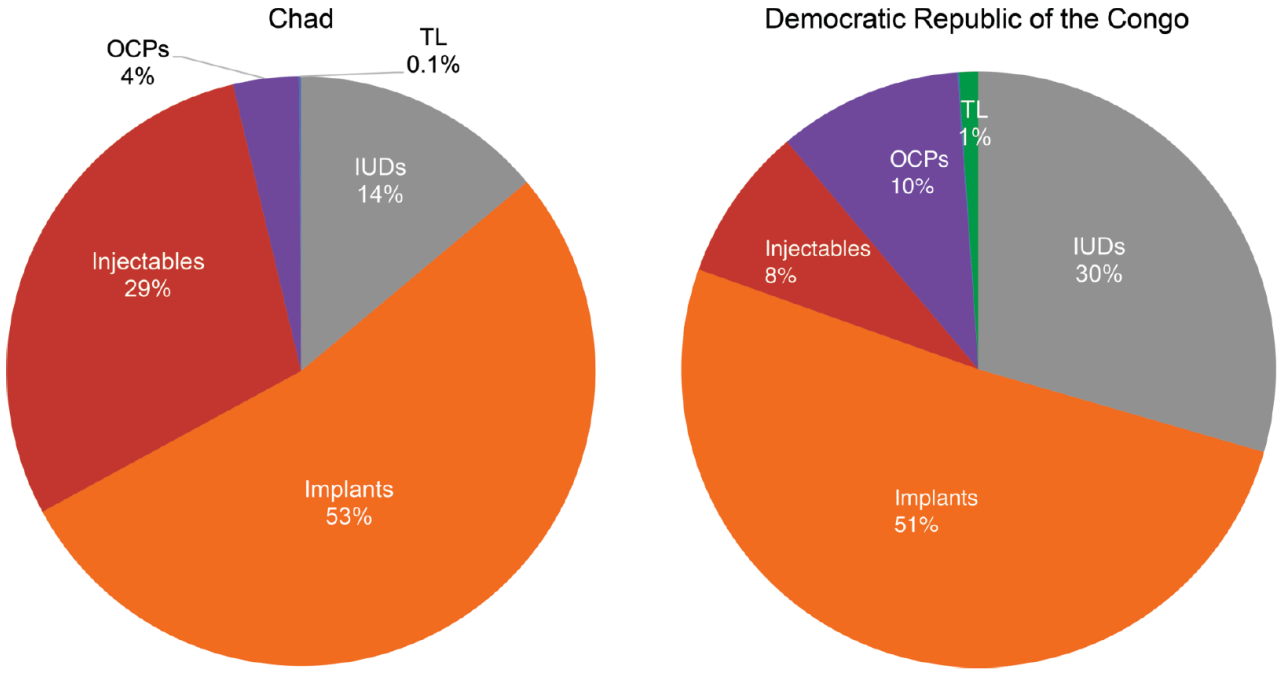
- Over 40 million women worldwide use injectable contraception, and **nearly half (47%) of modern contraception users in sub-Saharan Africa rely on injectable or implantable contraceptives to prevent pregnancy.**
- Returning to a health care provider for an injection every 2-3 months is considered a 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 not used by millions of women in sSA. Cost per generic implant is less than $15 USD (≈$3 pppy for effective hormonal contraception).

Fok WK et al. Curr Opin Obstet Gynecol 2017;29:419-26.

Slide Courtesy of Charles Flexner, M.D.

Contraceptive Uptake and Method Mix in sub-Saharan Africa

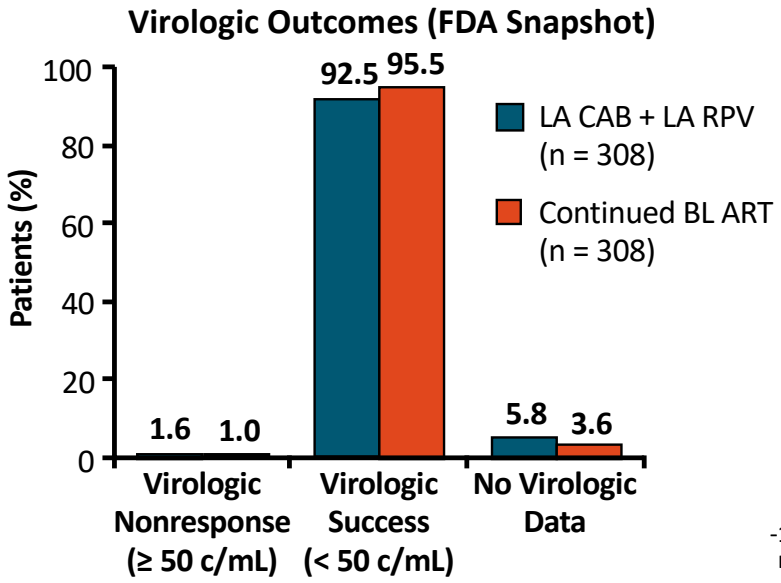
FIGURE 1. Contraceptive Method Mix Among New Family Planning Users in Program Areas in Chad[a] and DRC, June 2011 to November 2015

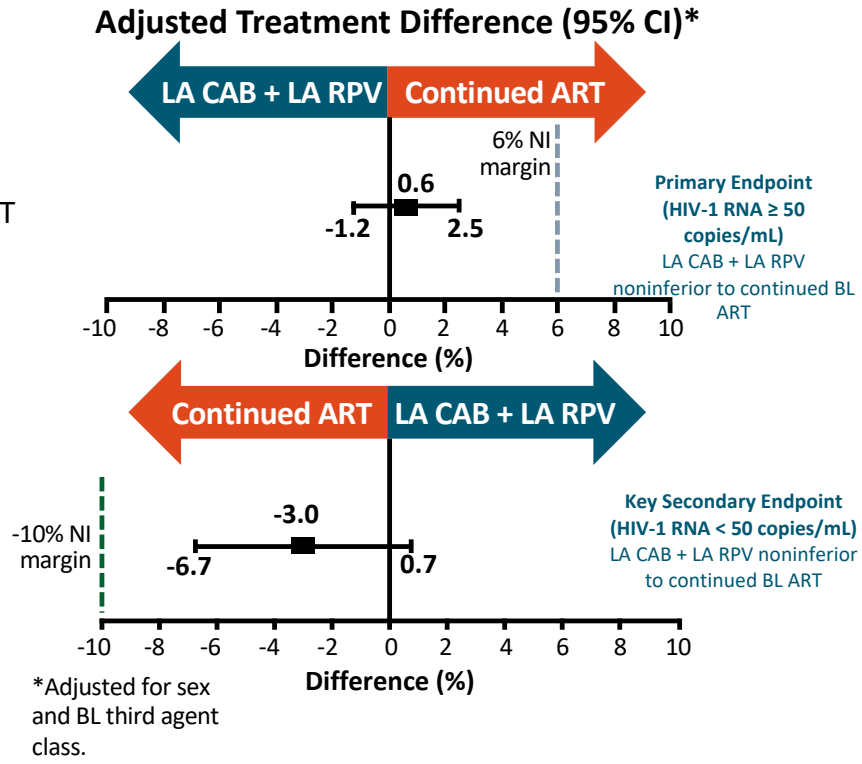


Rattan J et al. Global Health Science and Practice 2016;4: suppl 2 S5-S20.

A New Era for HIV Pharmacotherapy – Cabotegravir (CAB) and Rilpivirine (RPV) Long-Acting Injectables

ATLAS: monthly LA-CAB and RPV as switch therapy; efficacy at wk48 in ITT-E population





Swindells. CROI 2019. Abstr 139. Reproduced with permission.

Slide credit: clinicaloptions.com

ATLAS and FLAIR Adverse Events

	FLAIR CAB+RPV (LA) N=283	FLAIR DTG/ABC/3TC N=283	ATLAS CAB+RPV (LA) N=308	ATLAS Combo ART N=308
Any AE (≥10%), n (%)				
Any event (per participant)	246 (87)	225 (80)	264 (86)	220 (71)
Nasopharyngitis	56 (20)	48 (17)	52 (17)	42 (14)
Headache	39 (14)	21 (7)	34 (11)	17 (6)
Upper resp tract infection	38 (13)	28 (10)	32 (10)	25 (8)
Diarrhea	32 (11)	25 (9)	NR	NR
Drug-related AEs (≥3%), n (%)				
Any event (per participant)	79 (28)	28 (10)	88 (29)	8 (3)
Fatigue	NR	NR	11 (4)	0
Headache	14 (5)	4 (1)	11 (4)	0
Pyrexia	13 (5)	0	11 (4)	0
Nausea	NR	NR	11 (4)	0
AEs leading to withdrawal	9 (3)	4 (1)	10 (3)	5 (2)

Swindells S, et al. CROI 2019; Seattle, WA. Abstract 139; Orkin C, et al. CROI 2019; Seattle, WA. Abstract 140.

Long-acting injectables work – now what?

- Who is the best candidate for LA administration, for therapy, for prevention?
- And, what about children, adolescents, pregnant women?
- How do you stop and manage the long PK tail?
- Oral lead in – what, how long, can it be eliminated?
- What is the optimal LA dose and frequency – and evidence for that that meets regulatory purposes?
- Can injection volumes be reduced?
- How do you manage toxicities, acute and long term?
- How do you manage missed doses?
- How do you manage potential drug-drug interactions, short-term and chronic concomitant therapy?
- Logistics: convenience in delivery equal to that of the product.

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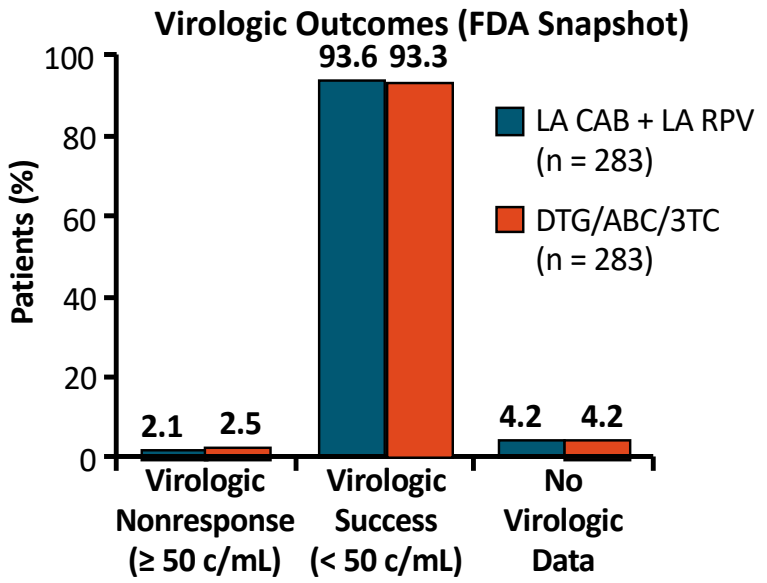
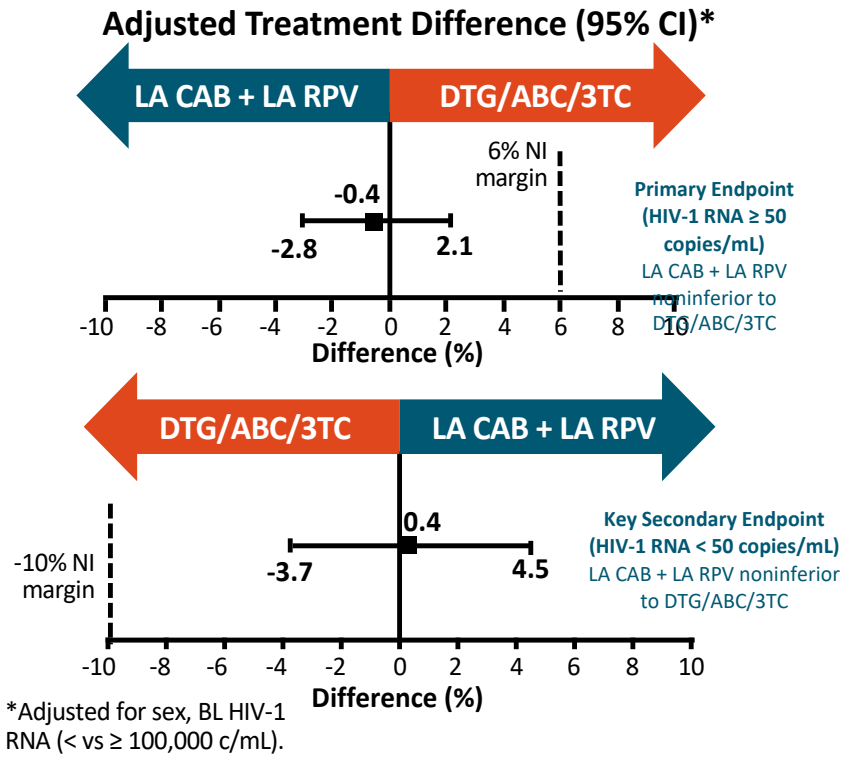
FLAIR: efficacy at wk 48 in ITT-E population



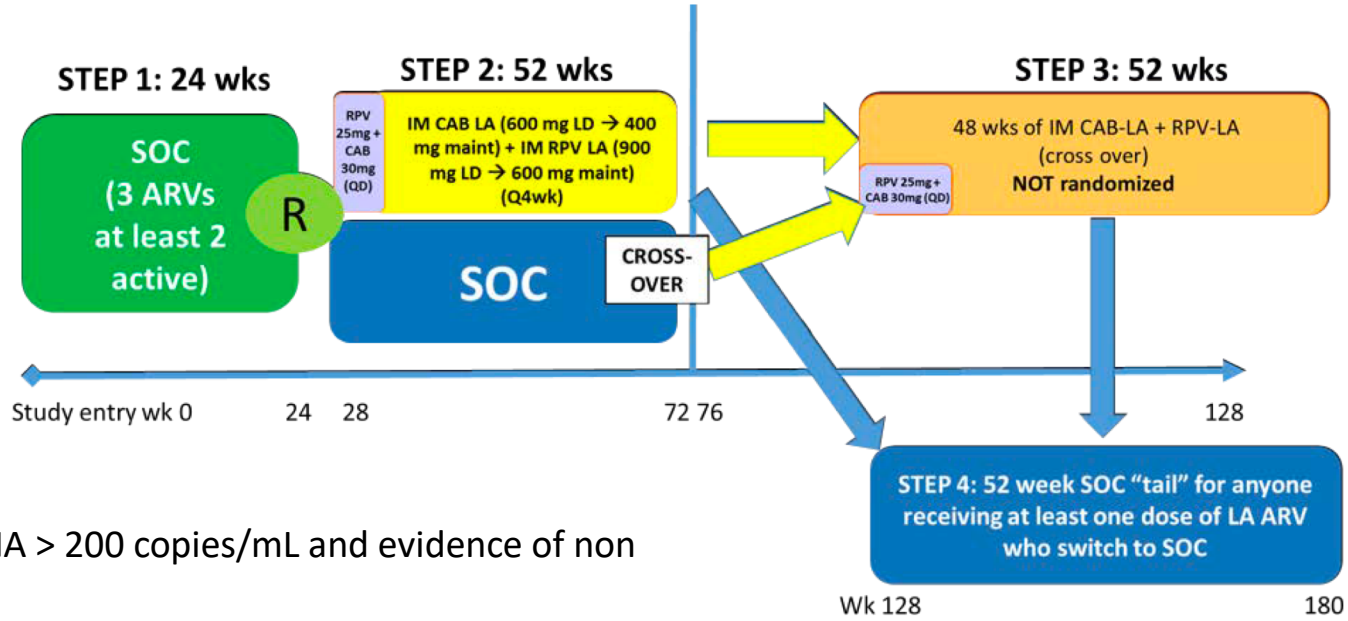


*Adjusted for sex, BL HIV-1 RNA (< vs ≥ 100,000 c/mL).

Orkin. CROI 2019. Abstr 140LB. Reproduced with permission.

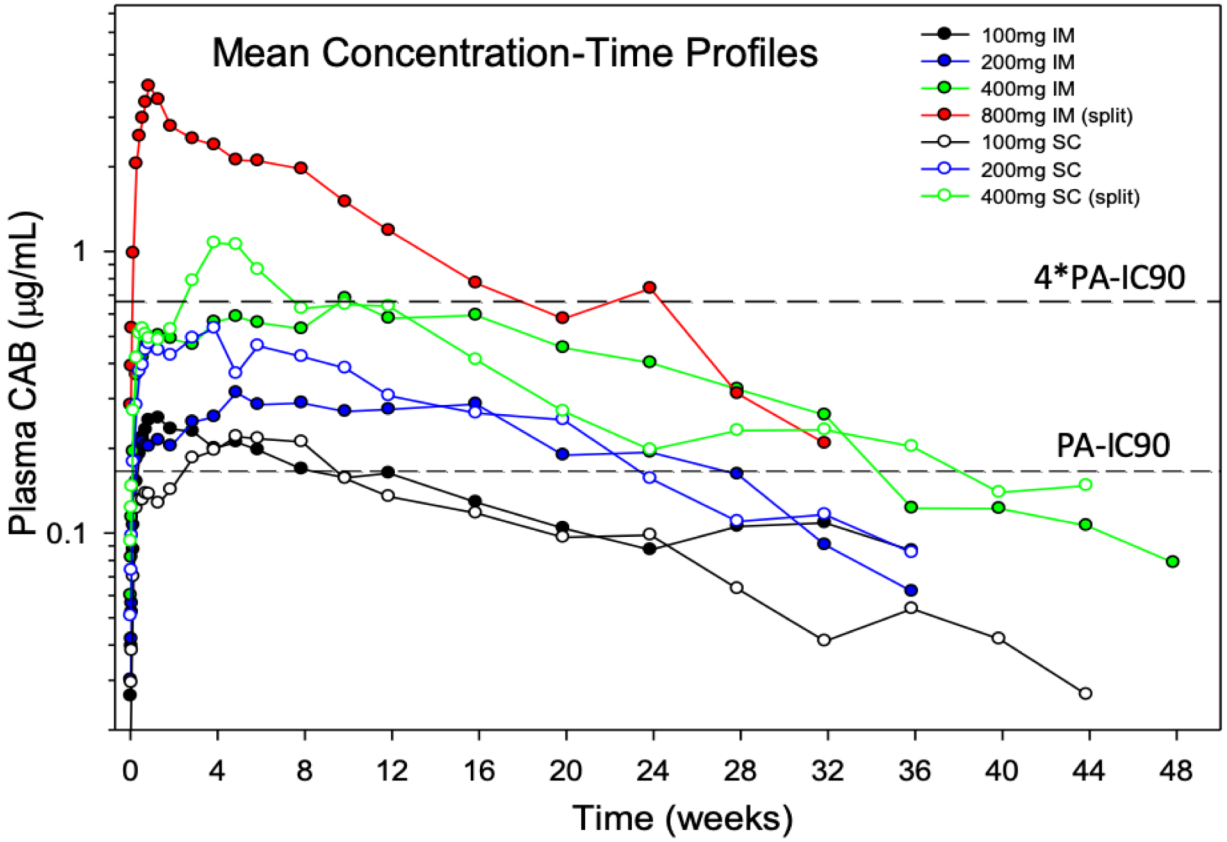
Slide credit: clinicaloptions.com

ACTG 5359, Long-acting ARV Therapy in Non-Adherent Persons



- HIV-infected with HIV-RNA > 200 copies/mL and evidence of non adherence
  - Poor virologic response in last 18 months: <1 log decrease in HIV RNA or HIV-RNA > 200 copies/mL
  - Loss to clinical follow up in last 18 months: ART non-adherence (≥ 7 days of missed doses) and missed clinic visits
- No RPV or INSTI resistance mutations
- Step 1 must achieve HIV-RNA < 50 copies/mL to progress to Step 2; conditional economic incentives are provided (total of $676 in step 1).

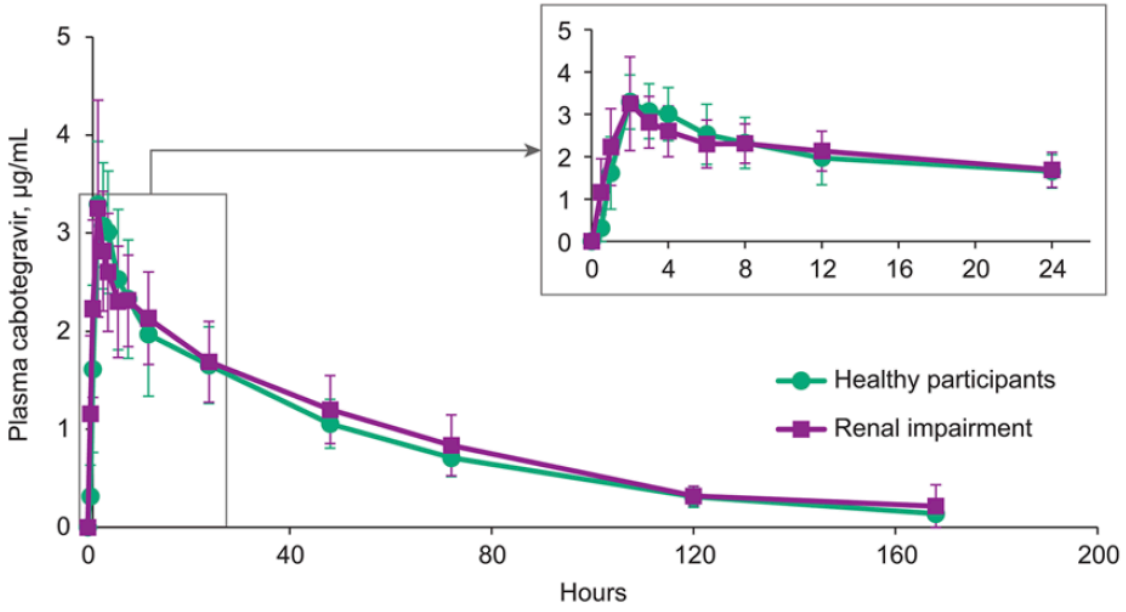
CAB-LA Single Injection Provides Detectable Drug in Plasma for 48 Weeks



Spreen et al. JAIDS 2014; Aug 21, Epub

Oral CAB in severe renal impairment

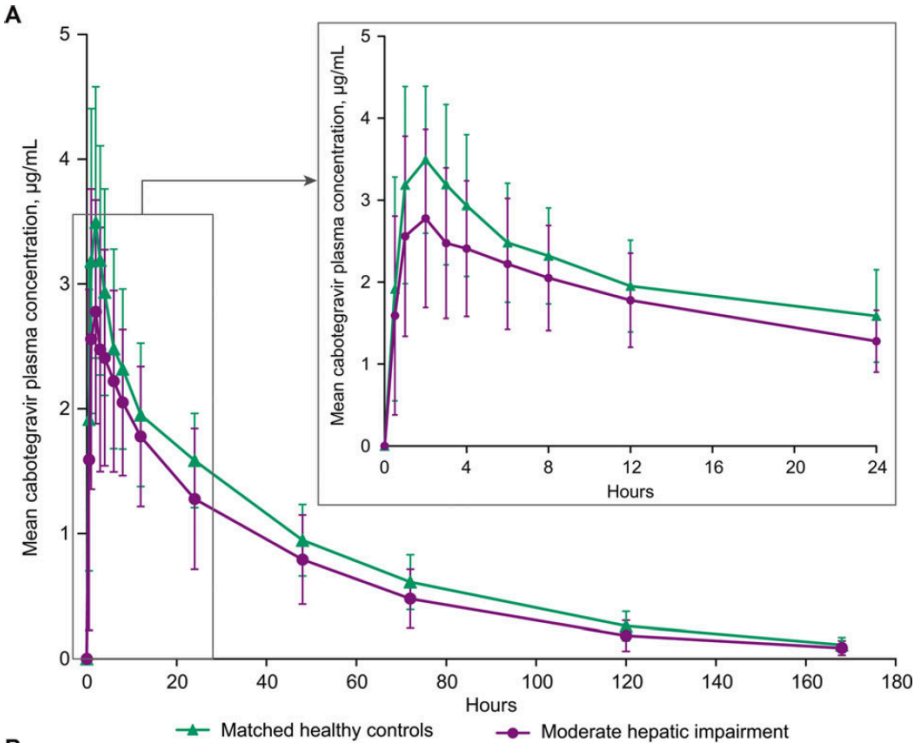
- CAB PK were determined after a 30 mg oral dose to healthy volunteers and 8 persons with severe renal impairment (CrCL < 30 mls/min).
- AUC ratio was 0.97.
- Severe renal impairment did not affect CAB PK.



Parasrampuria R et al. Clin Pharmacol Drug Dev 2019; Feb 27. doi: 10.1002/cpdd.664.

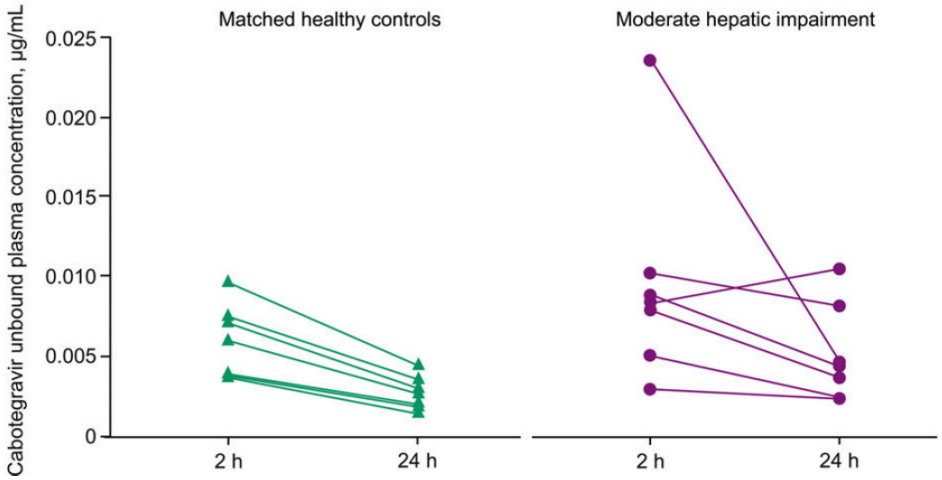
Oral CAB in moderate hepatic impairment

- CAB PK were determined after a 30 mg oral dose to healthy volunteers and 8 persons with moderate hepatic impairment (Child-Pugh score, 7-9).
  - AUC ratio: 0.73
  - Cmax ratio: 0.69
  - Cmin ratio: 0.73
  - F_u24h (%): 1.90
- The changes in CAB PK with mild to moderate hepatic insufficiency are unlikely to be clinically significant.
- The effect of severe hepatic impairment is unknown.

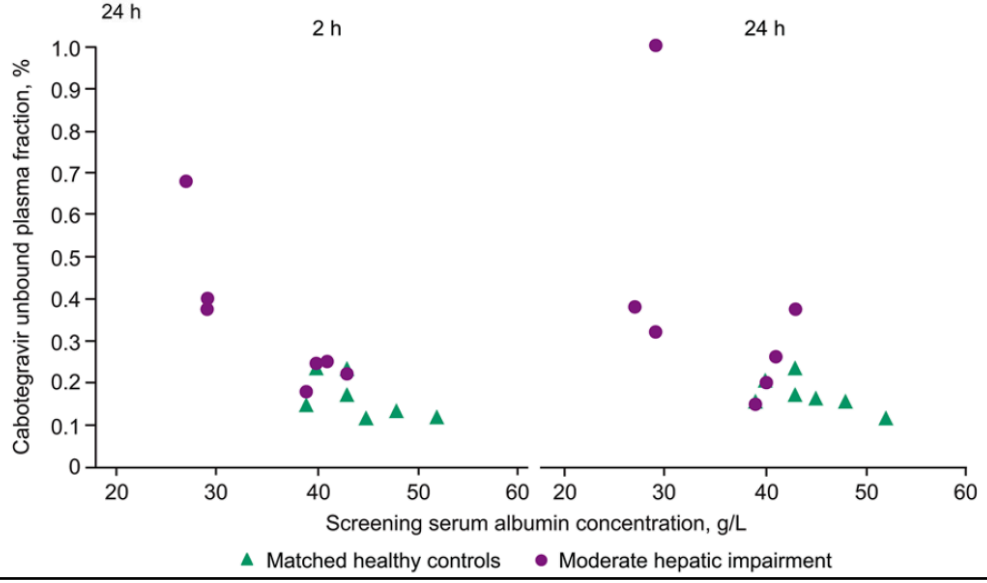


Shaik JSB et al. Clin Pharmacol Drug Dev 2019; Feb 27. doi: 10.1002/cpdd.655.

CAB Unbound Concentrations and Unbound Free Fraction



$$CL = f_u \bullet CL'_{int}$$



Recommended ARV Regimens for Initial Therapy in HIV-Infected Children

Preferred Regimens				
Age	**Regimens**		**FDC Available** (see Fixed-Dose Combinations)	
Infants, Birth to Age <14 Days[a,b]	Two NRTIs **plus** NVP		No	
	Weight ≥2 kg	Two NRTIs **plus** RAL[c]	No	
Children Aged ≥14 Days to <3 Years	Two NRTIs **plus** LPV/r		No	
	Weight ≥2 kg	Two NRTIs **plus** RAL[c]	No	
Children Aged ≥3 Years	Weight <25 kg	Two NRTIs **plus** ATV/r	No	
		Two NRTIs **plus** twice-daily DRV/r[d]	No	
		Two NRTIs **plus** RAL[c]	No	
	Weight ≥25 kg	Two NRTIs **plus** DTG[f]	Yes	*
		Two NRTIs **plus** EVG/COBI[e]	Yes	*
Adolescents Aged ≥12 Years with SMR 4 or 5	Refer to the Adult and Adolescent Antiretroviral Guidelines		Yes	

Triumeq (DTG/ABC/3TC) package insert states approval for ≥ 40 kg
Genvoya (EVG/cobi/FTC/TAF) is approved for pediatric patients ≥ 25 kg
Stribild (EVG/cobi/FTC/TDF) is approved for pediatric patients ≥ 35 kg.

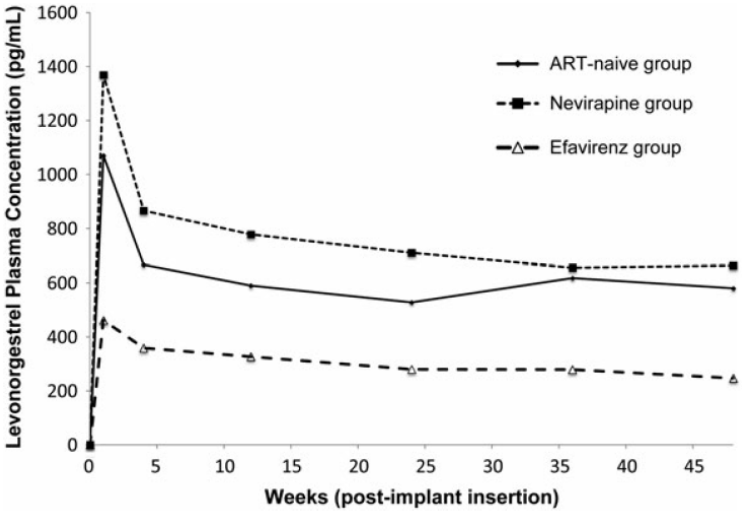
Aripiprazole One Day LAI Initiation Regimen

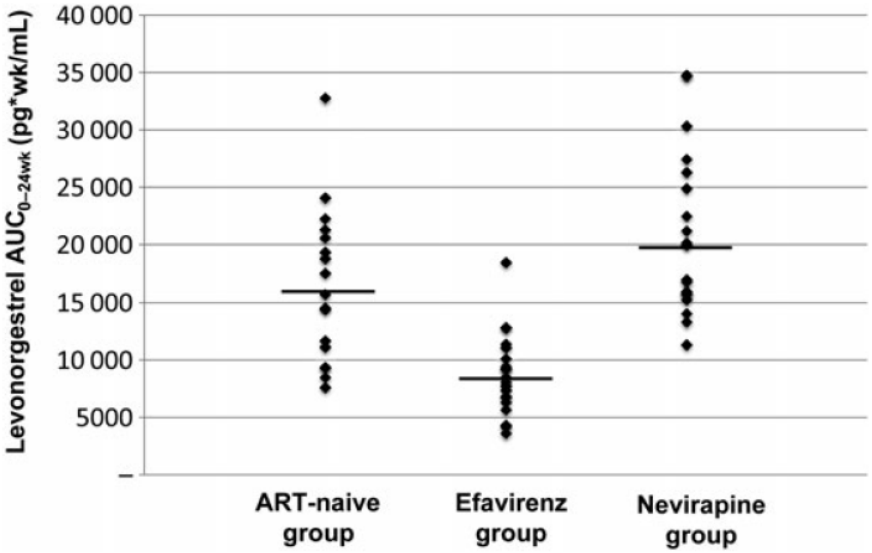
Dosage Form	Tmax	Half-Life
Oral tablet	3-5 hours	75 hours
IM suspension, nano particle size (Initio)	16-35 days (27d)	15-18 days
IM suspension, micron particle size (Aristada)	36 days	54-57 days

Aripiprazole One Day LAI Initiation Regimen Recommendations for Missed Doses

DOSE OF LAST ARISTADA INJECTION	LENGTH OF TIME SINCE LAST INJECTION		
	No supplementation required	Supplement with a single dose of ARISTADA INITIO[a]	Reinitiate with a single dose of ARISTADA INITIO and a single dose of 30 mg oral aripiprazole[b]
1064 MG EVERY 2 MONTHS	≤10 weeks	>10 and ≤12 weeks	>12 weeks
882 MG MONTHLY & EVERY 6 WEEKS	≤8 weeks	>8 and ≤12 weeks	>12 weeks
662 MG MONTHLY	≤8 weeks	>8 and ≤12 weeks	>12 weeks
441 MG MONTHLY	≤6 weeks	>6 and ≤7 weeks	>7 weeks

Levonorgestrel PKPD with Efavirenz-based ART





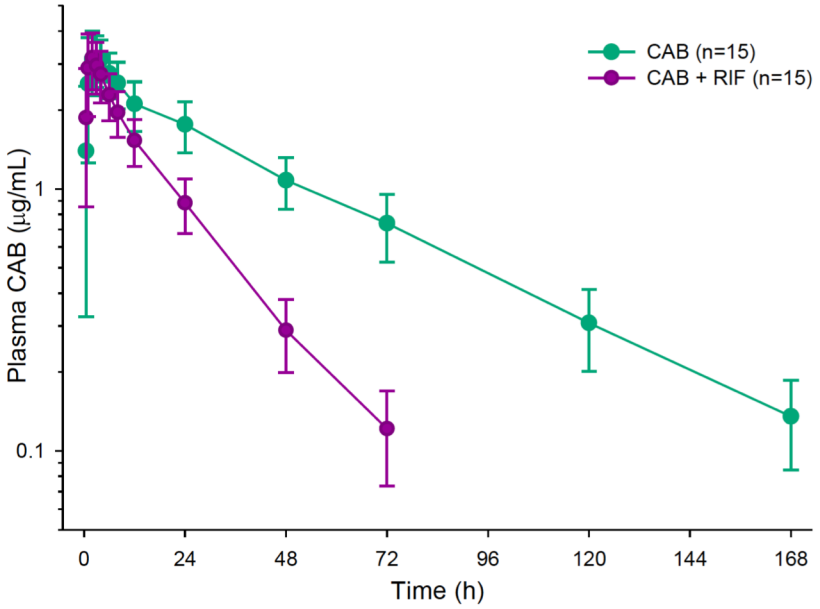
- EFV reduced levonorgestrel concentrations 47-57% after 24-48 weeks.
- 3 unintended pregnancies occurred (3/20, 15%) in the EFV recipients, while none occurred in the NVP or ART naïve groups.

Scarsi K. Clin Infect Dis 2016; 62:675-82.

Drug-Drug Interactions – oral vs. parenteral CAB and RPV

ORAL CAB and RPV	PARENTERAL CAB and RPV
CAB: CAB must be taken 2h before or 6h after taking a divalent cation containing product.	No restriction.
RPV: antacids must be taken 2h before or 4h after.	No restriction.
RPV: proton pump inhibitors are contraindicated; H2 antagonists must be taken 12h before or 4h after.	No restriction.
RPV: must be taken with a meal.	No restriction.

Rifampin decreases cabotegravir concentrations after oral administration



Plasma CAB Parameter	Treatment Geometric Mean (95% CI)		Treatment Comparison CAB + RIF: CAB (Test:Reference) GLSM Ratio (90% CI)
	CAB (Reference) (n=15)	CAB + RIF (Test) (n=15)	
AUC(0-∞), µg•h/mL	146 (128, 167)	59.7 (52.8, 67.5)	0.41 (0.36, 0.46)
Cmax, µg/mL	3.61 (3.28, 3.96)	3.39 (3.05, 3.76)	0.94 (0.87, 1.02)
CL/F, L/h	0.205 (0.180, 0.234)	0.502 (0.444, 0.568)	2.4 (2.2, 2.8)
$t_{1/2}$, h	38.5 (35.7, 41.6)	16.4 (14.7, 18.2)	0.43 (0.39, 0.46)

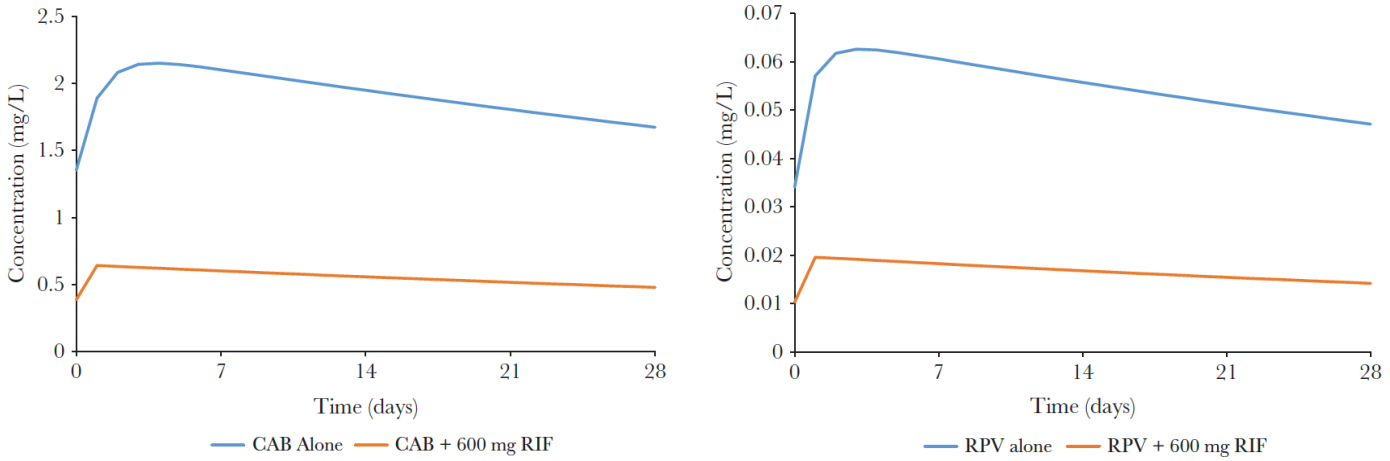
Oral CAB (30 mg once daily) plus Rifabutin (300 mg once daily). Geometric least squares values of CAB+RBT vs. CAB alone.

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)

Antivir Ther 2019 Mar 21. doi: 10.3851/IMP3306.

Ford S et al. Antimicrob Agents Chemother 2017; 61: DOI: 10.1128/AAC.00487-17

Prediction of Drug-Interactions Between CAB-LA and RPV-LA with Rifampin



- CAB-LA, 400 mg IM q4 wks with RIF, 600 mg orally once daily: predicted reduction in CAB-LA concentrations of 41-46%
- RPV-LA, 600 mg q4 IM wks with RIF, 600 mg orally once daily: predicted reduction in RPV-LA concentrations of 82%.

Rajoli R, . . . Siccardi M. J infect Dis 2019;219:1735-42.

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.*

Clinical Experience with Long-Acting ART

RESEARCH ARTICLE

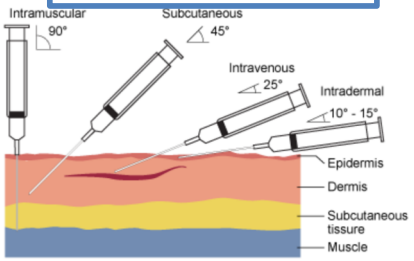
Experiences with long acting injectable ART: A qualitative study among PLHIV participating in a Phase II study of cabotegravir + rilpivirine (LATTE-2) in the United States and Spain

Deanna Kerrigan[1☯*], Andrea Mantsios[1☯], Miguel Gorgolas[2], Maria-Luisa Montes[3], Federico Pulido[4], Cynthia Brinson[5], Jerome deVente[6], Gary J. Richmond[7], Sarah W. Beckham[1‡], Paige Hammond[1‡], David Margolis[8], Miranda Murray[9]

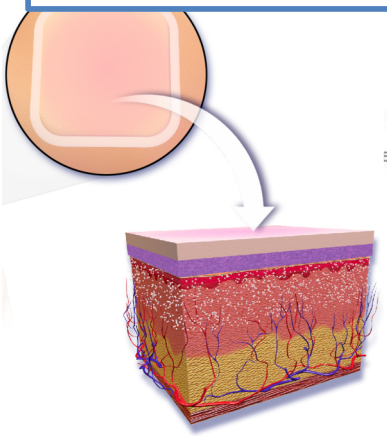
PLOS ONE | https://doi.org/10.1371/journal.pone.0190487 January 5, 2018

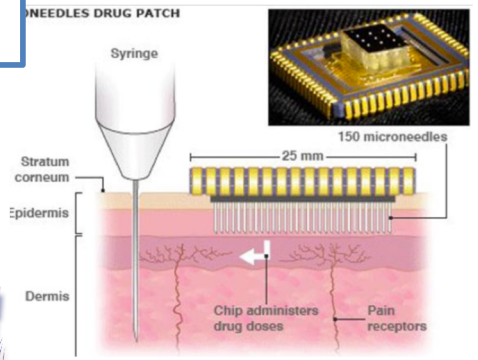
Technology for Drug Delivery

Long-acting depot injections

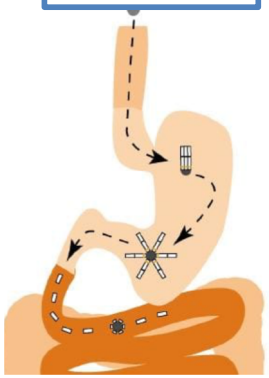


Microneedle drug patch

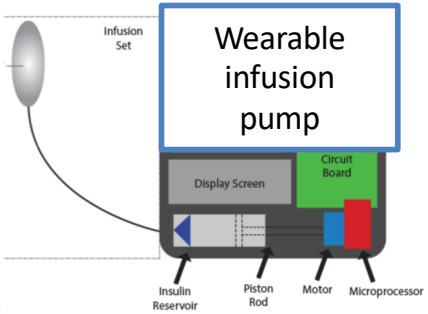




Novel oral formulations



Wearable infusion pump



Vaginal rings

Subdermal implant

Long-acting Antiretroviral Agents in Development

Table 1 Long-acting antiretroviral agents

Mechanistic drug class	Agents	Formulation	Stage of development
Nucleoside reverse transcriptase inhibitors	EFdA (MK-8591)	Implant	Preclinical
	Tenofovir alafenamide	Implant	Preclinical
	GS-9131	Implant	Preclinical
Nonnucleoside reverse transcriptase inhibitors	Rilpivirine	Injectable	Phase III
	Elsulfavirine	Injectable	Preclinical
Protease inhibitors	Atazanavir	Injectable	Preclinical
	Ritonavir	Injectable	Preclinical
Integrase inhibitors	Cabotegravir	Injectable	Phase III
	Raltegravir	Injectable	Preclinical
Entry inhibitors	Ibalizumab	Intravenous	US FDA approved
	PRO 140	Intravenous	Phase II
	Albuvirtide	Intravenous and subcutaneous	Approved in China
	Broadly neutralizing antibodies	Intravenous	Phase II/III
	Combinectin	Intravenous	Preclinical
Capsid inhibitors	GS-CA1	Injectable	Preclinical

Gulick R and Flexner C. Ann Rev Med 2019;70:137-50.

General Pharmacokinetic Characteristics of Therapeutic Antibodies

Process	Characteristics
Size	Large; ≈ 150kDa (vs <1 for small molecule drug)
Route of delivery	Parenterally (IV, SC, IM)
Absorption	Limited to none after oral administration; absorption after SC or IM administration involves uptake by the lymphatic system
Distribution	Lymphatic system involved is distribution throughout body; Slowly distributes to tissues, can be minutes to hours; Nonlinear binding to target of interest may occur, as can nonspecific binding within tissues; Volume of distribution is dependent on affinity for tissue sites; Clearance mechanisms may be present in tissues
Elimination	Elimination is largely by catabolism in endosomal space of cells (vs. hepatic metabolism or renal elimination); Target mediated drug disposition often results in nonlinear pharmacokinetics

Examples of Antibody Pharmacokinetics

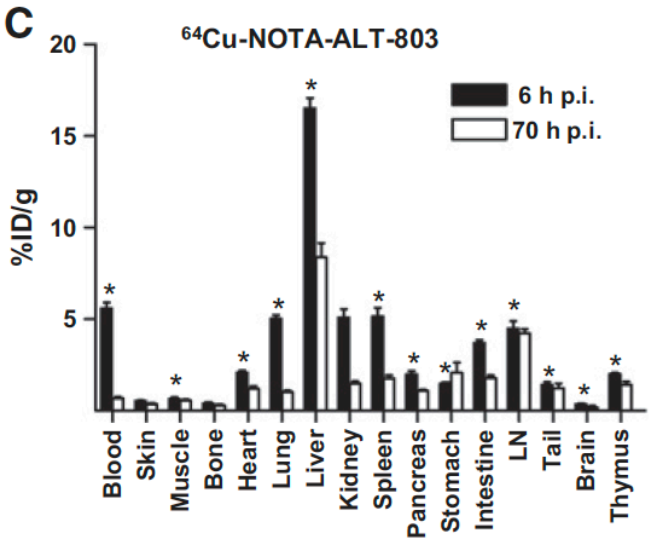


Table 4. VRC01LS mean PK parameter values.

Group and dose	C_{max}	T_{max}	CL	$t_{1/2\beta}$	AUC
			Mean (s.d.)		
IV dosing					
5 mg/kg ($n = 3$)	246 (78)	0.07 (0.08)	40 (7)	83 (11)	4896 (499)*
20 mg/kg ($n = 8$)	1,221 (397)	0.2 (0.3)	33 (8)	76 (19)	23,368 (5279)*
40 mg/kg ($n = 5$)	2,234 (548)	0.05 (0.02)	38 (9)	55(7)	57,099 (13679)
Overall IV ($n = 16$)			36 (8)	71 (18)	
SC dosing					
5 mg/kg ($n = 9$)	69 (15)	9.0 (7.9)	61 (5)+	66 (24)	3,777 (814)

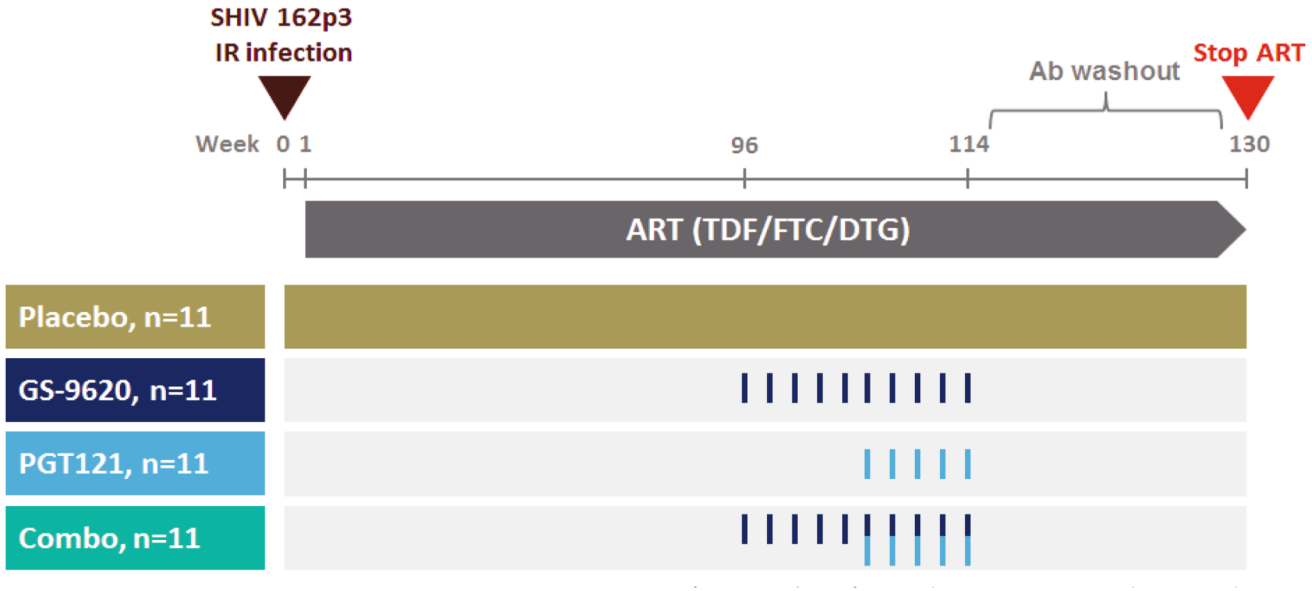
TABLE I. Pharmacokinetic characteristics (median and range) of PRO 542 after multiple doses every 7 days

	PRO 542 20 mg/kg (n = 13)	PRO 542 10 mg/kg (n = 6)†	*P* value
AUC	11,714 (5964-17,870 µg*h/mL	11,362 (8531-13,124) µg*h/mL	.7257
CL	1.71 (1.12-3.35) mL/h/kg	0.88 (0.76-1.17) mL/h/kg	.0009
$T_{½}$	1.82 (1.22-2.43) days	2.13 (1.54-2.58) days	.1144
Cmax	337 (84.8-517.8) µg/mL	274 (229-322) µg/mL	.2926
C-7 days	8.77 (1.90-22.3) µg/mL	6.95 (2.87-14.7) µg/mL	.5393

Rhode PR et al. Cancer Immunol Res 2015; 4:49-60.
Gaudinski MR, et al. PLoS Medicine 2018;15:1-20.
Fletcher CV, et al. J Allergy Clin Immunol 2007;119: 747-50.

PGT121 + vesatolimod (GS-9620) in SHIV-Infected Monkeys

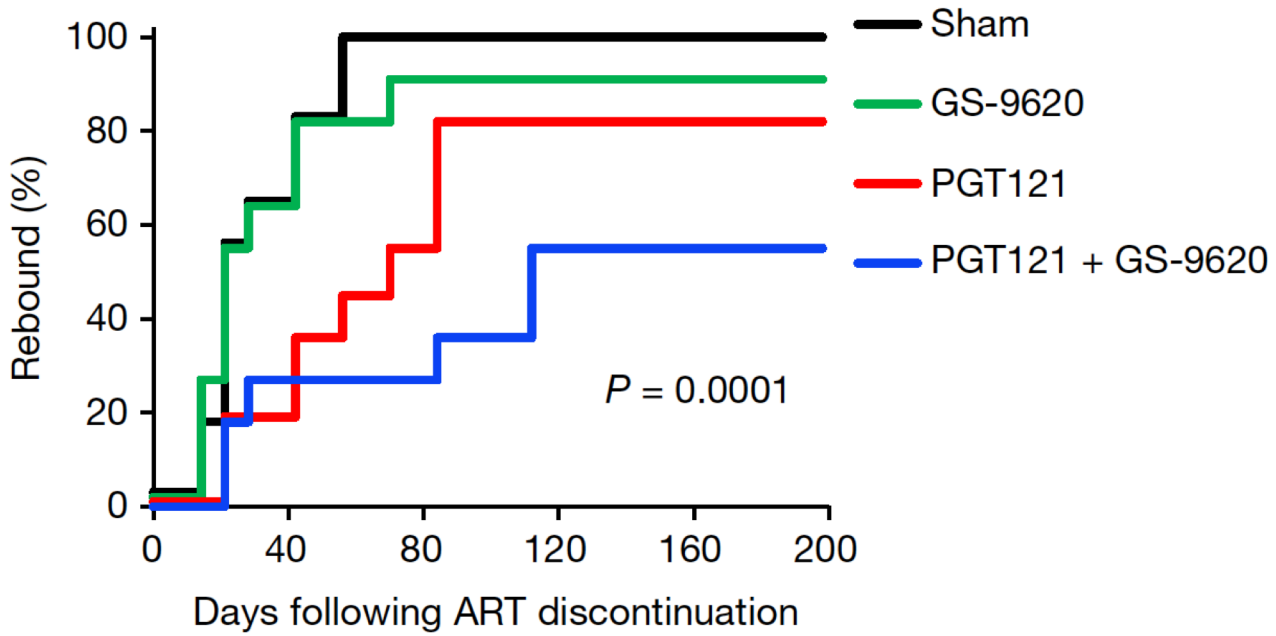
- The bNAb PGT121 and vesatolimod (a TLR7 agonist; innate immune stimulant) alone and in combination were given during ART (DTG/FTC/TDF) in acutely treated monkeys.
- Time to viral rebound was evaluated after ATI.



Borducchi E, et al., Barouch D. Nature 2018; 563:360-79.

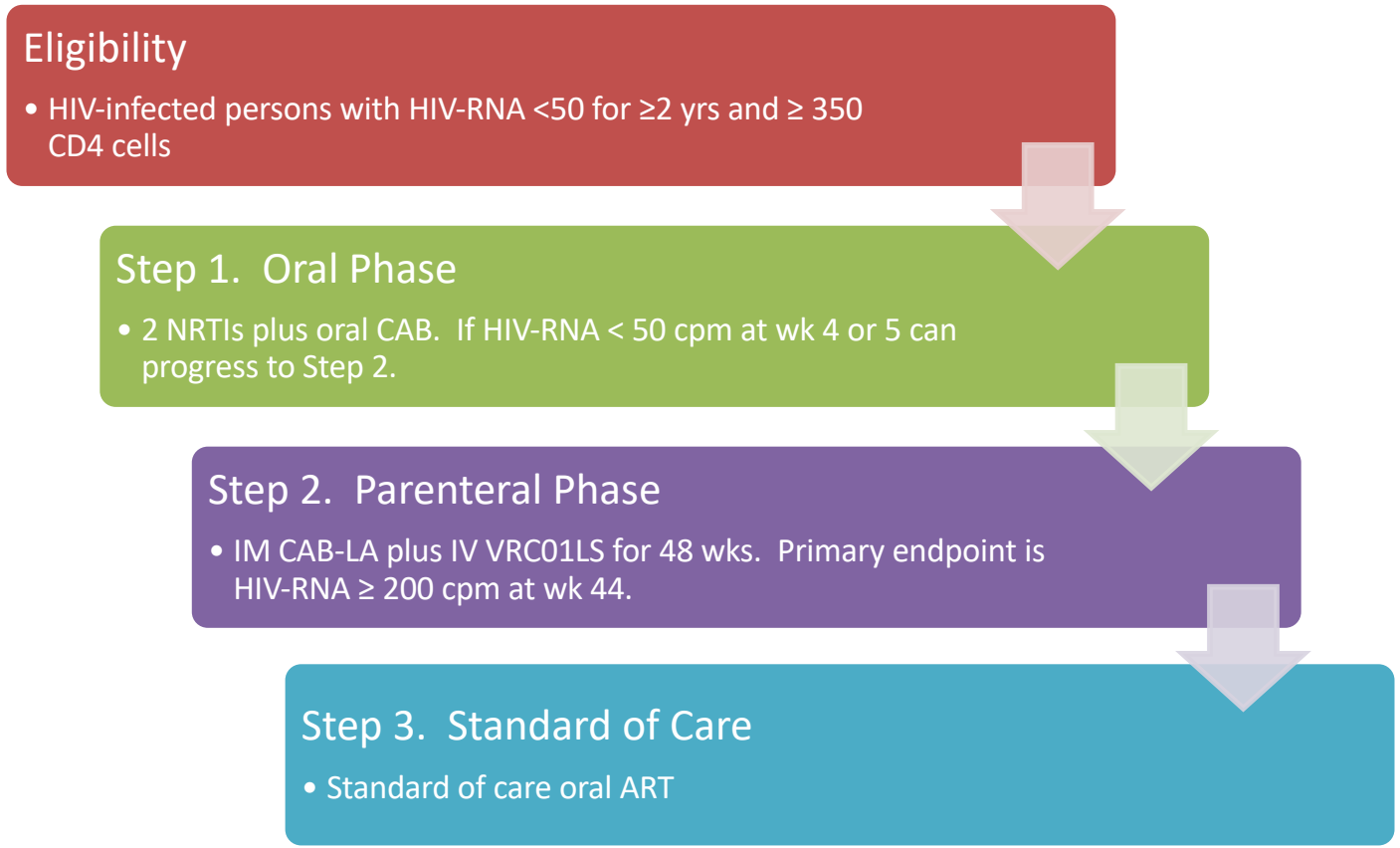
PGT121 + vesatolimod (GS-9620)

- 5 of 11 monkeys showed no rebound for > 6 months
- bNAb plus an innate immune stimulant may represent a strategy to target the viral reservoir; the mechanism includes cell activation and binding/elimination of virally-infected cells.



Borducchi E, et al., Barouch D. Nature 2018; 563:360-79.

ACTG 5357, CAB-LA plus VRC01LS to Maintain Viral Suppression in Adults



Novel ARV Drug Delivery: opportunities to improve patient care and some needs

- Long acting
  - *Nanoformulated injectables and implants to achieve sustained (one month, three months) drug delivery*
- New drugs
  - *Highly potent, selective agents with novel mechanisms of action and additive-to-synergistic with existing agents*
- Targeted delivery
  - *Nanoformulated injectables and implants to achieve improved tissue/organ distribution such as to brain and lymphoid tissues (C_t or $C_c = C_p$)*
- Pediatric formulations and fixed dose combinations:
  - *New formulations and combinations; nanoformulations*

It is our task, both in science and in society at large, to prove the conventional wisdom wrong and to make unpredictable dreams come true.

Freeman Dyson

Thank You