New Drugs in Development
Are We Ready for Long-Acting ART?

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Learning Objectives

After attending this presentation, learners will be able to:

- Discuss the efficacy and challenges of long acting therapy with CAB LA + RPV LA
- Describe the mechanisms of action and pharmacokinetic profiles for MK-8591, GS 6207 and PRO 140
- Describe the efficacy and safety of fostemsavir in treatment experienced patients

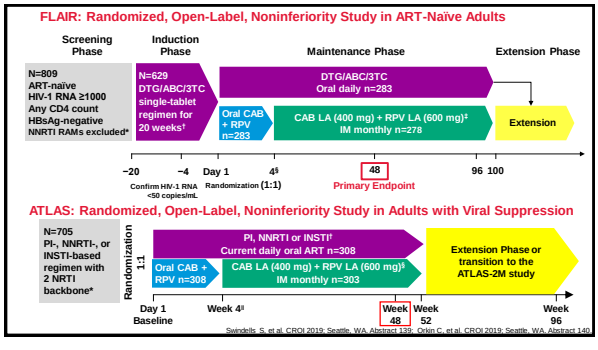
Compound	Class	Sponsor	Ph I	Ph II	Ph III	Comments
CAB LA + RPV LA	INSTI/NNRTI	ViiV			x	IM monthly
Fostemsavir	Attachment Inhibitor	ViiV			x	Treatment-experienced pts Twice daily
MK 8591 (EFdA)	NRT Translocation Inhibitor	Merck		x		Long acting potential; treatment & prevention
PRO 140 (leronlimab)	Anti-CCR5 mAb	CytoDyn		IIb/III		SC once weekly
Albuvirtide	Fusion inhibitor	Frontier		x		Approved in China; no US data available yet
3BNC117	bNAb	Rockefeller; Frontier		x		Ph II w/ albuvirtide; no data available
GS-9131	NRTI	Gilead		X		Active against NRTI resistant viruses
GSK-2838232	Maturation Inhibitor	GSK		IIa		Requires boosting; resistance concerns
GS-6207	Capsid Inhibitor	Gilead	x			Long acting potential
PGT121	bNAb	IAVI*	x			*GS 9722 licensed to Gilead
TAF Implant	NRTI	Gilead, others				

Long Acting Cabotegravir and Rilpivirine

FLAIR and ATLAS

CAB LA + RPV LA: Summary

- Monthly CAB LA + RPV LA noninferior to
  - DTG/ABC/3TC as initial therapy
  - Combo ARV for maintenance of viral suppression
- Rare grade 3/4 or serious AEs
- Low rates of virologic failure, but some with treatment emergent mutations for both NNRTI and INSTI
- Injection site reactions common, grade 1-2
- Patient-reported satisfaction high in both studies
- Limited expanded access for those unable to take pills: GSKClinicalSupportHD@gsk.com; 877-379-3718



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

FLAIR & ATLAS Baseline Characteristics

	FLAIR Total N=566	ATLAS Total N=616
Median age (range) – year	34 (18–68)	42 (18–82)
Age ≥50 years – n (%)	62 (11)	162 (26)
Female – n (%)	127 (22)	203 (33)
Race – n (%)		
White	417 (74)	421 (68)
Black or African American	103 (18)	139 (23)
Other or missing	46 (8)	56 (9)
HIV-1 RNA, copies/mL – n (%)		
<100,000	454 (80)	
≥100,000	112 (20)	
Median baseline CD4+ cell count (IQR) cells/mm^3	444 (320, 604)	653 (150–2543)
HIV-1–HCV co-infection – n (%)	28 (5)	
Median duration of prior ART (range) – year		4 (1–21)
Baseline third ART agent class – n (%)*		
NNRTI		310 (50)
INSTI		201 (33)
PI		105 (17)

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

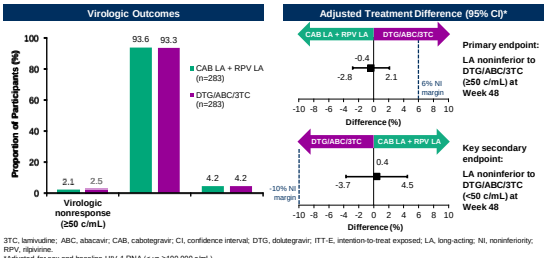
FLAIR & ATLAS Adverse Events

	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.

FLAIR Virologic Snapshot ITT-E Outcomes at Week 48

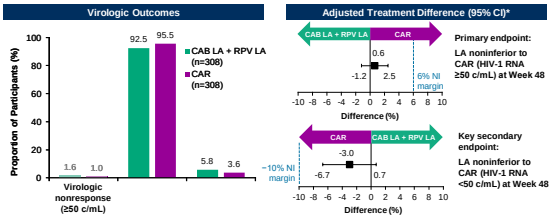
Noninferiority Achieved for Primary and Secondary Endpoints



3TC, lamivudine; ABC, abacavir; CAB, cabotegravir; CI, confidence interval; DTG, dolutegravir; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority; RPV, rilpivirine.
*Adjusted for sex and baseline HIV-1 RNA (< vs ≥100,000 c/mL).

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

ATLAS Virologic Snapshot ITT-E Outcomes at Week 48
Noninferiority Achieved for Primary and Secondary Endpoints



CAB, cabotegravir; CAR, current antiretroviral; CI, confidence interval; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority; RPV, rilpivirine.
*Adjusted for sex and baseline third agent class.

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

Confirmed Virologic Failure	FLAIR		ATLAS	
Virologic failure (VF) rate, CAB + RPV arm (week of suspected VF)	1.4% (Wk 20, 28, 48)		1% (Wk 8, 12, 20)	
HIV RNA at confirmed VF	287 - 488 c/mL		258 - 25,745 c/mL	
Mutations at baseline	**RT** None	**INSTI** L74I x 3	**RT** E138E/A, K V108V/I	**INSTI** L74I x 2
Mutations at VF **(Treatment Emergent)**	**RT** **E138A/K/T** **K101E** **E138K**	**INSTI** L74I x 3 **Q148R** **G140R**	**RT** E138A, K V108I*	**INSTI** L74I x 2 **N155H** **E138E/K**
HIV-1 subtype	All A1; Russia		2 – A/A1; Russia 1 – AG; France	

* 1 pt with prior nevirapine use had NNRTI but no INSTI mutations at VF

What About the Practical Implications?

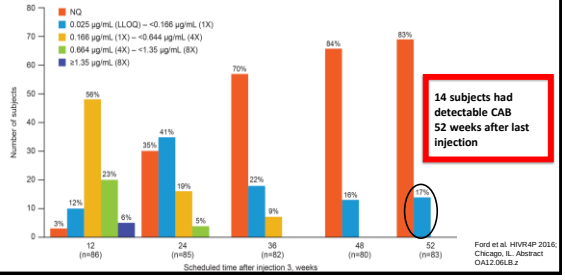
Considerations for In-Clinic Administration of LA CAB/RPV

- Loading = 2 injections of 3mL; maintenance = 2 injections of 2mL
  - Need private space for administration
- IM administration technique: Z-tracking into gluteus medius
  - Will require staff training
  - Not tested in persons with buttock implants
- Staffing for retention to ensure monthly (bimonthly?) injections
- Alternative delivery systems: Pharmacy? Home health? Mobile units?
- Visit reminders: running out of pills often triggers visits

Cost Considerations

- How will the drugs be priced?
- Who will purchase the drugs? Patient or provider?
  - Availability of drugs "in stock" for drop in visits for patients who do not keep scheduled appointments? Shelf life?
  - Copay cards do not cover drugs purchased and administered by clinics
- Will reimbursement cover drug cost?
  - Cautionary tale: benzathine penicillin G reimbursed at below drug cost
- Will administration be reimbursed?
- What will be the impact on ADAP and health system costs as a whole?

ÉCLAIR Study: Cabotegravir Concentration Post Injection: Drug Persists in 17% of Subjects 52 Weeks After Last Injection



Ford et al. HIVR4P 2016; Chicago, IL. Abstract OA12.06LB.z

Management of Long Acting Treatments

- Will we see INSTI/NNRTI resistance for those who do not return for treatment?
- How will we manage treatment-emergent drug-related toxicities?
- How will we manage drug interactions, including for TB treatment?
- Will teratogenicity be a problem (neural tube defects)?

ARS 1: For what proportion of your patients would you prescribe CAB LA + RPV LA?

- 0% (Interesting but I'm just not there yet)
- < 10%
- 11-25%
- 26-50%
- 51-75%
- 100% (Greatest thing since sliced bread)
- It will totally depend on logistics and reimbursement

ARS 2: What is your primary concern about CAB LA + RPV LA?

- Patients won't come back for visits
- Toxicity management
- Pregnancy and potential teratogenicity
- Out of pocket costs to patient (or clinic)
- Logistics of administration
- I have no major concerns. Bring it on!

MK-8591: NRTTI

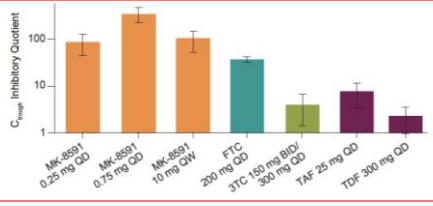
A Nucleoside Reverse Transcriptase Translocation Inhibitor

MK 8591 for Treatment and Prevention

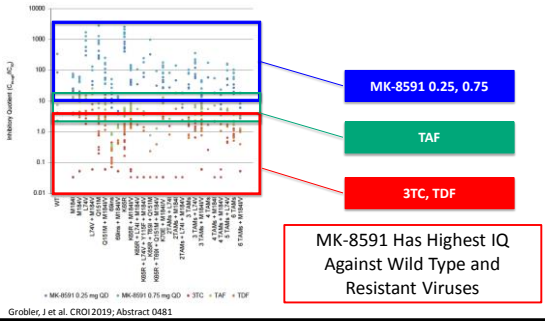
- Nucleoside reverse transcriptase translocation inhibitor (NRTTI)
  - Blocks translocation and terminates the DNA chain
  - Also has delayed chain termination effect after incorporation
  - Also known as EFdA (4'ethynyl-2 fluoro-2'deoxyadenosine)
- Very potent: dose as low as 0.25mg for treatment
- Very long half-life of tri-phosphate form: 78-128 hours
  - MK 8591-TP levels above pharmacokinetic target ≥ 30 days after last oral dose (0.25 – 5.0 mg)

Matthews R, CROI 2018; Markowitz M, CROI 2018; Grobler, J et al. CROI 2019; Abstract 0481

MK 8591: Higher Inhibitory Quotient (C_{trough} /IC_{90}) than FTC, 3TC, TAF, TDF



Grobler, J et al. CROI 2019; Abstract 0481



MK-8591 Has Highest IQ Against Wild Type and Resistant Viruses

Grobler, J et al. CROI 2019; Abstract 0481

MK 8591: Long Acting Implant Formulations

Antimicrobial Agents and Chemotherapy

Extended Duration MK-8591-Eluting Implant as a Candidate for HIV Treatment and Prevention

Stephanie E. Barrett, Ryan S. Teller, Seth P. Forster, Li Li, Megan A. Mackey, Daniel Skomski, Zhen Yang, Kerry L. Fillgrove, Gregory J. Doto, Sandra L. Wood, Jose Lebron, Jay A. Grobler, Rosa I. Sanchez, Zhen Liu, Bing Lu, Tao Niu, Li Sun, Marian E. Gindy

DOI: 10.1128/AAC.01058-18

- Potentially therapeutic TP levels in rodents persist > 6 months

Barrett S, AAC. July, 2018. DOI: 10.1128/AAC.01058-18

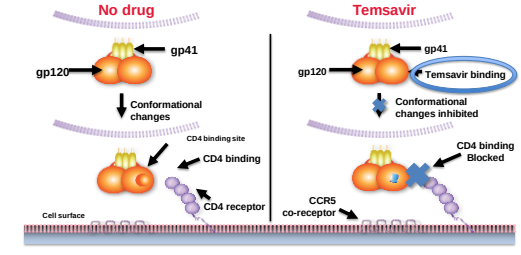
MK-8591: Summary

- Highly potent: IC50 of MK-8591-TP >4-fold lower than any marketed NRTI
- More active against NRTI-resistant viruses than TDF, TAF, 3TC
- High genetic barrier to resistance
- Very long TP intracellular half-life = potential for weekly oral dosing, long acting parenteral
- Being developed simultaneously for treatment and prevention based on positive macaque studies

Grobler, J et al. CROI 2019; Abstract 0481

Fostemsavir: Attachment Inhibitor

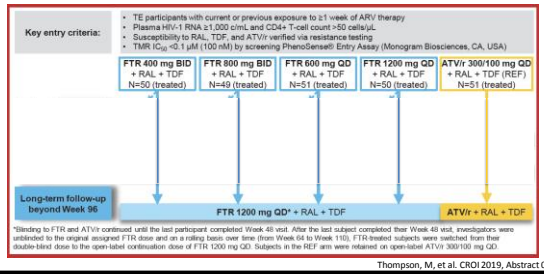
Fostemsavir : Proposed Mechanism of Action



Langley DR *et al.* Proteins 2015; 83:331–350.

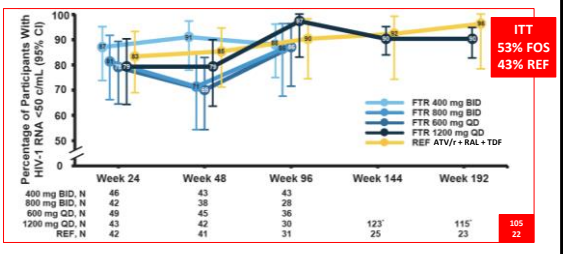
Llamoso C *et al.* HIV Glasgow 2016; Glasgow, UK. Oral # 335A/B.

Fostemsavir in Treatment Experienced Patients – 192 Weeks



Thompson, M, et al. CROI 2019, Abstract 0483

Fostemsavir: Virologic Response to Week 192 - Observed



Thompson, M, et al. CROI 2019, Abstract 0483

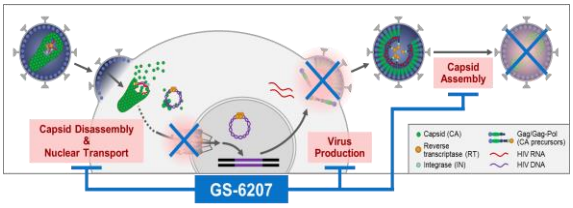
Fostemsavir: Summary

- HIV RNA and CD4 response comparable to ATV/r-RAL-TDF through 192 weeks
- Fewer safety events compared with ATV/r-RAL-TDF
  - Lower rates of Grade 2–4-drug related AEs, Grade3–4 AEs, and AEs leading to discontinuation
- Requires twice-daily dosing
- Development slowed due to manufacturing issues
- Phase 3 Highly Treatment Experienced (BRIGHTE) study ongoing

Thompson, M, et al. CROI 2019, Abstract 0483

GS–6207: Capsid Inhibitor

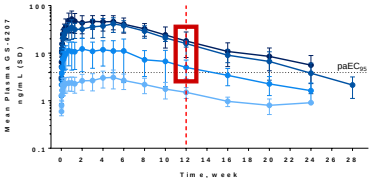
GS-6207: HIV Capsid Inhibitor



- GS-6207 inhibits multiple processes essential for viral replication
- GS-6207 modulates the stability and/or transport of capsid complexes

Sager, J et al. CROI 2019. Abstract 141

GS-6207: Support for Dosing Interval of ≥ 12 Weeks



Dose	IQ at week 12
450 mg	4.7
300 mg	4.1
100 mg	1.3
30 mg	0.4

$IQ = C_{trough}/paEC_{95}$

- At doses ≥100 mg, GS-6207 plasma concentrations at 12 weeks were above the $paEC_{95}$ of 3.87 ng/mL

Sager, J et al. CROI 2019. Abstract 141

*EC_{95} determined in MT-4 T-Cell Line with WT HIV-1 (IIIB strain). C_{trough}, GS-6207 plasma concentration on Day 84; IQ, inhibitory quotient; $paEC_{95}$, protein adjusted EC_{95}

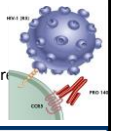
GS-6207: Summary

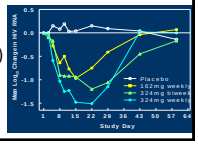
- HIV capsid inhibitor with picomolar antiviral activity
- Following a single subcutaneous dose in healthy volunteers:
  - No serious safety issues (safety still blinded)
  - Maintained systemic exposure for ≥ 24 weeks; most doses exceeded $paEC_{95}$ for ≥ 12 weeks
- Potential for quarterly or less frequent dosing
- Ongoing Phase I in persons living with HIV

PRO-140 (leronlimab): Anti-CCR5 mAb

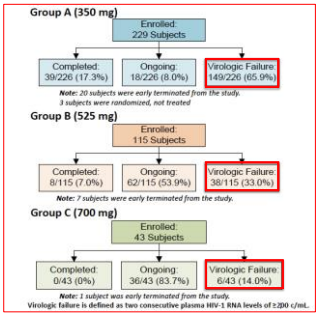
PRO 140: A CCR5-Directed Monoclonal Antibody

- Humanized IgG4 monoclonal antibody blocks HIV-1 entry
- High genetic barrier to resistance
- Active against multidrug resistant viruses, including those r
  resistant to maraviroc
- Weekly SC injections
- Single dose HIV RNA reduction to 1.83 log
- Tx-experienced: ≥ 0.5 $\log_{10}$ HIV RNA decline (1 wk)
- Rolling FDA BLA: plan to file for approval 4Q2019





Jacobsen J, et al. J Infect Dis 2010; May 15;201(10):1481-7;



CD-03 PRO 140 Monotherapy
Maintenance of Viral Suppression

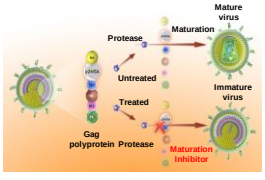
- Stable ART with < 50 c/mL for 6 months
- CD4 > 350/µL; nadir > 200/µL
- Improved response with higher doses; study still enrolling; n=500

Dhody K, et al, CROI 2019, Abstract 486

GSK 2838232: Maturation Inhibitor

Mode of Action: Maturation Inhibitors

MAs bind to the *gag* protein, inhibiting the last proteolytic cleavage event between the p24 CA and SP1



Development of previous maturation inhibitors halted:

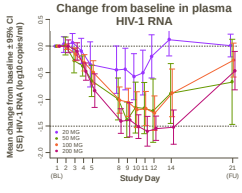
- Bevirimat: naturally occurring polymorphism in HIV-1 Gag at or near its site of activity[1]
- BMS-955176: issues with resistance and gastrointestinal tolerability[2]

Figure originally presented at CROI 2015 (Abstract 114LB) and included by kind permission of Dr M Lataillade

[1]Dybowski JN, et al. *BioData Min*. 2011;4:26; [2]Morales-Ramirez J, et al. *PLoS One*. 2018, https://doi.org/10.1371/journal.pone.0205368

Antiviral Activity of Cobicistat-Boosted GSK'232 10 Day Monotherapy

Robust reductions in 50 mg, 100 mg, and 200 mg cohorts; maximal effect in 200 mg cohort



	20 mg (n=7)	50 mg (n=8)	100 mg (n=10)	200 mg (n=8)
Plasma HIV RNA (copies/mL)				
Max. decline from baseline, mean (SD)	-42,095 (37,576)	-49,066 (71,340)	-32,948 (54,291)	-33,149 (31,786)
Max. decline from baseline (log 10-transformed), mean (SD)	-0.67 (0.41)	-1.56 (0.67)	-1.32 (0.44)	-1.70 (0.38)
>1.5 log10 copies/mL decrease from baseline, n (%)	0	2 (25)	2 (20)	5 (63)
<400 copies/mL, n (%)	0	2 (25)	2 (20)	4 (50)
CD4 count				
Change from baseline, mean (SD)	-1.4 (95.3)	52.0 (145.4)	40.7 (94.5)	11.1 (75.2)

BL, baseline; CI, confidence interval; FU, follow-up; HIV, human immunodeficiency

DeJesus, E. et al. CROI 2019, O142

GSK2838232: Summary

- Potency at 3 highest doses, highest at 200mg
- Requires boosting for once-daily use
- 2 patients with treatment-emergent *Gag* mutations
  - One patient with "less sensitive" virus at baseline
- Mild-moderate AEs, no serious safety issues

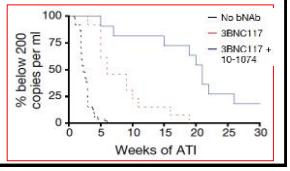
bNAbs (or bnAbs?)

Broadly neutralizing monoclonal antibodies for prevention, treatment, cure

Combination therapy with anti-HIV-1 antibodies maintains viral suppression

Pilar Mendoza[1,19], Henning Gruell[2,3,4,19], Lilian Nogueira[1], Joy A. Pai[1], Allison L. Butler[1], Katrina Millard[1], Clara Lehmann[3,4,5], Isabelle Suárez[3,4,5], Thiago Y. Oliveira[1], Julio C. C. Lorenzi[2], Yehuda Z. Cohen[1], Christoph Wyen[3,6], Tim Kümmerle[3,6], Theodora Karagounis[1], Ching-Lan Lu[1], Lisa Handl[7], Cecilia Unson-O'Brien[1], Roshni Patel[1], Carola Ruping[2], Malke Schlotz[2], Maggi Witmer-Pack[1], Irina Shimeliovich[1], Gisela Kremer[3], Eleonore Thomas[3], Kelly E. Seaton[8], Jill Horowitz[1], Anthony P. West Jr[9], Pamela J. Bjorkman[9], Georgia D. Tomaras[8,10,11,12], Roy M. Gulick[13], Nico Pfeifer[7,14,15,16], Gerd Fätkenheuer[3,4], Michael S. Seaman[17], Florian Klein[3,4,5,20]*, Marina Caskey[1,20]* & Michel C. Nussenzweig[1,18,20]*

- Antibody infusions: 0, 3, 6 wks
- 9 pts maintained HIV RNA < 200c/mL up to median 21 weeks
- Well tolerated



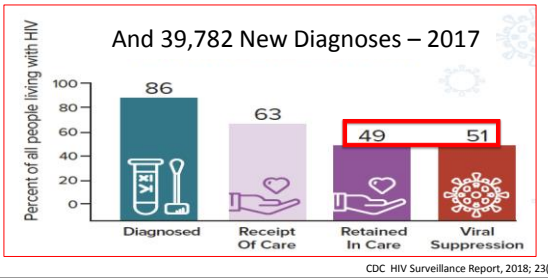
Mendoza P, et al. Nature HIV. Sept 2018.

Questions About Long-Acting Agents

- How long is long enough?
- How long is too long? (resistance, toxicity, teratogenicity)
- What is the optimal administration mode? SC, IM, IV, implant, stent, microneedle patch? Self-administered v provider-administered?
- For clinic-administered therapy, what will be the impact on patient flow, provider time?
- What will the drugs cost, and will cost of administration be reimbursed? Impact on health care financing as a whole?
- Will they solve or just reinvent issues with adherence?

But…the half life doesn't matter if the drug doesn't get into the patient!

US Care Continuum (2015)



CDC HIV Surveillance Report, 2018; 23(3)

Acknowledgements

- Many patients participated in clinical trials to generate the results presented today – Thank You!
- Thanks for sharing slides:
  - Gilead: Diana Brainard, Hal Martin
  - Merck: Kathleen Squires, Boris Rejifo
  - GSK/ViiV: Mark Shaefer, Max Latillade, Brian Donovan, Cathy Schubert
  - PRO 140: Kush Dhody (Amarex)