New Directions in HIV Treatment:

Implications for Antiretroviral Therapy Adherence

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BENJAMIN YOUNG: DISCLOSURES

- Research support*:
  - Gilead Sciences, Merck & Co., ViiV Healthcare
- Consultant or Advisory Board
  - Bristol-Myers Squibb, Gilead Sciences, Merck & Co., ViiV Healthcare
- Speakers Bureau
  - Merck & Co.

*APEX Research, Denver, CO

HIV TREATMENT WORKS

- Preserves or restores immune function
- Prevents progression to AIDS
- Prevents serious illness and death
- Prevents transmission to others

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- Prevents transmission to others
- *In tested individuals able to adhere to care and treatment*

NEW DIRECTIONS IN HIV TREATMENT

- Treatment initiation guidelines
- Currently approved ART
- Emerging data on investigational drugs/approaches*
  - For treatment
  - For PrEP

*may include off-label or investigational medications

NEW DIRECTIONS IN ART INITIATION

World Health Organization

GUIDELINES

GUIDELINE ON WHEN TO START ANTIRETROVIRAL THERAPY AND ON PRE-EXPOSURE PROPHYLAXIS FOR HIV

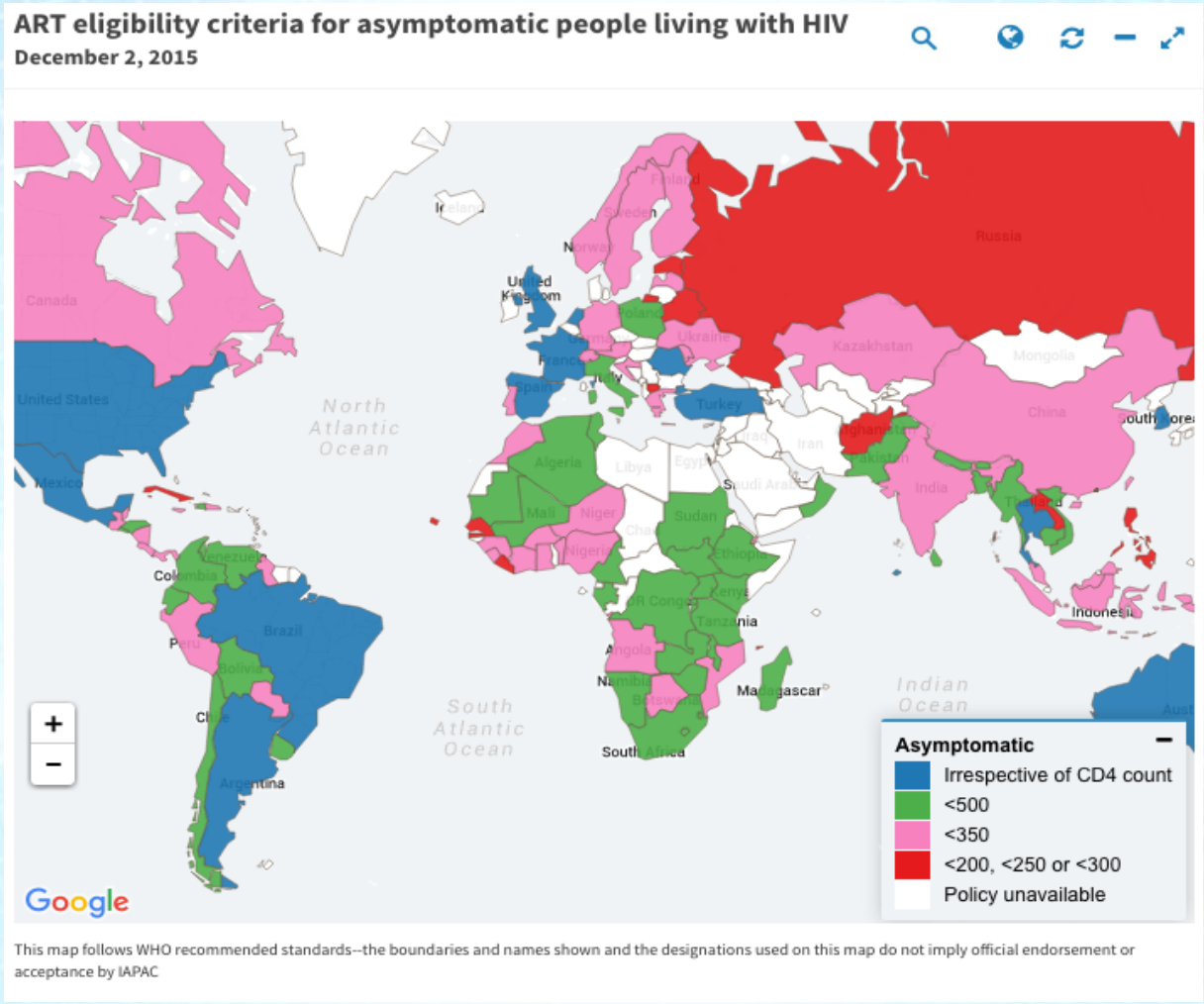
SEPTEMBER 2015

Summary of recommendations in this guideline

Recommendation 1: When to start ART among people living with HIV			
Target population	Specific recommendation	Strength of the recommendation	Quality of the evidence
Adults[a] (>19 years)	ART should be initiated in all adults living with HIV at any CD4 cell count	*Strong*	*Moderate* NEW
	As a priority, ART should be initiated in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count ≤350 cells/mm^3	*Strong*	*Moderate*
Pregnant and breastfeeding women	ART should be initiated in all pregnant and breastfeeding women living with HIV at any CD4 cell count and continued lifelong	*Strong*	*Moderate* UPDATED

Recommendation 2: Oral pre-exposure prophylaxis to prevent HIV acquisition			
Target population	Specific recommendation	Strength of the recommendation	Quality of the evidence
HIV-negative individuals at substantial risk of HIV infection[b]	Oral PrEP (containing TDF) should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches	*Strong*	*High* NEW

ART ELIGIBILITY: HIVpolicywatch.org



NEW SERVICE DELIVERY MODELS: PEPFAR

- Changing clinic appointments to every 6-12 months, and ART refills to every 3-6 months
- Predicts 50-75% increase in capacity at similar cost
- Improve retention/adherence?

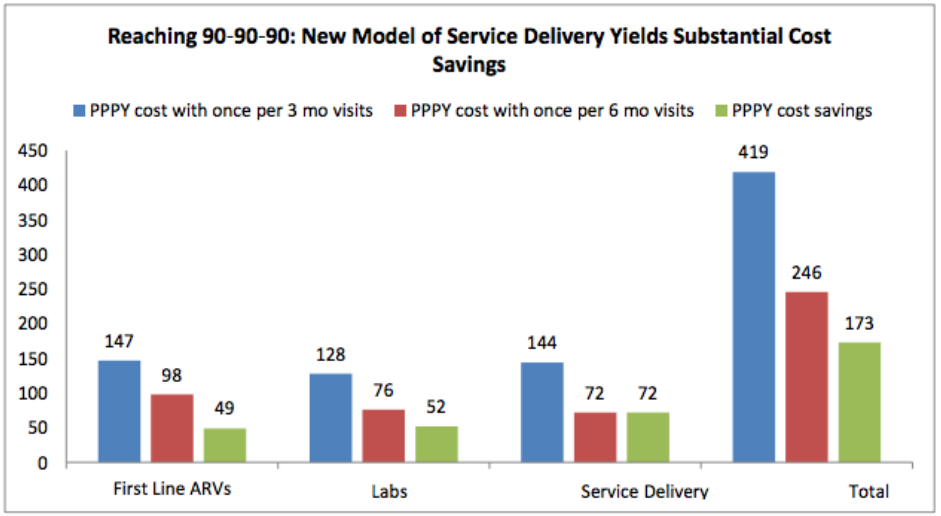


Figure 4. This illustrates how by reducing first-line costs per patient per year (PPPY), number of visits, annual labs, and service delivery, it is possible to double coverage with similar resource envelope. Further reductions can be obtained with additional reductions in antiretroviral treatment (ART) delivery costs (e.g., fewer and less expensive labs, less costly first-line regimens, less frequent clinic visits). Source: PEPFAR, Stover.

NEW DIRECTIONS IN ART

DHHS ART GUIDELINES: 2016

Recommended Regimen Options

(Drug classes and regimens within each class are arranged in alphabetical order.)

INSTI-Based Regimens:

- DTG/ABC/3TC[a]—**only** for patients who are HLA-B*5701 negative (**AI**)
- DTG plus TDF/FTC[a] (**AI**)
- EVG/c/TAF/FTC—**only** for patients with pre-treatment estimated CrCl ≥30 mL/min (**AI**)
- EVG/c/TDF/FTC—**only** for patients with pre-treatment estimated CrCl ≥70 mL/min (**AI**)
- RAL plus TDF/FTC[a] (**AI**)

PI-Based Regimens:

- DRV/r plus TDF/FTC[a] (**AI**)

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PREFERRED AND ALTERNATIVE FIRST-LINE ART REGIMENS

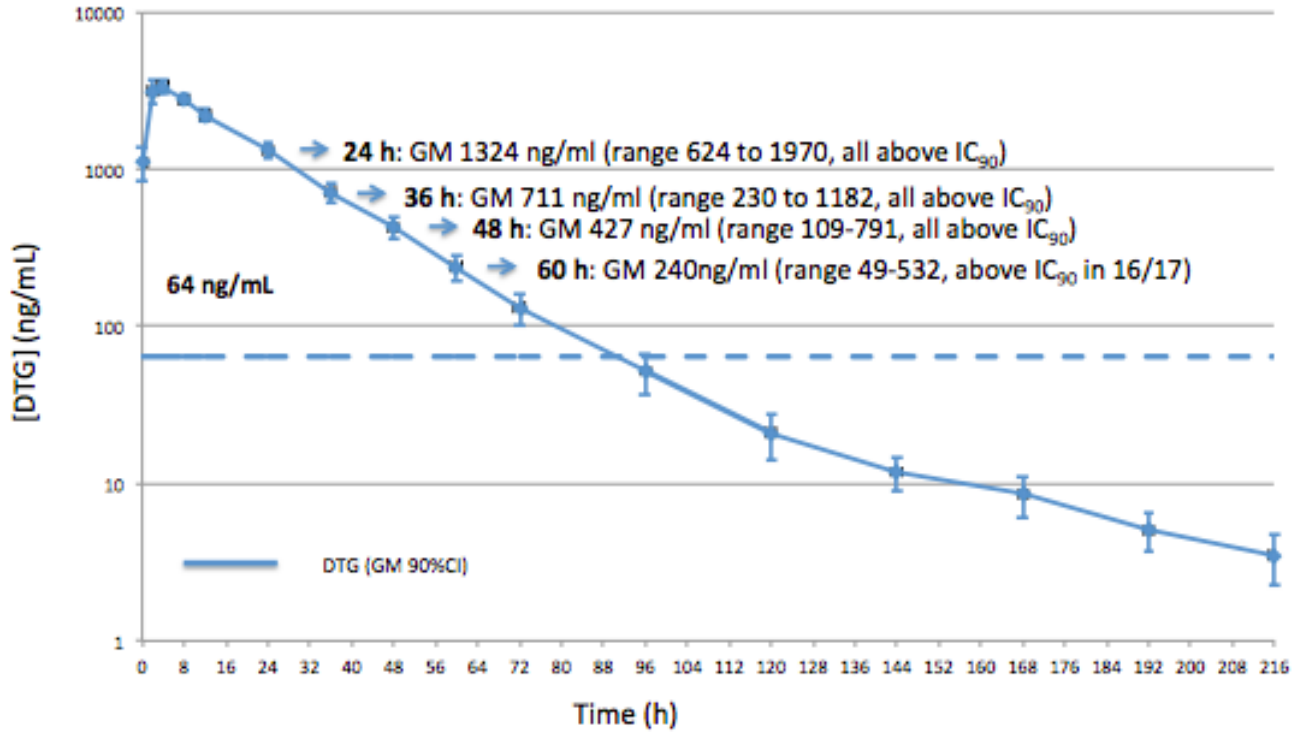
First-line ART	Preferred first-line regimen	Alternative first-line regimens[1,2]
Adults	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + DTG[3,4] TDF + 3TC (or FTC) + EFV_{400}[3,4,5] TDF + 3TC (or FTC) + NVP

World Health Organization, November 2015

Journal of Antimicrobial Chemotherapy

Dolutegravir and elvitegravir plasma concentrations following cessation of drug intake

Emilie Elliot[1,2], Alieu Amara[2], Akil Jackson[1,2], Graeme Moyle[1], Laura Else[2], Saye Khoo[2], David Back[2], Andrew Owen[2] and Marta Boffito[1,3,*]



At 60 hrs post dose, 16 out 17 study subjects had dolutegravir concentrations above the cut off and this ranged between 49 and 532 ng/ml

Elliott, JAC 2016

TENOFOVIR ALAFENAMIDE
POTENTIAL NEW COFORMULATIONS

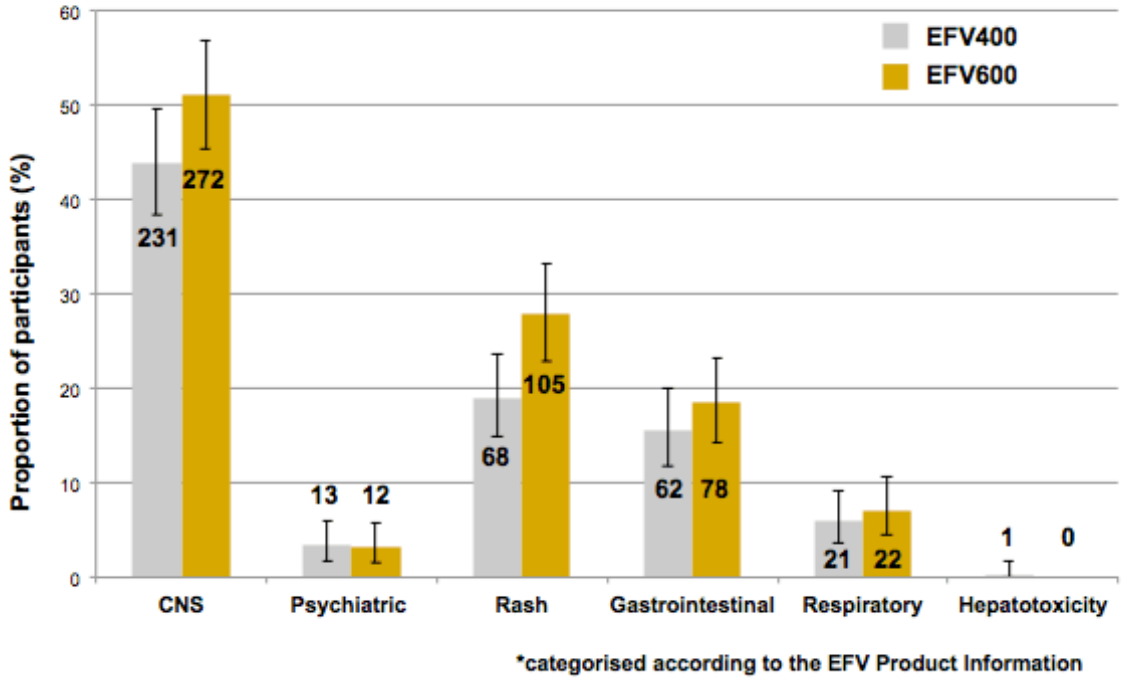
- Tenofovir disoproxil fumarate (TDF) 300 mg
- Tenofovir alafenamide (TAF) 25 mg

- TAF: lower renal and bone adverse events
- New co-formulation potential:
  - TDF/FTC + DRV/c
  - TAF/FTC/DRV/c

Efficacy and safety of efavirenz 400 mg daily versus 600 mg daily: 96-week data from the randomised, double-blind, placebo-controlled, non-inferiority ENCORE1 study

ENCORE1 Study Group†

Efavirenz adverse events*



ENCORE Study Group, Lancet 2014

FUTURE DIRECTIONS IN ART?

Dolutegravir-Lamivudine as Initial Therapy in HIV-infected, ARV Naive Patients: First Results of the PADDLE Trial

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Viral Suppression at Week 24

#	SCR	BSL	Day 2	Day 4	Day 7	Day 10	W.2	W.3	W.4	W.6	W.8	W.12	W.24
1	5.584	10.909	3.701	383	101	71	<50	<50	<50	<50	<50	<50	<50
2	8.887	10.233	5.671	318	<50	<50	<50	<50	<50	<50	<50	<50	<50
3	67.335	151.569	37.604	1.565	1.178	266	97	53	<50	<50	<50	<50	<50
4	99.291	148.370	11.797	3.303	432	179	178	55	<50	<50	<50	<50	<50
5	34.362	20.544	4.680	1.292	570	168	107	<50	<50	<50	<50	<50	<50
6	16.024	14.499	3.754	1.634	162	<50	<50	<50	<50	<50	<50	<50	<50
7	37.604	18.597	2.948	819	61	<50	<50	<50	<50	<50	<50	<50	<50
8	25.071	24.368	6.264	1.377	Not done	268	105	<50	<50	<50	<50	<50	<50
9	14.707	10.832	Not done	516	202	<50	<50	<50	<50	<50	<50	<50	<50
10	10.679	7.978	5.671	318	<50	<50	<50	<50	<50	<50	<50	<50	<50
11	50.089	273.676	160.974	68.129	3.880	2.247	784	290	288	147	<50	<50	<50
12	13.508	64.103	3.496	3.296	135	351	351	84	67	<50	<50	<50	<50
13	28.093	33.829	37.350	26.343	539	268	61	<50	<50	<50	<50	<50	<50
14	15.348	15.151	3.994	791	198	98	<50	61	64	<50	<50	<50	<50
15	23.185	23.500	15.830	4.217	192	69	<50	<50	<50	Not done	<50	<50	<50
16	11.377	3.910	370	97	143	<50	<50	<50	<50	<50	<50	<50	<50
17	39.100	25.828	11.879	1.970	460	147	52	<50	<50	<50	<50	<50	<50
18	60.771	73.069	31.170	2.174	692	358	156	<50	<50	<50	<50	<50	<50
19	82.803	106.320	35.517	2.902	897	352	168	76	<50	<50	<50	<50	<50
20	5.190	7.368	3.433	147	56	<50	<50	<50	<50	<50	<50	<50	<50

From Week 8 onwards all patients had pVL < 50 copies/mL

Figueroa, EACS 2015

INVESTIGATIONAL NNRTI: DORAVIRINE (DOR)

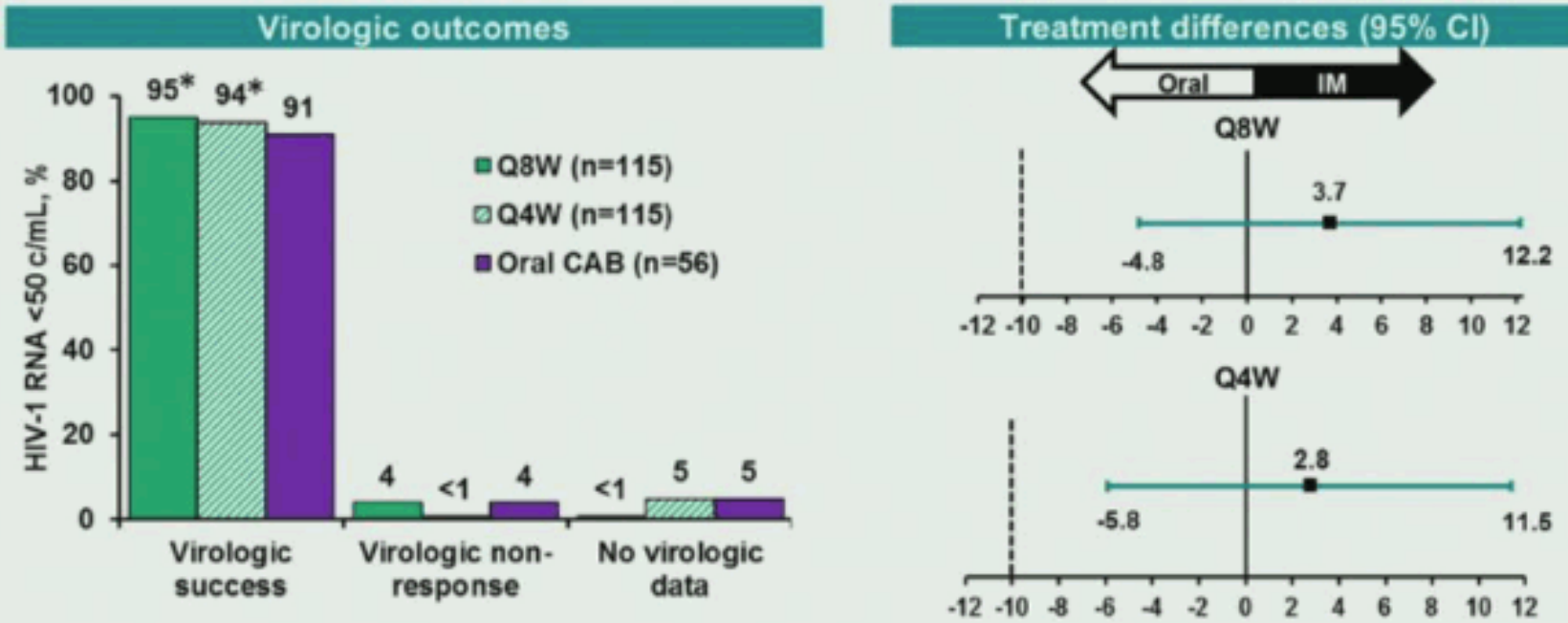
- 48 week, phase 2 dose-ranging study of TDF/FTC + EFV vs DOR
- Similar virologic activity and immunologic effect
- Statistically lower rates of drug-related AEs
- Phase 3 studies underway

Clinical Adverse Events (%)			
	DOR 100 mg (N=108)	EFV 600 mg (N=108)	Difference [DOR – EFV] (95% CI)
One or more adverse events (AE)	87.0	88.9	-1.9 (-10.9, 7.1)
Serious AE†	6.5	8.3	-1.9 (-9.5, 5.6)
Death	0	0	
Discontinued due to AE	2.8	5.6	-2.8 (-9.2, 3.0)
Drug-related‡ AE	31.5	56.5	-25.0 (-37.3, -11.8)
Diarrhea	0.9	6.5	–
Nausea	7.4	5.6	–
Dizziness	6.5	25.9	–
Headache	2.8	5.6	–
Abnormal dreams	5.6	14.8	–
Insomnia	6.5	2.8	–
Nightmares	5.6	8.3	–
Sleep disorder	4.6	6.5	–

†Two serious AEs in the EFV group were considered drug-related: depression (1) and dizziness (1).
‡Determined by investigator to be related to study therapy; specific AEs with >5% incidence are listed.
Specific AEs causing discontinuation (n): DOR – hallucination (1), B-cell lymphoma (1), Hodgkin's disease (1); EFV – dysaesthesia (1), hallucinations (2), drug eruption (1), dizziness (1), disturbance in attention (1).

LONG ACTING ART: RILPIVIRINE/CABOTEGRAVIR

LATTE-2 Week 32 Primary Endpoint: HIV-1 RNA <50 c/mL by Snapshot (ITT-ME)



Both Q8W and Q4W comparable to oral CAB at Week 32

*Met pre-specified threshold for concluding IM regimen is comparable to oral regimen (Bayesian posterior probability >90% that true IM response rate is no worse than -10% compared with the oral regimen).

Margolis et al. CROI 2016; Boston, MA. Abstract 31LB.

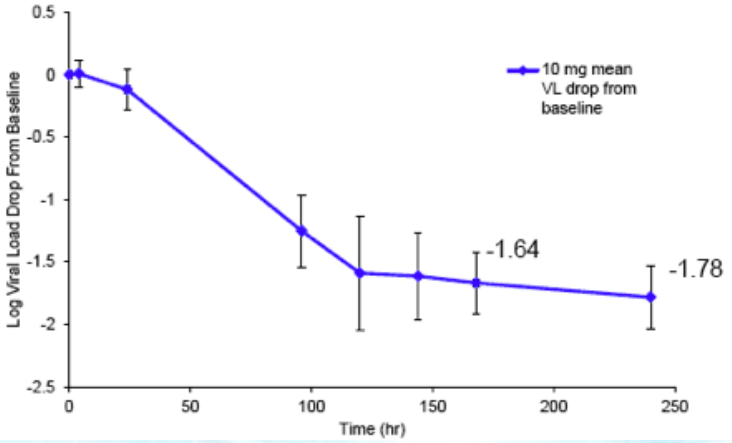
Margolis, CROI 2016

VERY LONG ACTING NRTI

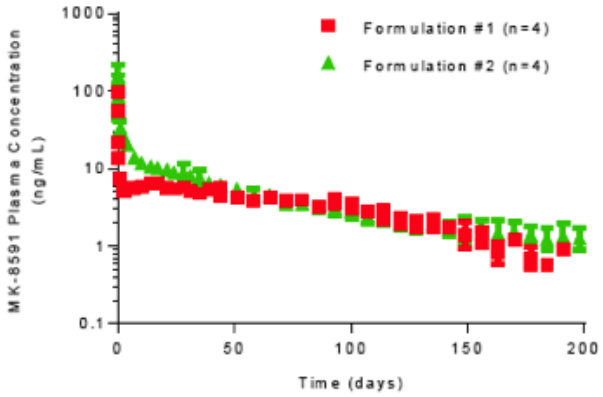
- **EFdA**- nucleoside RT inhibitor
- Very long $t_{1/2}$
- Effective viral reduction dosed orally once—weekly
- Parenteral PK supportive of q6 month dosing

MK-8591 is Effective in HIV patients when Dosed Once-Weekly: Results from ongoing Ph1b study

Friedman, et al., Poster 437LB



MK-8591 Parenteral Formulations Release Effective Drug Levels for >180 days



NEW DIRECTIONS IN PrEP

Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study

Robert M Grant, Peter L Anderson, Vanessa McMahan, Albert Liu, K Rivet Amico, Megha Mehrotra, Sybil Hosek, Carlos Mosquera, Martin Casapia, Orlando Montoya, Susan Buchbinder, Valdilea G Veloso, Kenneth Mayer, Suwat Chariyalertsak, Linda-Gail Bekker, Esper G Kallas, Mauro Schechter, Juan Guanira, Lane Bushman, David N Burns, James F Rooney, David V Glidden, for the iPrEx study team

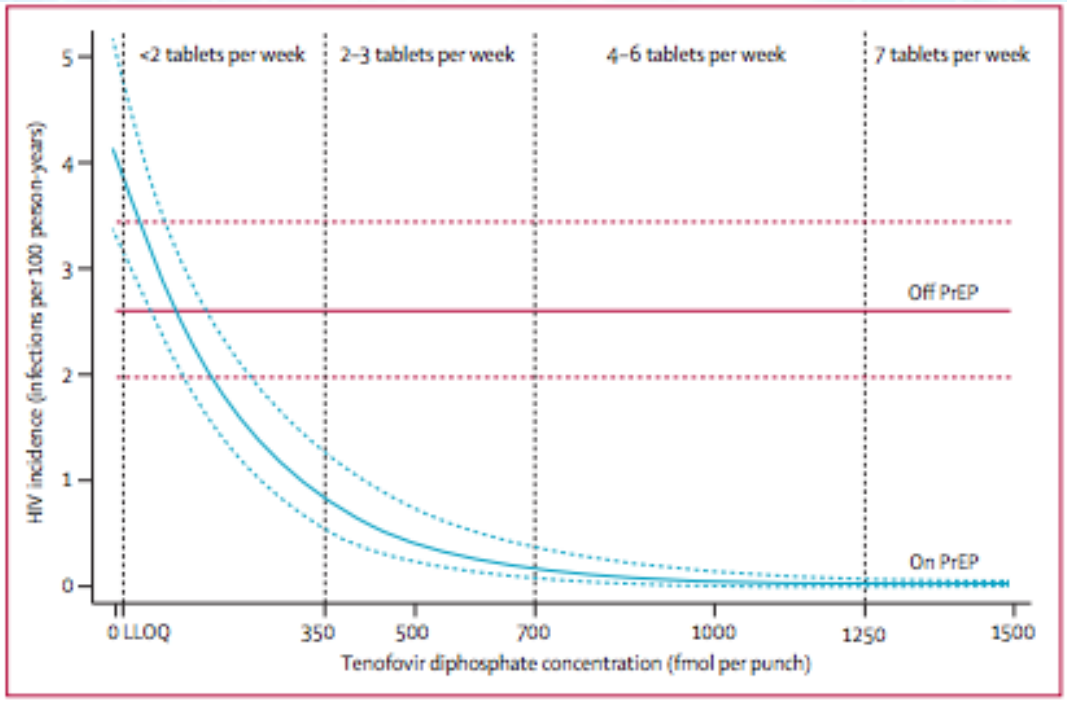


Figure 2: **Pre-exposure prophylaxis and HIV incidence**
For those visits on PrEP, the incidence of HIV is estimated by exponential regression by tenofovir diphosphate in dried blood spots. The incidence for the concomitant off-PrEP group is depicted as a constant for reference. The dotted lines represent the estimate bounded by 1 SE. Dosing for each interval is estimated by pharmacokinetic modelling. LLOQ=lower limit of quantitation.

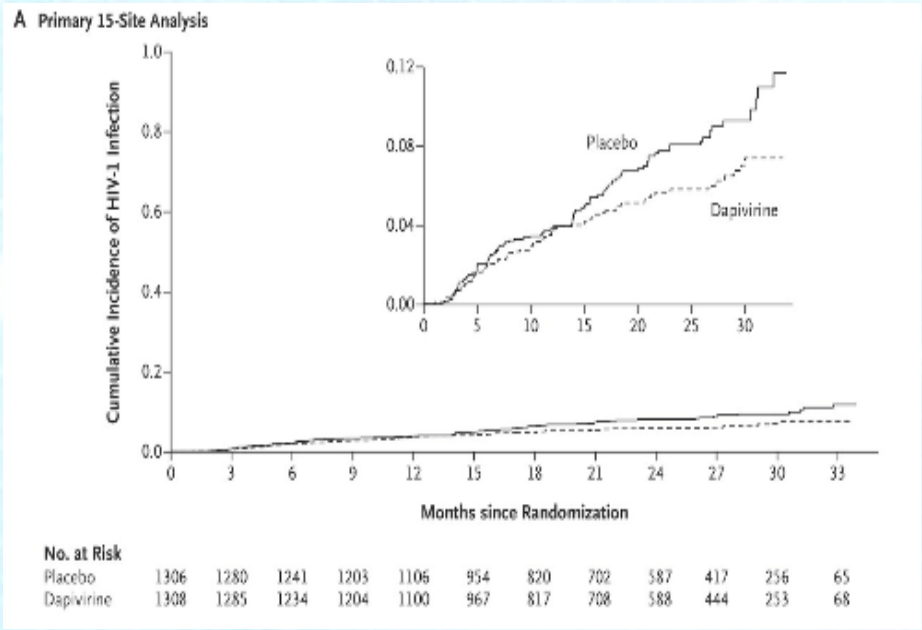
Grant, Lancet, 2014

NEW APPROACHES TO PrEP: Dapirivirine vaginal ring; Maraviroc

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Use of a Vaginal Ring Containing Dapivirine for HIV-1 Prevention in Women



CROI 2016 BOSTON

HPTN 069/ACTG 5305: Phase II Study of Maraviroc-Based Regimens for HIV PrEP in MSM

HPTN 069 / A5305: Conclusions

- MVC-containing regimens were comparably safe and well-tolerated to TDF+FTC when used over 48 weeks as HIV PrEP.
- Comparable specific GI and renal toxicities.
- No drug-drug interactions with MVC, FTC, TDF.
- ~80% of pts. had detectable plasma drug conc.
- 5 new HIV infections (incidence 1.4%)
  - all R5 virus without drug resistance
  - plasma drug concs. were absent, low, or variable

Baeten, NEJM 2016; CROI2016
Gulick, CROI2016

ECLAIR: Phase 2A Safety and PK Study of Cabotegravir LA in HIV-Uninfected Men

Martin Markowitz,[1] Ian Frank,[2] Robert M. Grant,[3] Kenneth H. Mayer,[4] David A. Margolis,[5] Krischan J. Hudson,[5] Britt S. Stancil,[6] Susan L. Ford,[6] Alex R. Rinehart,[5] William R. Spreen[5]

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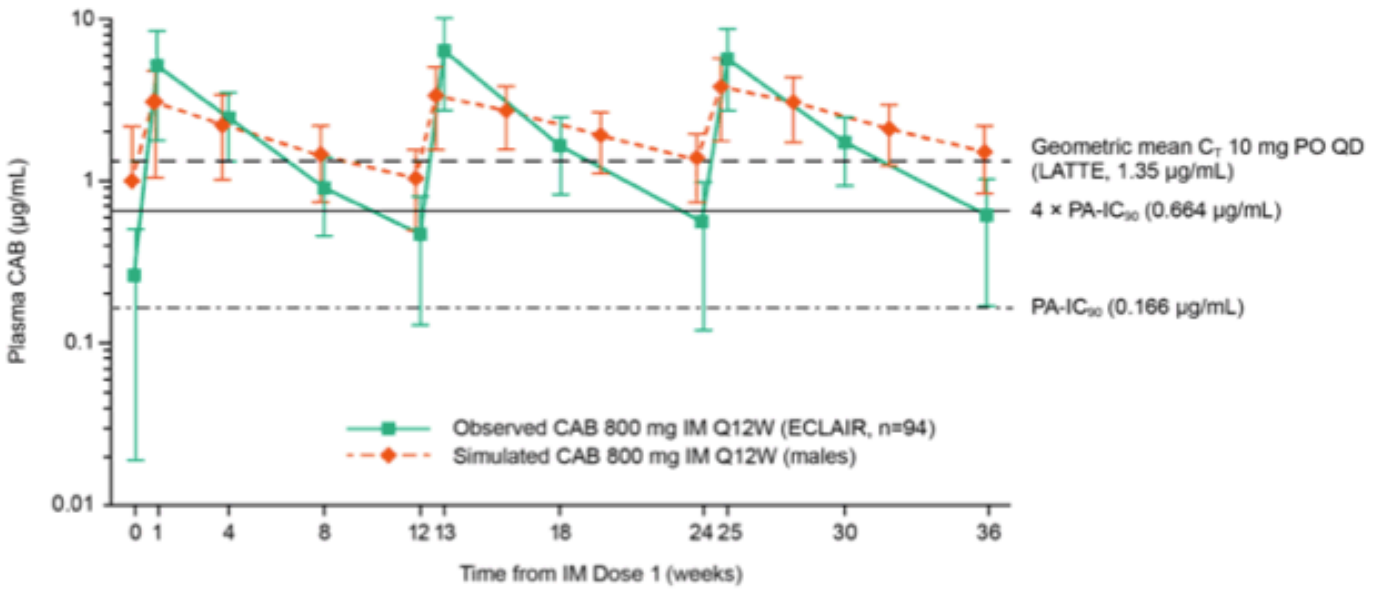
Predicted and Observed Mean (SD) CAB Concentration



C_T, concentration at the end of the dosing interval; PA-IC_{90}, protein binding–adjusted 90% inhibitory concentration; SD, standard deviation.

- Results suggestive of every 8 week dosing. Phase 3 program ongoing.

NEW DIRECTIONS IN ART:
ADHERENCE IMPLICATIONS

- Universal access to ART should improve continuum
- Improvements in currently approved ART
  - EFV_{400}, TAF, INSTIs
- Investigational medications and strategies
  - Dual drug therapy with DTG
  - LA oral and injectable meds for Tx and PrEP
  - Vaginal ring for PrEP
- Critical need to evaluate adherence and continuum implications

Thank you!
Gracias!
Mercî!
Asanti sana!
Спасибо!
Obrigado!
谢谢

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