Updates from HIV Glasgow 2016

Infectious Disease and Infection Control Forum
2 May 2017

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hivglasgow.org

HIV Drug Therapy GLASGOW 2016

- Home
- Committees
- > 2016 WEBCASTS
- > 2014 WEBCASTS
- > 2012 WEBCASTS
- General Information
- > SCIENTIFIC ABSTRACTS
- > 2016 ABSTRACTS
- > 2014 ABSTRACTS
- > 2008-2012 ABSTRACTS
- Scientific Posters
- > 2016 POSTERS

We are all deeply saddened to hear of the tragic death of Professor Mark Wainberg. Mark was a wonderful colleague and whole hearted supporter of the Glasgow conference. His contribution to HIV research, teaching and advocacy has been immense. He will be fondly remembered and greatly missed.

hivglasgow.org/webcasts-2016

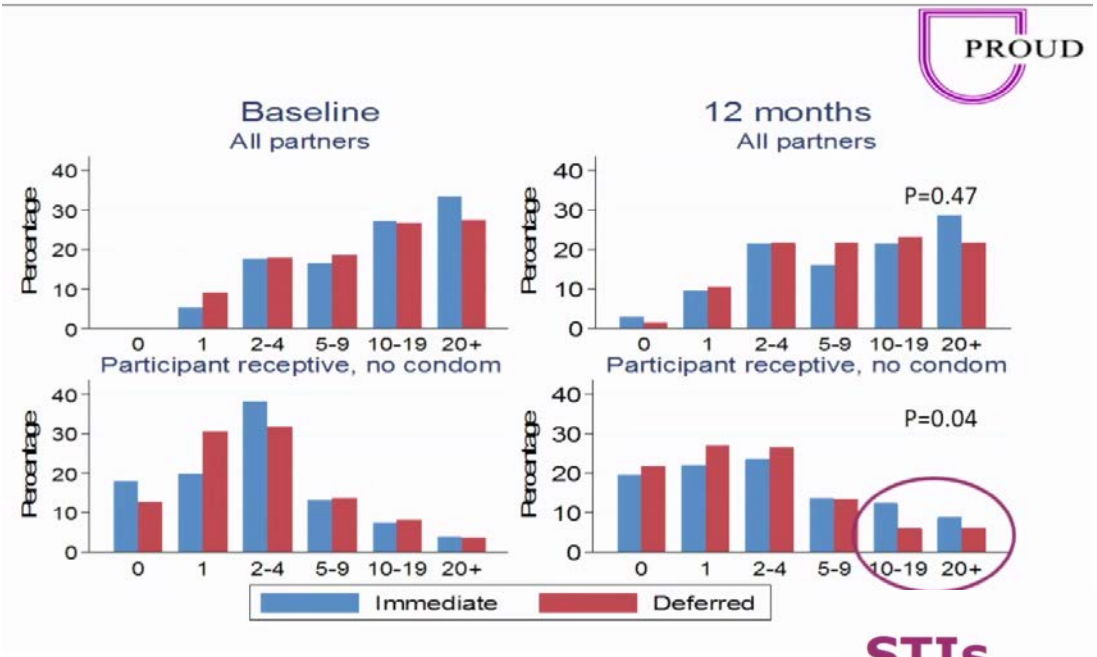
Outline

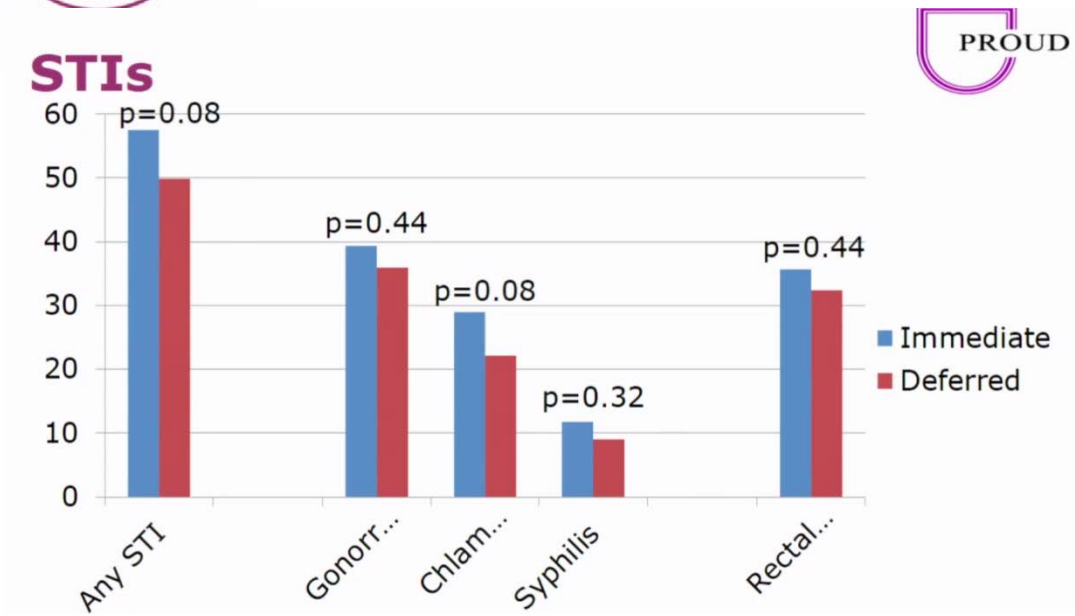
- Pre-exposure prophylaxis
  - Efficacy, cost-effectiveness, implementation
- Anti-retroviral therapy
  - Benefits of early ART
  - New ARVs and new strategies
- Availability and access of treatment
  - Generic drugs, lower cost for more patients, online access

1. PrEP

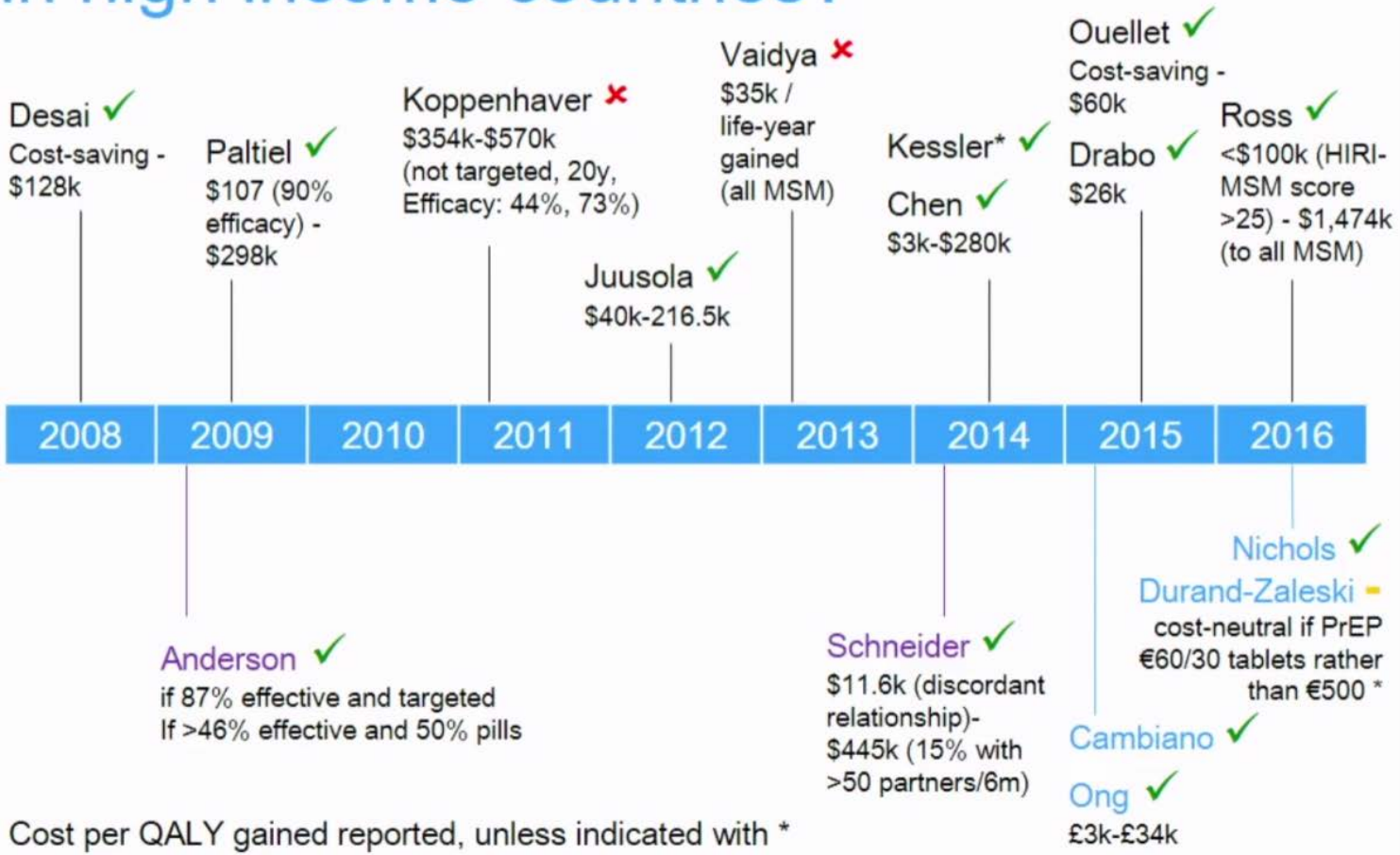
Evidence: population, drug, regimen

Population	Trials	Reduction in HIV incidence	Drug, delivery, regimen	Gaps in evidence
MSM and transgender	• iPrEX • PROUD • IPERGAY	44% 86% 86%	TDF/FTC Oral Daily/on demand	TDF Topical
Heterosexual men and women	• Partners PrEP • TDF2	63 - 84% 62%	TDF +/- FTC Oral Daily	 On demand
Women	• CAPRISA • FACTS • FEM-PREP • VOICE • ASPIRE • The Ring	39% 0% 6% -49% - 15% 27% - 61% 31%	TDF +/- FTC Gel/Oral Daily/on demand Dapivirine IVR, monthly	 Adherence, especially young <25 women
People who inject drugs	• BTS	49%	TDF Oral Daily	Route of transmission


PROUD
Baseline
All partners
12 months
All partners
P=0.47
Participant receptive, no condom
Participant receptive, no condom
P=0.04
Percentage
0
1
2-4
5-9
10-19
20+
Immediate
Deferred

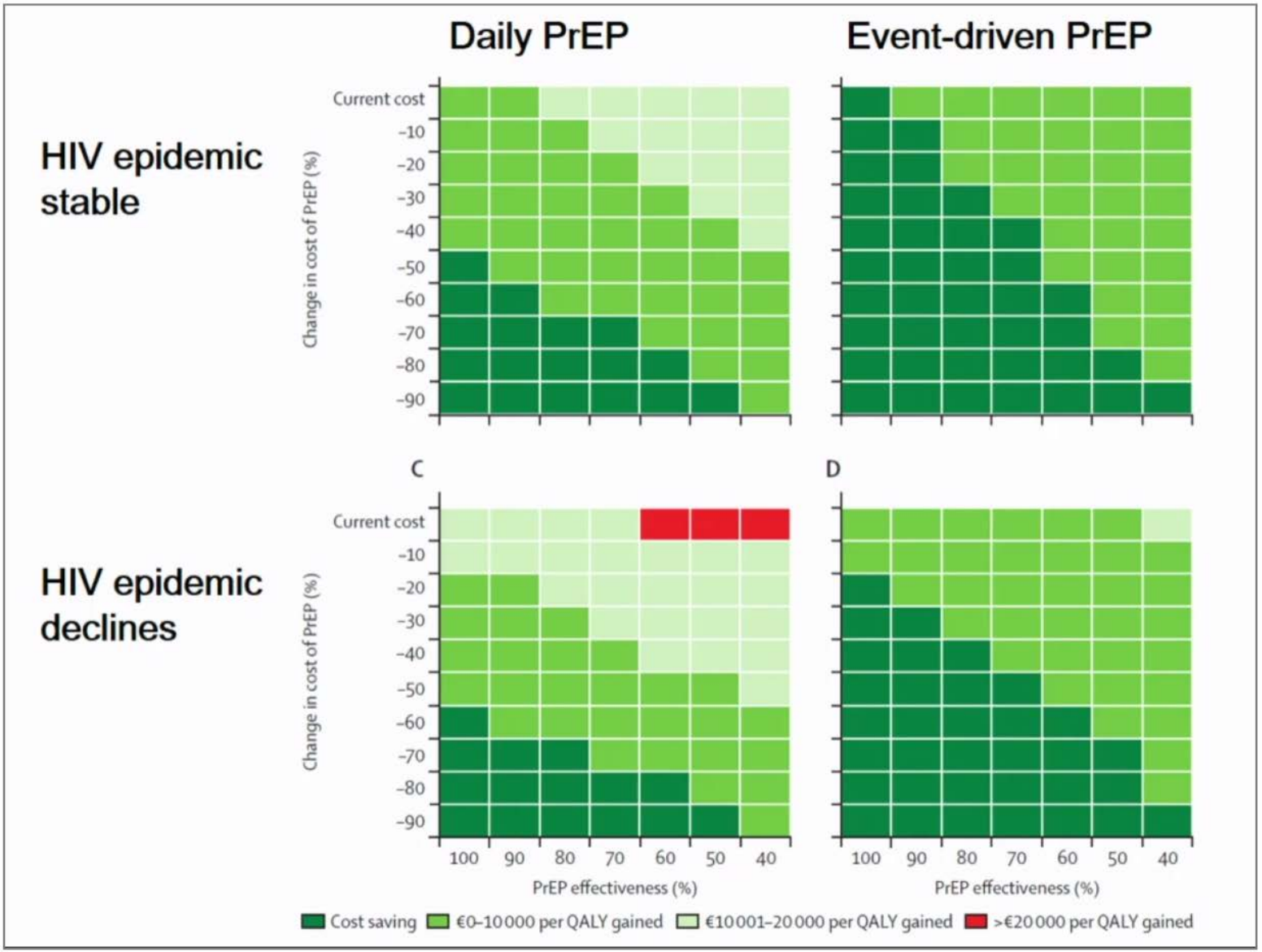

PROUD
STIs
p=0.08
p=0.44
p=0.08
p=0.32
p=0.44
Any STI
Gonorr...
Chlam...
Syphilis
Rectal...
Immediate
Deferred

Could PrEP be CE for MSM population in high income countries?



Cost per QALY gained reported, unless indicated with *

Cost-effectiveness modelling in the Netherlands



ECDC opinion on PrEP April 2015

- Countries should give consideration to integrating PrEP into their existing HIV prevention package for those most at-risk, starting with MSM
- Issues related to PrEP implementation will need to be addressed in the context of each Member State's health system
- ECDC will provide support to Member States and the European Commission with regards to PrEP implementation

European Centre for Disease Prevention and Control

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Pre-exposure prophylaxis to prevent HIV among MSM in Europe

30 Apr 2015

Evidence suggests that the use of pre-exposure prophylaxis (PrEP) for men who have sex with men (MSM) is an effective HIV prevention tool for Europe.

Pre-exposure prophylaxis (PrEP) is an antiretroviral therapy-based HIV prevention strategy to prevent or at least reduce the risk of HIV infection in adults who have not been infected with the virus but are at high risk of infection.

The results of two clinical studies assessing the effectiveness of PrEP among MSM in the EU/EEA were released at the annual Conference on Retroviruses and Opportunistic Infections (CROI 2015) in Seattle: the Pragmatic Open-Label Randomised Trial of Pre-exposure Prophylaxis (PROUD) conducted in the United Kingdom, and the double-blind placebo controlled trial Intervention Préventive de l'Exposition aux Risques avec et pour les Hommes Gays (IPERGAY) conducted in France and Canada, accompanied by press releases by Public Health England (PHE) and Recherche Nord & Sud SIdaHIV et Hépatites (ANRS). This came after early evidence of effectiveness led to the interruption of the non-treatment arm in both studies in October 2014.

The PROUD and IPERGAY study participants were MSM at high risk of acquiring HIV. During the course of the study, a high incidence of HIV (8.9 and 6.6 per 100 person-year, respectively) was observed among those men not assigned to the treatment arm. In both studies PrEP was incorporated into the existing risk reduction package, with either daily recommended administration (PROUD) or following an exposure/event-driven schedule (IPERGAY). Overall, PrEP was shown to have a high level of protection among the treated participants, reducing the risk of infection by 86% in both studies. There was no difference in the number of men diagnosed with other STIs between those taking PrEP and those not on PrEP, nor appreciable changes in condom use or sexual behaviour during the study period.

These results add to the growing body of evidence that PrEP should be considered as an additional prevention option for persons at high risk of HIV infection. Currently, PrEP is recommended as an additional prevention choice within a comprehensive HIV prevention package for MSM by the World Health Organization and for MSM and other high-risk groups by the Centers for Disease Control and Prevention.

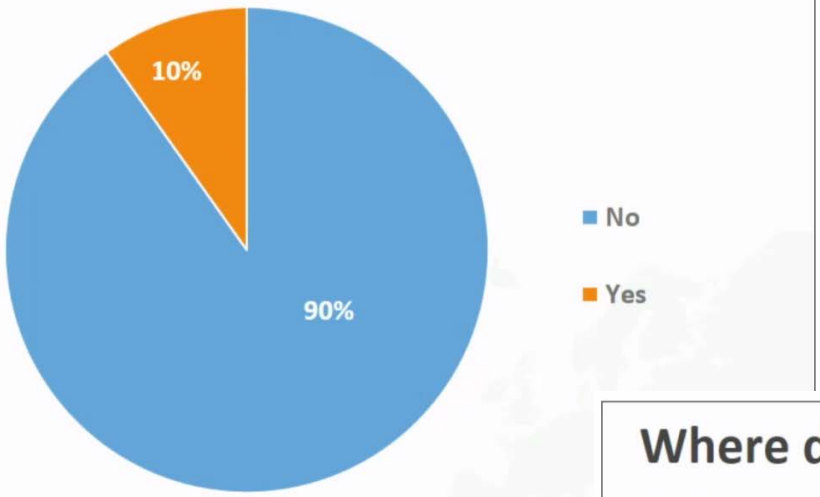
ECDC comment on PrEP in Europe

The promising results of the PROUD and IPERGAY studies are of particular importance in the EU/EEA where the HIV epidemic is largely concentrated among MSM, and newly diagnosed infections in this group have increased by more than 30% during the past decade.

On the basis of the new evidence, EU Members States should give consideration to integrating PrEP into their existing HIV prevention package for those most at-risk of HIV infection, starting with MSM. Issues related to large-scale PrEP implementation, such as cost-effectiveness, appropriate models of care and access points, provider training, routine monitoring of patients, including adherence to

Are you currently taking PrEP?

n= 8048 (excludes HIV-positive respondents)

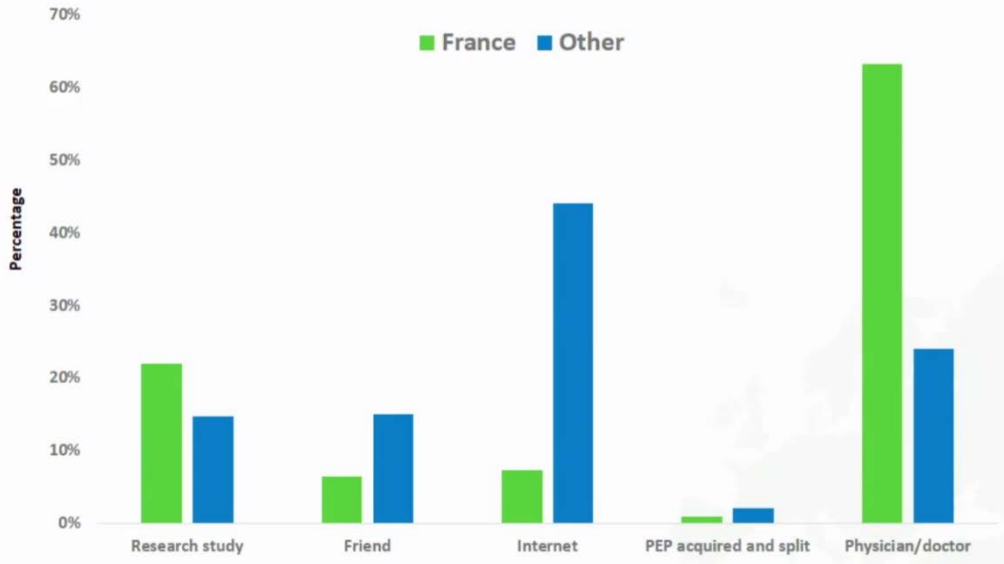


69% of those on PrEP said their sexual health provider was aware that they

ECDC. Evidence brief: Pre-exposure prophylaxis for HIV prevention in Europe. Stockholm: ECDC; 2016.

Where did you obtain PrEP?

n= 528 persons on PrEP responding to this question

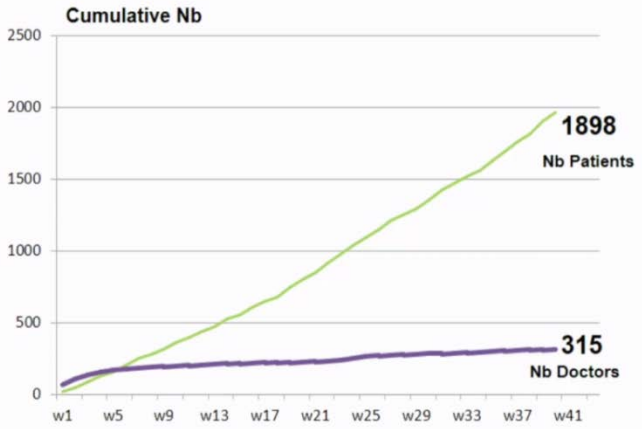


ECDC. Evidence brief: Pre-exposure prophylaxis for HIV prevention in Europe. Stockholm: ECDC; 2016.

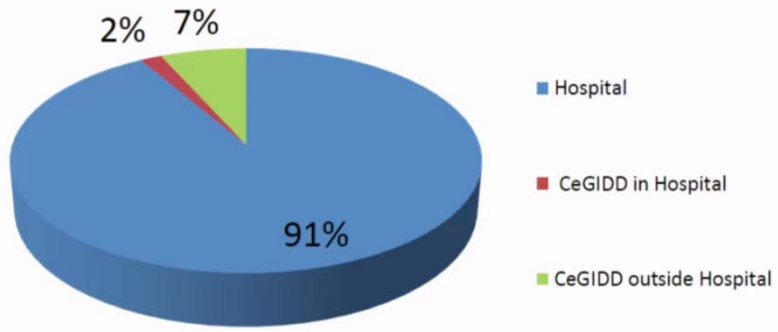
PrEP was approved in France for temporary use with full reimbursement by the health care system (November 2015)

PrEP Implementation in France in 2016

- **> 120 PrEP clinics have opened, initially in ANRS Ipergay sites (Paris, Lyon, Nice, Lille, Nantes)**
- **AIDES Website: http://www.aides.org/info-sante/prep**
- **TDF/FTC can be obtained at private and hospital pharmacies**



Where is PrEP Delivered ? France 01 to 09/2016



DF/FTC can be prescribed by hospital-based HIV specialists and CeGIDD (STI clinics) since June 2016

Lessons Learned in France

- Close **partnership with the community** and strong political support have led to PrEP approval
- Increase **PrEP awareness** among doctors and people at risk (MSM, transgender, and heterosexual migrants)
- Adapt available resources to provide **comprehensive sexual health care including PrEP**
- Define best models of care and access points (hospitals, sexual health clinics, GP)
- **Monitor** and evaluate PrEP implementation
- High risk people self-select for PrEP: HIV-infection detected at screening or soon after PrEP initiation
- Demonstrate the **public health benefit** of PrEP implementation ANRS « PREVENIR » project

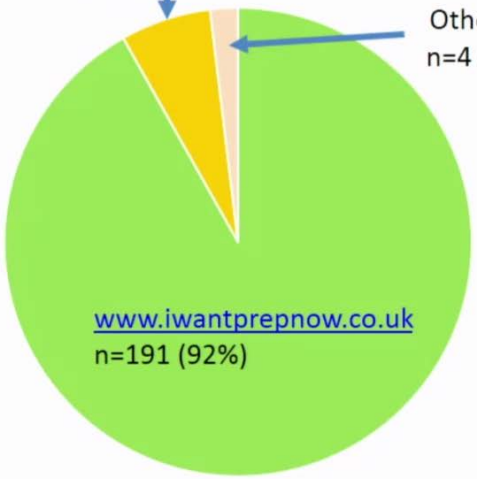
Generic TDF/FTC preparations used

Cipla TENVIR-EM
n=181

Emcure TAVIN-EM, n=2

Mylan RICOVIR-EM, n=1

Online PrEP suppliers



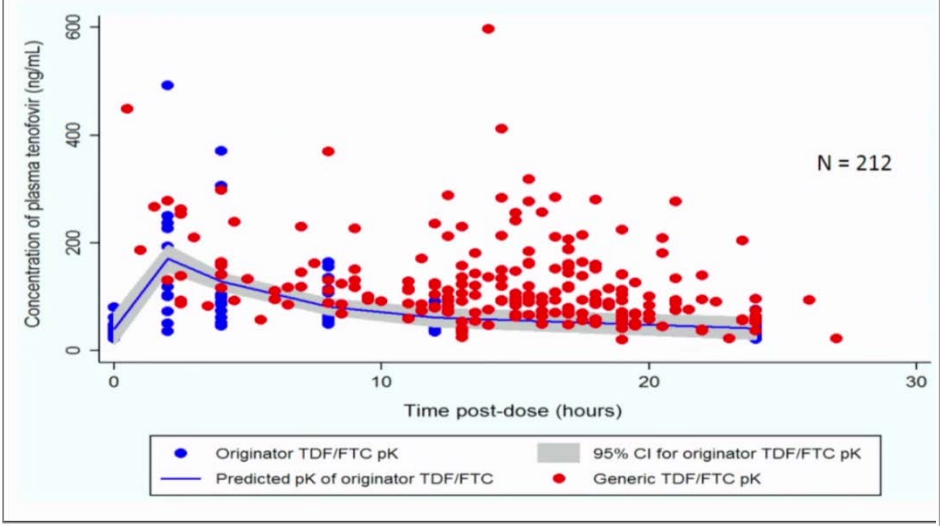
*Within www.iwantprepnow.co.uk:

www.unitedpharmacies-uk.md n=131
www.alldaychemist.com n=37
www.Iwantprepnow.co.uk n=20
www.aids-drugs-online.com n=3

**Other suppliers (1 person each):
www.everydaypharmacy.co.uk
www.buylowdrugs.com
www.clearskypharmacy.biz
www.inhousepharmacy.vu

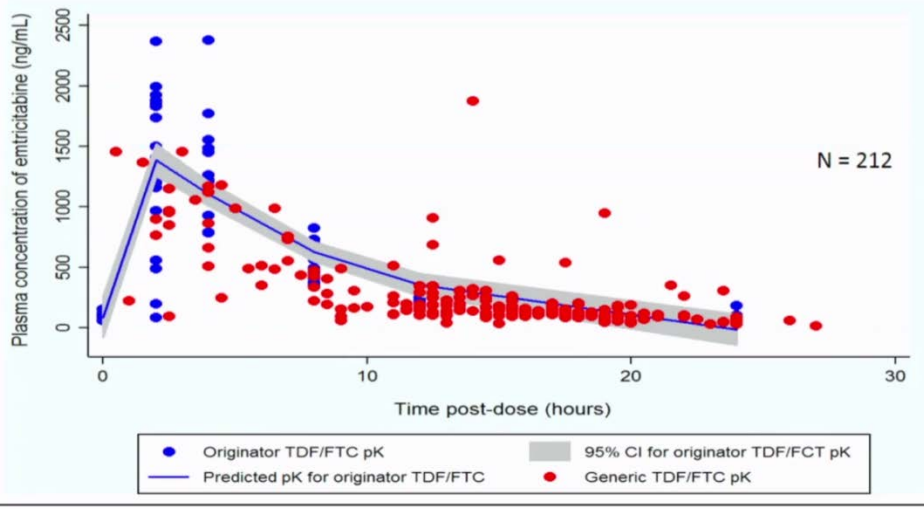
Plasma TFV concentrations

Median 103 ng/mL (range 21-597)
Time post-dose: median 15.5 hours (range 0.5 – 27)

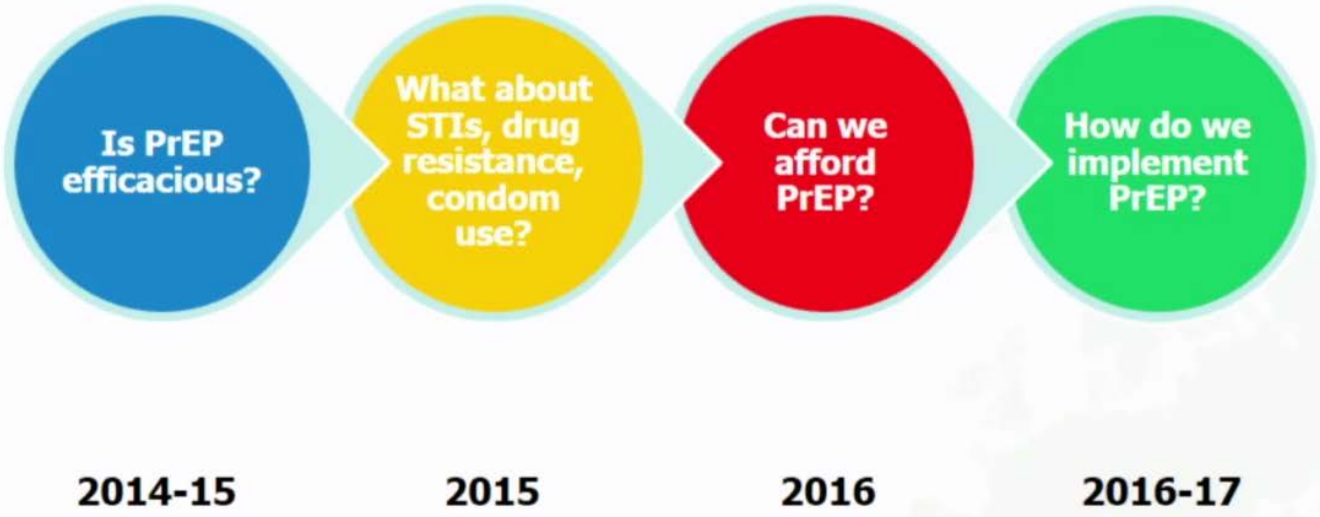


Plasma FTC concentrations

Median 142 ng/mL (range 17-1876)
Time post-dose: median 15.5 hours (range 0.5 – 27)



European discourse on PrEP: from a policy maker/public health perspective



2. Anti-retroviral therapy

When to Start? 2016

	AIDS/ symptoms	CD4 <200	CD4 200-350	CD4 350-500	CD4 >500
US DHHS 2016 www.aidsinfo.nih.gov	recommended				
IAS-USA 2016 JAMA 2016;316:191	recommended				
EACS 2016 www.europeanaidsclinicalsociety.org/	recommended				
UK 2016 www.bhiva.org	recommended				
WHO 2016 http://www.who.int/hiv/pub/guidelines/en/	strongly recommended *PRIORITY*			strongly recommended	

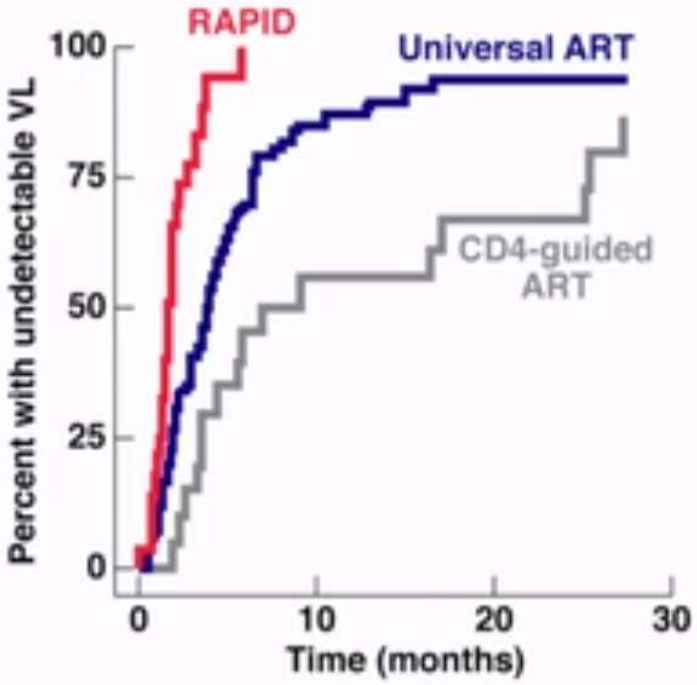
Treating HIV-Infected Individuals: A Triad of Pivotal ART Studies

- **SMART** — Episodic ART inferior to continuous ART
- **HPTN 052** — Early ART reduces HIV transmission to uninfected sexual partners by 93%
- **START** — Early ART reduces serious illness/death by 57%

San Francisco General Hospital RAPID Care Model

The Effect of Same-Day Observed Initiation of Antiretroviral Therapy on HIV Viral Load and Treatment Outcomes in a U.S. Public Health Setting

CD Pilcher, H Hatano et al.



The NEW ENGLAND JOURNAL of MEDICINE

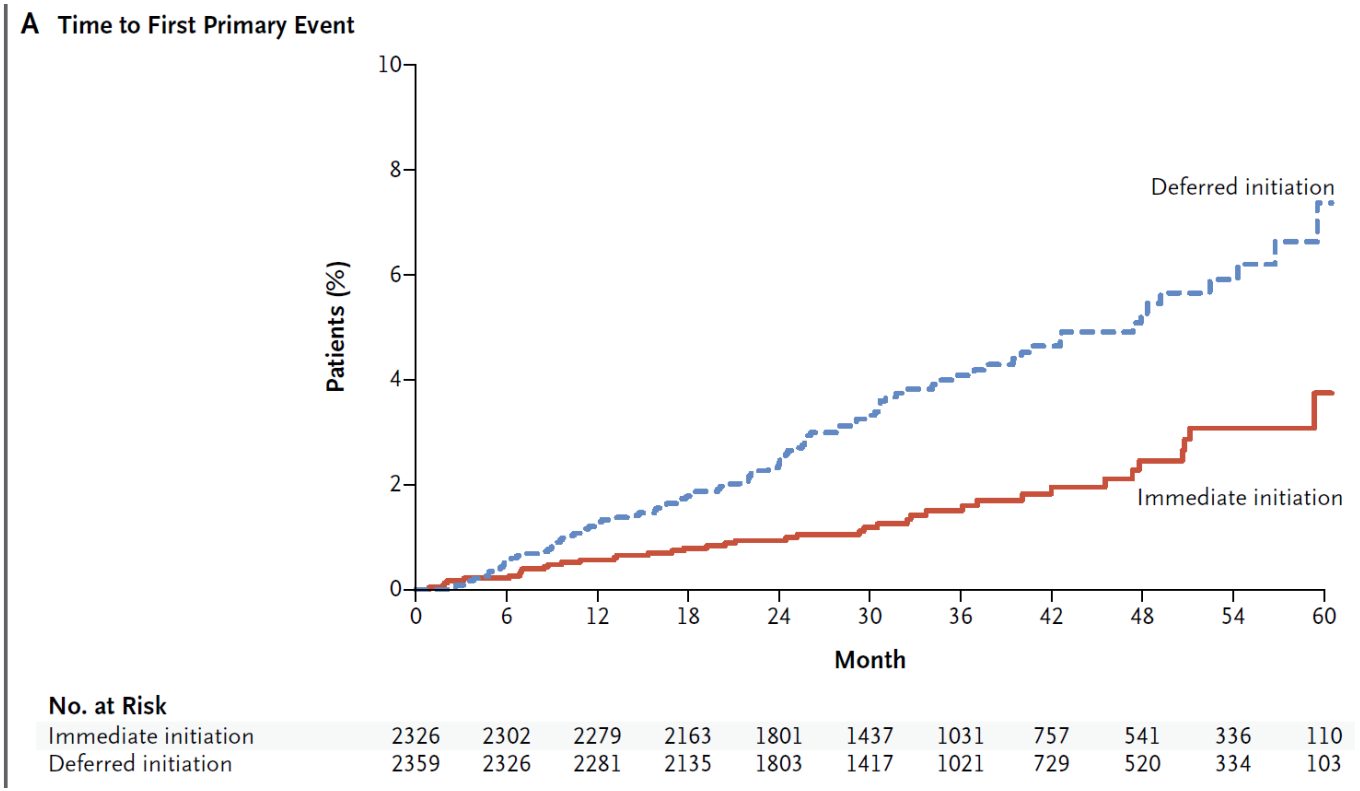
ESTABLISHED IN 1812 AUGUST 27, 2015 VOL. 373 NO. 9

Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group*

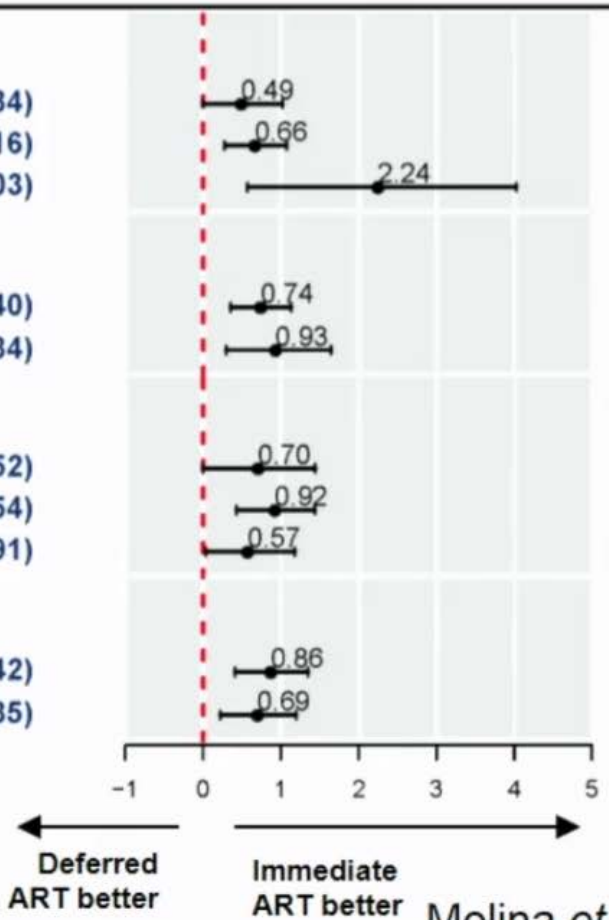
CD4 >500: immediate ART vs ART when CD4 <350

Primary end point = serious AIDS-related event or non–AIDS-related event (CVD, ESRF, decompensated liver disease, cancer)



Absolute risk reduction (ARR) and numbers need to treat (NNT) in subgroups -1

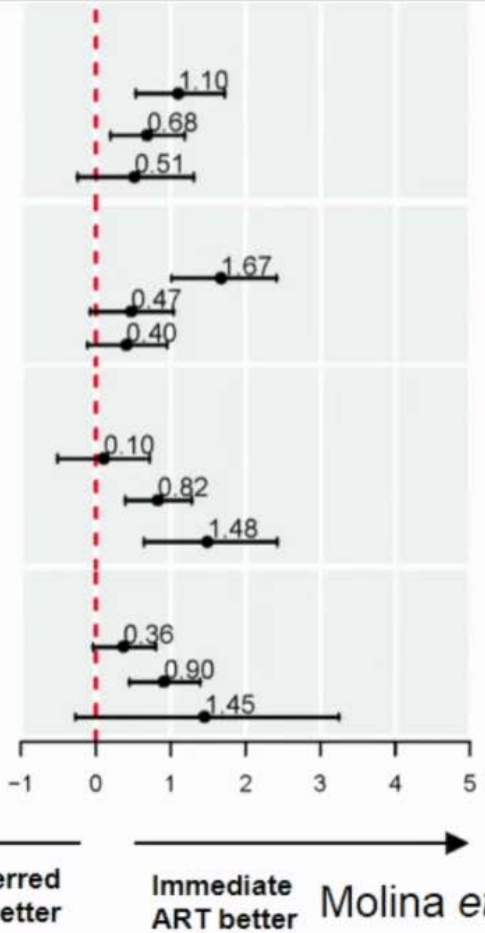
Subgroup	Pct. in Group	No. of Pts with Events (Rate per 100 PY) Imm. ART	Def. ART	ARR (Rate Def.−Imm.) with 95% CI	NNT	P−val. Homo−geneity
Age (years)						0.01
< 30	28.2	7 (0.36)	17 (0.84)	0.49	206	
30 – 49	60.0	21 (0.50)	48 (1.16)	0.66	151	
≥ 50	11.8	14 (1.78)	31 (4.03)	2.24	45	
Sex						0.63
Male	73.2	35 (0.66)	74 (1.40)	0.74	136	
Female	26.8	7 (0.42)	22 (1.34)	0.93	108	
Race						0.69
Black	30.1	15 (0.82)	28 (1.52)	0.70	142	
White	44.5	21 (0.63)	53 (1.54)	0.92	109	
Other	25.4	6 (0.34)	15 (0.91)	0.57	176	
Geographic region						0.62
High income	46.0	20 (0.56)	51 (1.42)	0.86	116	
Low/mod. inc.	54.0	22 (0.65)	45 (1.35)	0.69	144	



Molina *et al*, Durban 2016

ARR and NNT in Subgroups -2

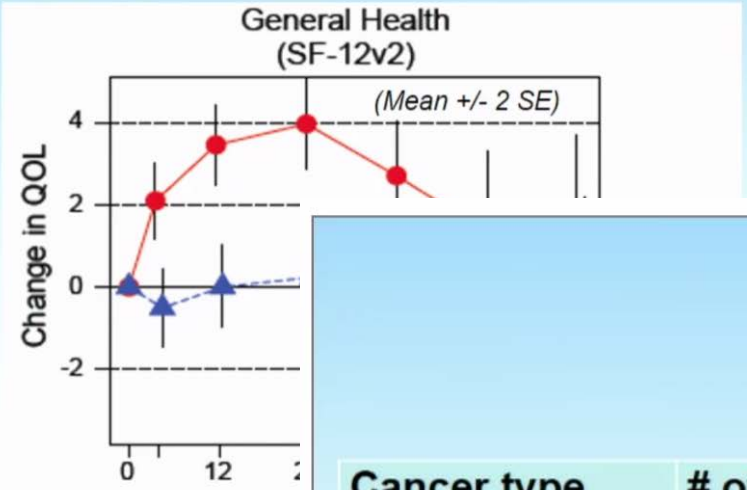
Subgroup	Pct. in Group	No. of Pts with Events (Rate per 100 PY) Imm. ART		Def. ART		ARR (Rate Def.−Imm.) with 95% CI	NNT	P−val. Homo−geneity
Baseline CD4 (cells/mm³)								0.41
< 600	31.5	10	(0.44)	35	(1.54)	1.10	91	
600 − 800	48.6	24	(0.70)	46	(1.38)	0.68	147	
> 800	19.9	8	(0.63)	15	(1.14)	0.51	196	
Baseline CD4:CD8 Ratio								0.005
< 0.5	27.8	7	(0.36)	40	(2.03)	1.67	60	
0.5 − 0.8	38.5	22	(0.81)	34	(1.27)	0.47	214	
> 0.8	33.7	12	(0.54)	21	(0.94)	0.40	248	
Baseline HIV RNA (cp/mL)								0.06
< 3,000	24.8	11	(0.67)	13	(0.77)	0.10	992	
3,000−50K	53.4	20	(0.53)	51	(1.36)	0.82	122	
>50K	21.7	11	(0.71)	32	(2.19)	1.48	67	
Framingham 10−year risk of CHD								0.13
<1.0	37.3	8	(0.32)	17	(0.68)	0.36	276	
1.0−9.9	53.1	21	(0.57)	54	(1.48)	0.90	111	
≥ 10	9.6	13	(1.90)	23	(3.34)	1.45	69	



Molina *et al*, Durban 2016

Change in QOL: General Health

Baseline: Mean (SD)= 72.5 (21.5) [GH scaled 0-100]



Similar

No. of participants:
Imm: 2091 1977 1
Def: 2119 1949 1
P-values, t-tests, unadju
<0.001 <0.001 <
Longitundinal mixed mo
Est. diff: 3.6 95% CI: 2.8

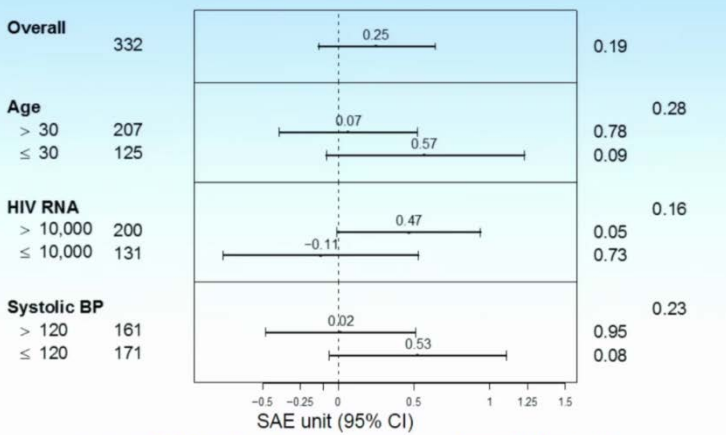
Cancer

Cancer type	# of events Immediate Group N=2326	# of events Deferred Group N=2359	Hazard Ratio (95% Confidence Interval)	P-value
Cancer, total[1]	14	39	0.36 (0.19-0.66)	0.001
Non-AIDS cancer	9	18	0.50 (0.22–1.11)	0.09
Kaposi's	1	11	0.09 (0.01–0.71)	0.02
Lymphoma	3	10	0.30 (0.08–1.10)	0.07

[1]Cervical cancer in 1 participant in the Immediate Group.

Borges et al, CID 2016

Small Arterial Elasticity: *Subgroup Analyses*



*Longitudinal Mixed Model, adjusted for baseline

Baker *et al*, CROI 2016

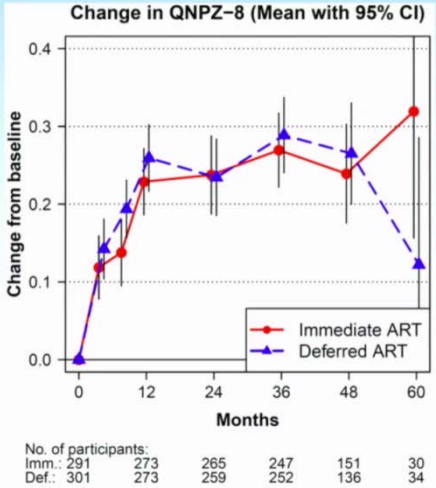
Pulmonary effects of immediate versus deferred antiretroviral therapy in HIV-positive individuals: a nested substudy within the multicentre, international, randomised, controlled Strategic Timing of Antiretroviral Treatment (START) trial

Ken M Kunisaki, Dennis E Niewoehner, Gary Collins, Bitten Aagaard, Nafisah B Atako, Elzbieta Bakowska, Amanda Clarke, Giulio Maria Corbelli, Ernest Ekong, Sean Emery, Elizabeth B Finley, Eric Florence, Rosa M Infante, Cissy M Kityo, Juan Sierra Madero, Daniel E Nixon, Ellen Tedaldi, Jørgen Vestbo, Robin Wood, John E Connett, for the INSIGHT START Pulmonary Substudy Group*

	FEV, slope (95% CI), mL/year	p value
Baseline smokers		
Immediate ART (n=135)	−32·9 (−58·5 to −7·4)	..
Deferred ART (n=155)	−29·7 (−54·3 to −5·0)	..
Difference	−3·3 (−38·8 to 32·2)	0·86
Baseline non-smokers		
Immediate ART (n=383)	−27·8 (−44·2 to −11·4)	..
Deferred ART (n=353)	−22·2 (−39·6 to −4·9)	..
Difference	−5·6 (−29·4 to 18·3)	0·65
Pooled analysis adjusted for baseline smoking status		
Immediate ART (n=518)	−29·1 (−42·9 to −15·4)	..
Deferred ART (n=508)	−24·5 (−38·6 to −10·3)	..
Difference	−4·7 (−24·4 to 15·1)	0·64
Pooled analysis adjusted for smoking status at each study visit		
Immediate ART (n=518)	−28·8 (−42·6 to −14·9)	..
Deferred ART (n=508)	−23·6 (−37·8 to −9·3)	..
Difference	−5·2 (−25·1 to 14·6)	0·61

Lancet Resp Med 2016

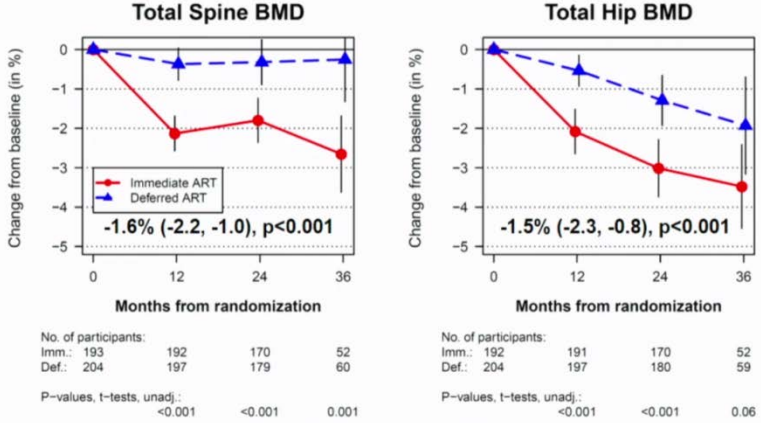
Quantitative neurological performance z score: 8 neuropsychological tests - % change from entry



- **Estimated difference Imm.– Def. groups:**
  -0.01 (95% CI: -0.06 to 0.03)
  P=0.63

Price, Wright et al, EACS 2015

BMD substudy % change from entry



Mean Follow-up – 2.2 years

Hoy, Grund Carr et al, EACS 2015

ART: What to Start? – Recommended/Preferred

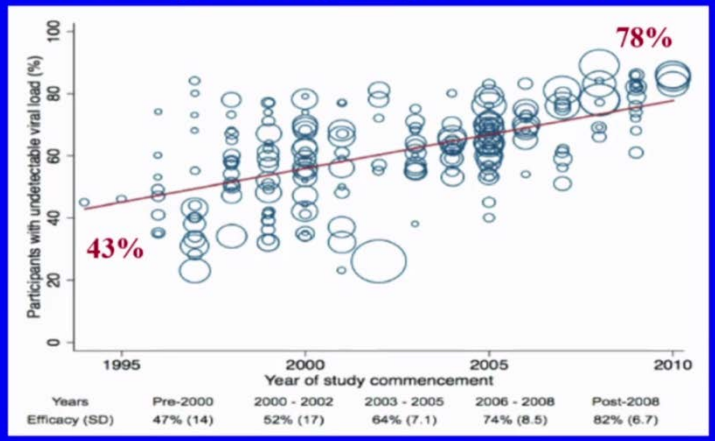
	NRTI	NNRTI	PI	II
US DHHS 2016 www.aidsinfo.nih.gov	TAF/FTC TDF/FTC ABC/3TC+	--	DRV/r	DTG, EVG, RAL
IAS-USA 2016 JAMA 2016;316:191	TAF/FTC ABC/3TC*	--	--	DTG, EVG, RAL
EACS 2016 www.europeanaidsclinicalsociety.org/	TAF/FTC TDF/FTC ABC/3TC+	RPV*	DRV/r or /c	DTG, EVG, RAL
UK 2016 www.bhiva.org	TAF/FTC TDF/FTC	RPV*	ATV/r DRV/r	DTG, EVG, RAL
WHO 2015 http://www.who.int/hiv/pub/guidelines/en/	TDF + 3TC or FTC	EFV	--	--

+ only with DTG

* performs less well/not recommended for baseline HIV RNA >100,000 and/or CD4 <200

ART Trials: Virologic Responses

114 studies through 2012, up to 3 years of f/u: ITT analyses



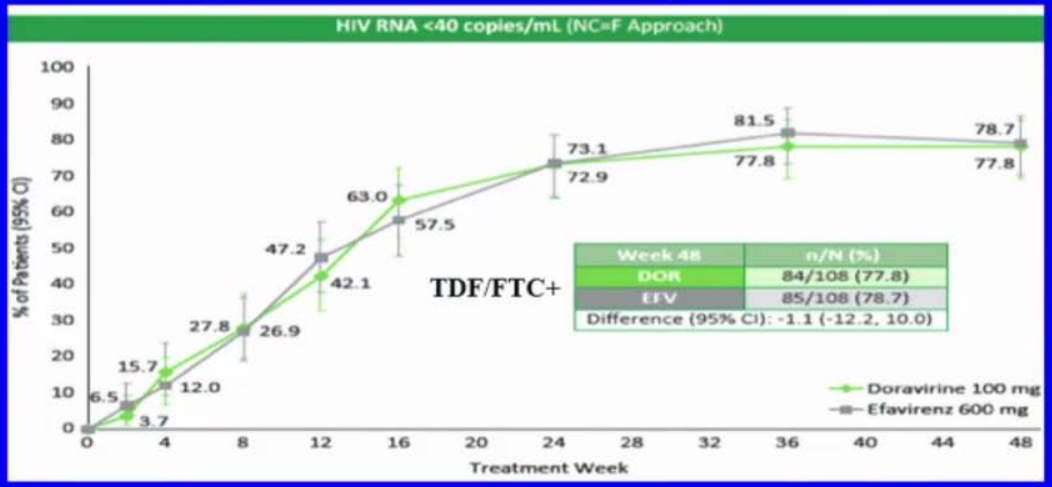
Carr PLoS One 2014;9:e97482

Virologic Responses – Newer Studies

Study (reference)	Study arm (N)	Regimen	HIV RNA <50 at 96 wks
ACTG 5257 Lennox Ann Intern Med 2014	605 601 603	2 NRTI + ATV/r 2 NRTI + DRV/r 2 NRTI + RAL	88% 89% 94%
SPRING-2 Raffi Lancet Infect Dis 2013	411	2 NRTI + DTG	81%
SINGLE Walmsley JAIDS 2015	414	ABC/3TC + DTG	80%
GS-US-2,92-01040111 Wohl JAIDS 2016	866 867	TAF/FTC/EVG/c TDF/FTC/EVG/c	87% 85%

Newer Approaches

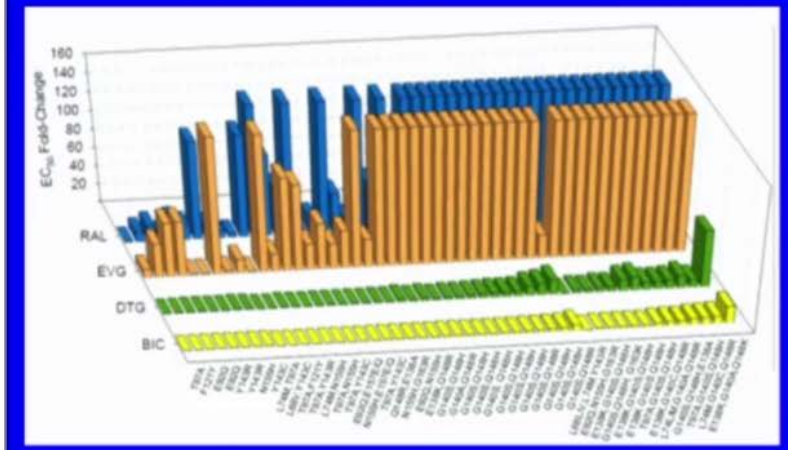
- Active against drug-resistant strains
  - Doravirine (NNRTI)
    - Active in vitro against viral strains with K103N, Y181C, G190A, E101K, E138K or K103N/Y181C Lai AAC 2014;58:1652-1663
    - Phase 1 (treatment-naïve, N=18): Schurmann AIDS 2016;30:57-63
    - Phase 2 (treatment-naïve vs. EFV): Gatell CROI 2016 #470

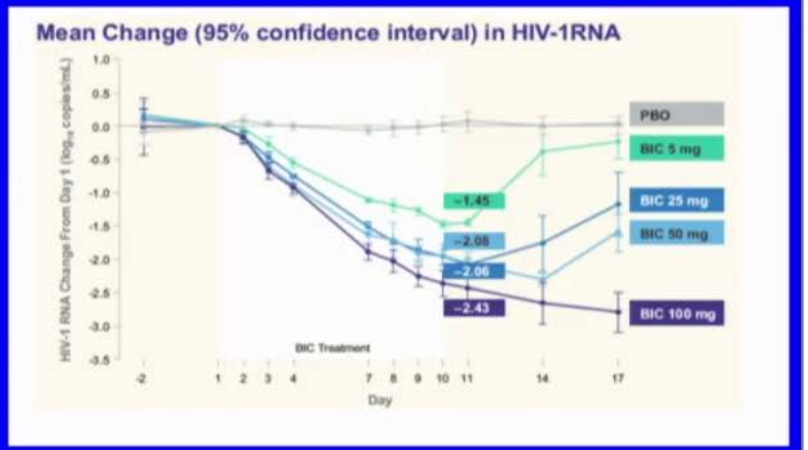


Drug-related adverse events:
DOR 31%
EFV 56%

Newer Approaches

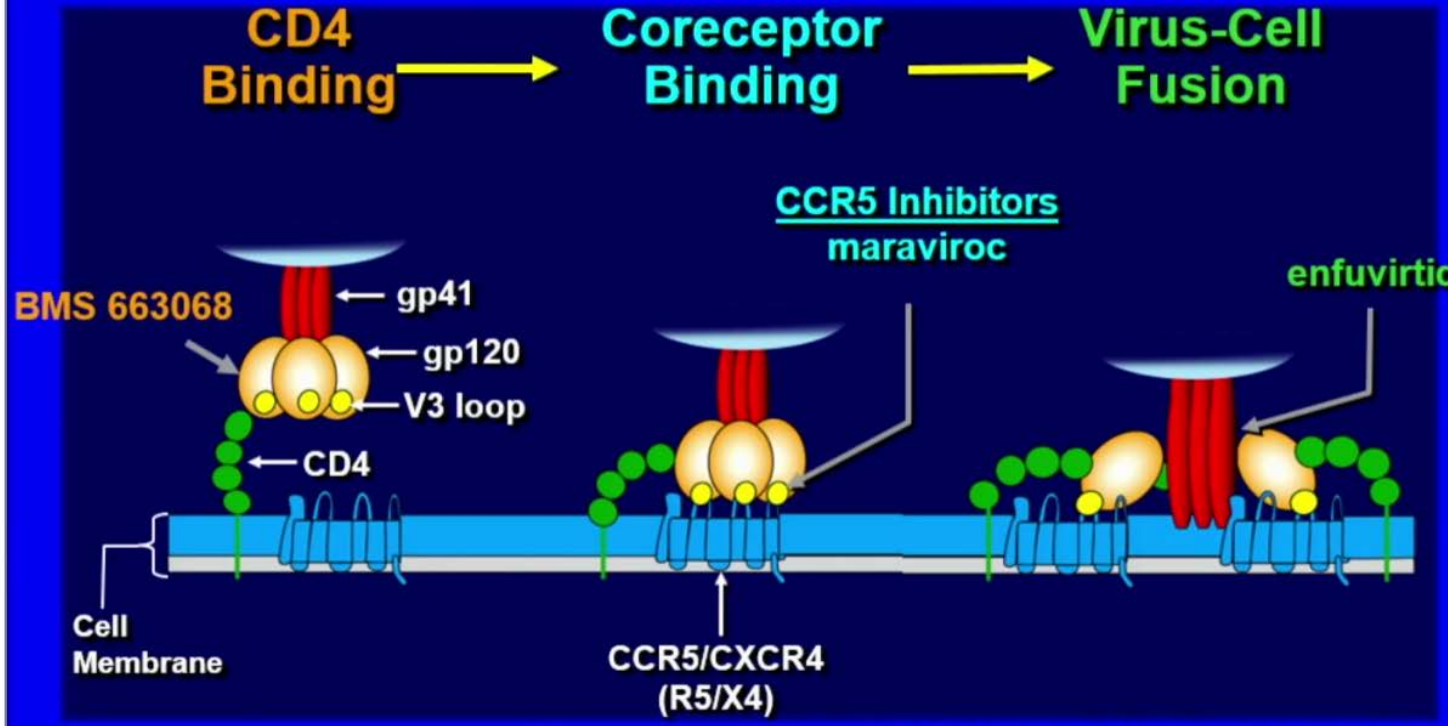
- Active against drug-resistant strains
  - Bictegravir
    - Active in vitro against viral strains with integrase resistance
      Tsiang Antimicrob Agents Chemo 2016 (epub 9/19/16)
    - Phase 1 (integrase inh naïve, N=20): Gallant ASM Microbe 2016 #415





- Phase 2/3 in progress

HIV Entry Inhibitors

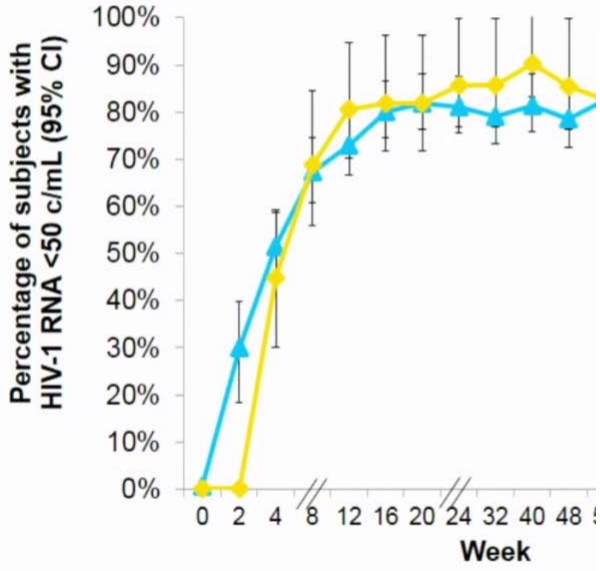


Adapted from Moore JP, *PNAS* 2003;100:10598-10602.

BMS-663068: Oral HIV Attachment Inhibitor

- Prodrug of **BMS-626529;** inhibits CD4 binding to gp120

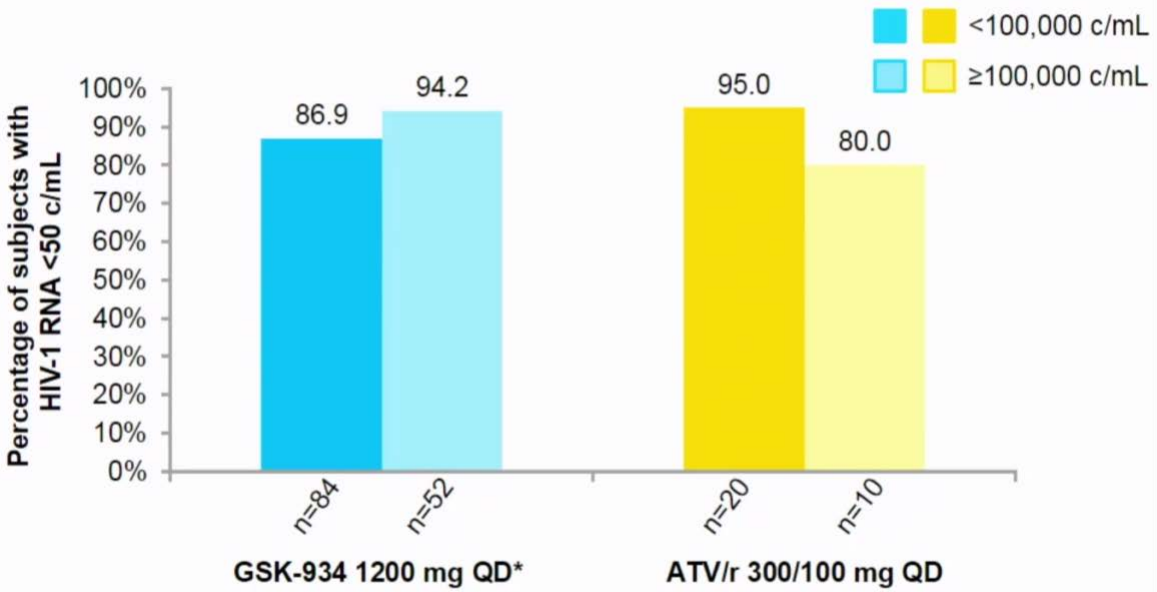
Efficacy At Week 96: Observed Analysis



* BMS-663068 1200 mg QD was selected as the open-label continuation dose after W
Previously presented in DeJesus E *et al.*, *CROI* 2016: Poster 472.
GSK3684934 was formerly BMS-663068.

HIV Glasgow; October 23-26,

HIV-1 RNA <50 c/mL by Baseline Viral Load: Observed

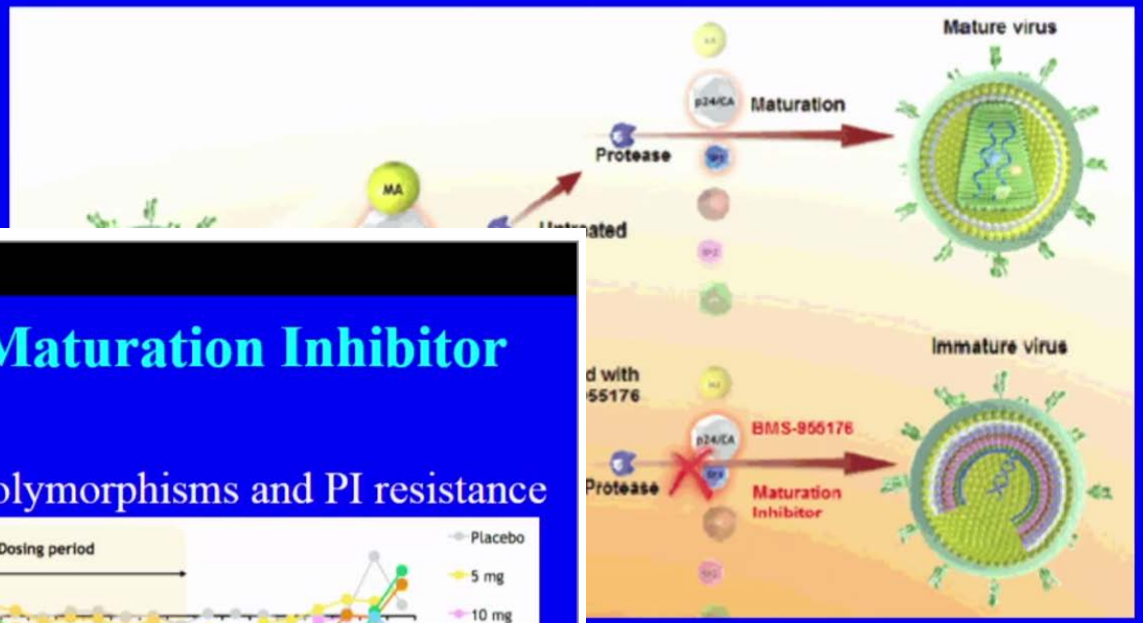


* BMS-663068 1200 mg QD was selected as the open-label continuation dose after Week 48.
Observed population: subjects receiving ≥1 dose of study drug and with plasma HIV-1 RNA data within the Week 96 window. GSK3684934 was formerly BMS-663068.

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

HIV Glasgow; October 23-26, 2016; Glasgow, UK

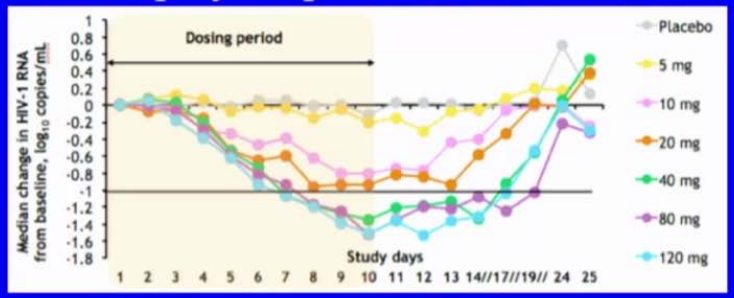
HIV Maturation Inhibitors (MI)



BMS-955176: Oral HIV Maturation Inhibitor

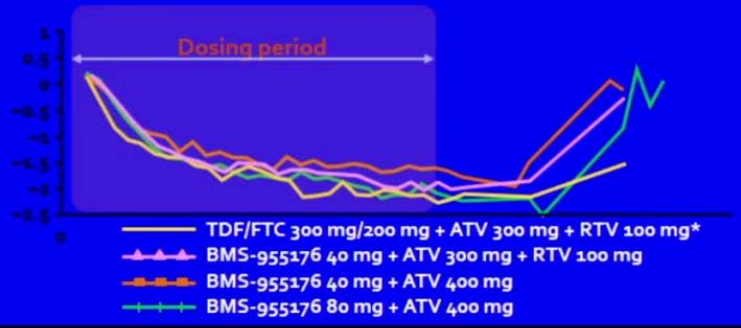
- Binds tightly to HIV GAG
- active *in vitro* against strains with polymorphisms and PI resistance
- Phase 1 (N=40)

  Hwang CROI 2015, #114LB

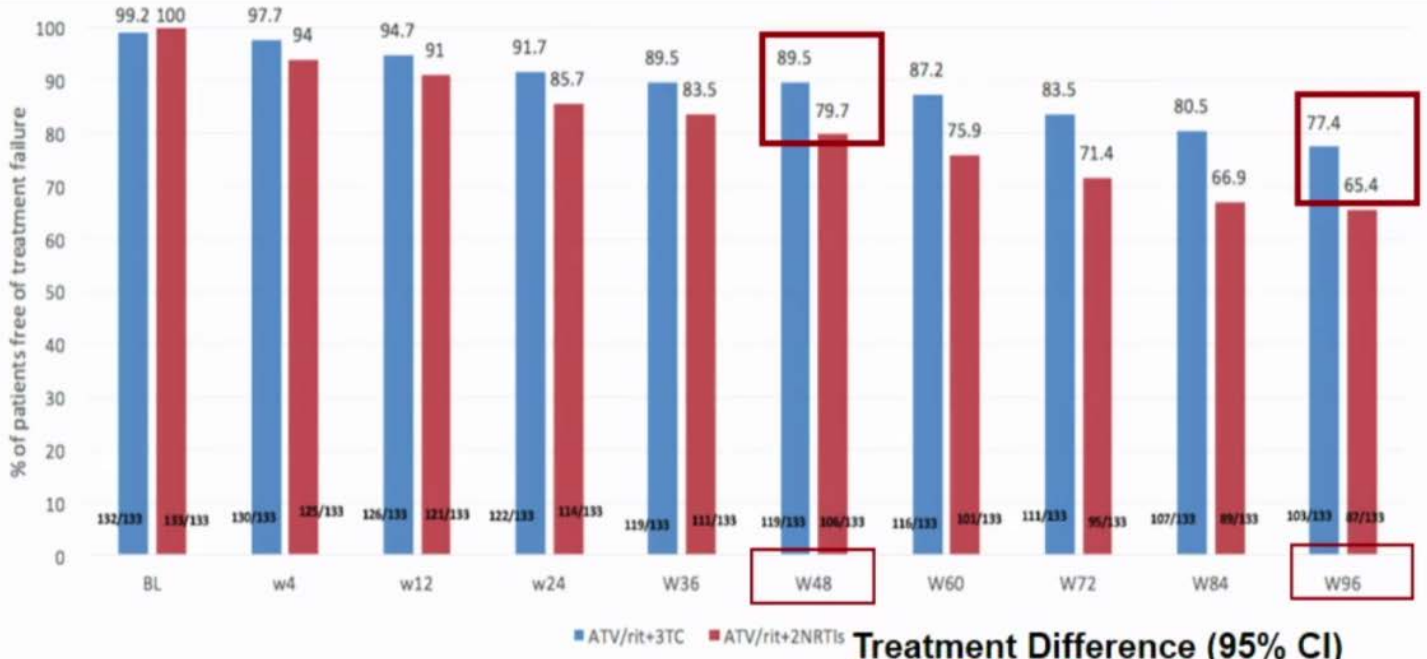


- Phase 2a (N=28)

  Hwang IAS 2015 #TUAB0106LB



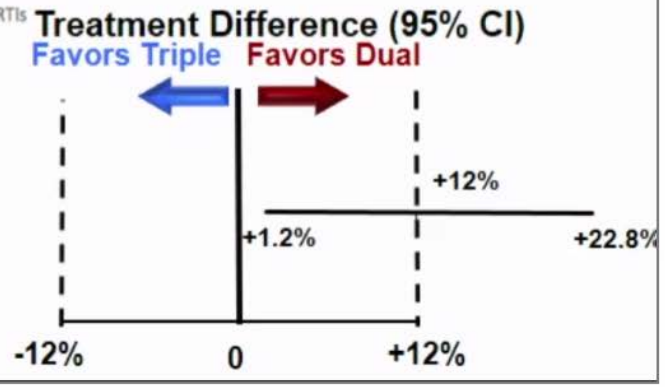
Patients free of treatment failure (ITT S=F)



96 weeks free of TF:

Dual therapy 77.4% (95% CI 70.3-84.5)

Triple therapy 65.4% (95% CI 57.3-73.5)



Causes of treatment failure

	ATV/rit+3TC N=133	ATV/rit+2 NRTIs N=133	p
Any cause	30 (22.6)	46 (34.6)	**0.030**
Virological Failure	2 (1.5)*	9 (6.8)	0.060
Adverse events (potentially treatment-related)[i]	7 (5.3)	11 (...)	...
Adverse events (not treatment related)[ii]	3 (2.3)	5 (...	
Withdrawal of consent	6 (4.5)	9 (6	
Loss to follow up	10 (7.5)	7 (5	
Other	2 (1.5)	5 (...	

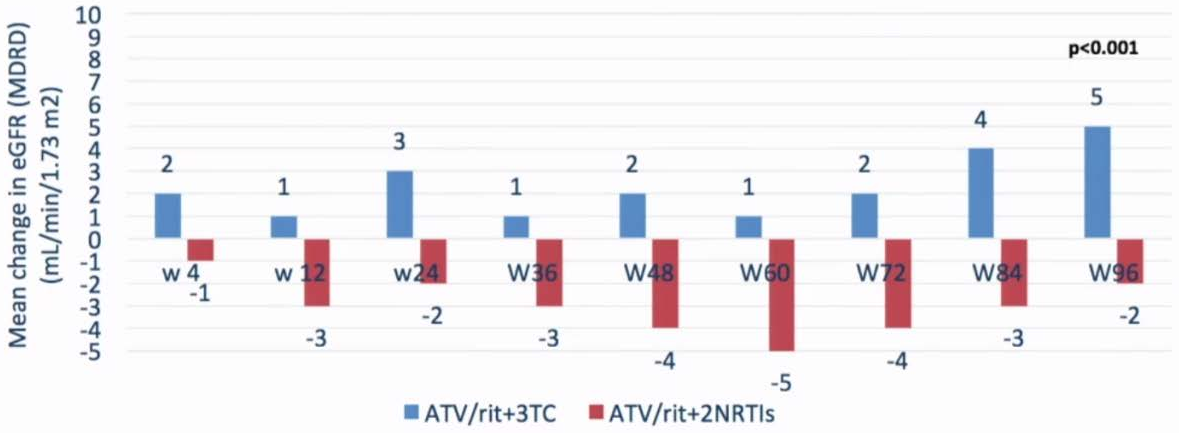
Values are expressed as n (%)
* One VF at baseline, before treatment simplification.

Notes:

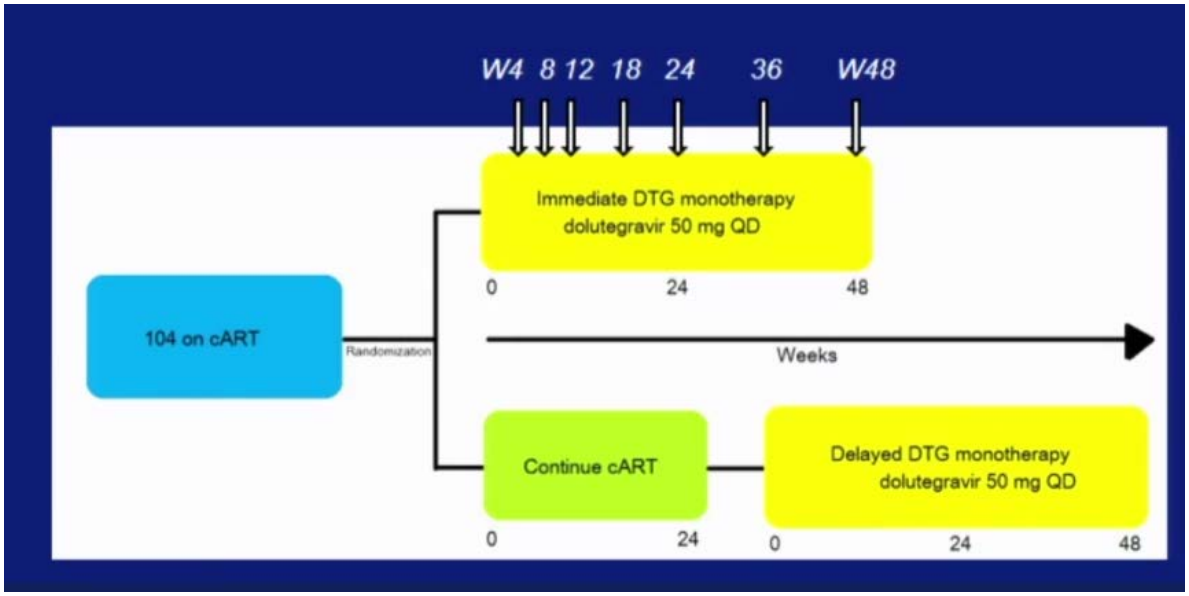
i. **DT**: skin rash (w4), renal colic (w26 and w49), biliary colic (w60), pancreatitis (w62), hypertriglyceridemia (w72), creatinine increase (w75); **TT**: creatinine increase (w3 and

Evolution of renal function

Renal function (eGFR MDRD)



DOMONO trial



Results primary endpoint :

Erasmus MC

Week 24 <200 c/ml DTG monotherapy versus cART

1/51 patient discontinued DTG at 12wks (with VL<50c/ml) for disturbed sleep

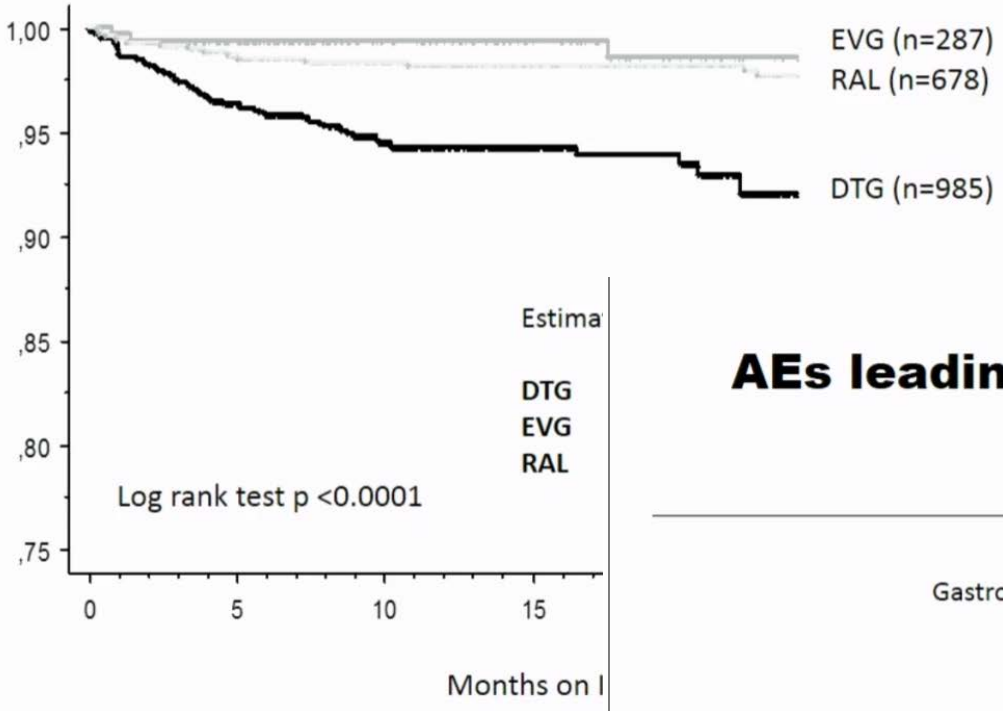
DTG n=49/50 (98%)
cART n=53/53 (100%)
} *Delta 2% Exact 95% C.I. +12% to -5% (*)*

⇒ 95 remaining and 85 have reached week 24

VL <200 in 83/85 (98%, 95% C.I. 91-99) ➞ *2 virological failures*

VL <50 in 79/85 (93%, 95% C.I. 85-97)

Discontinuation due to neuropsychiatric AEs (all other events censored)



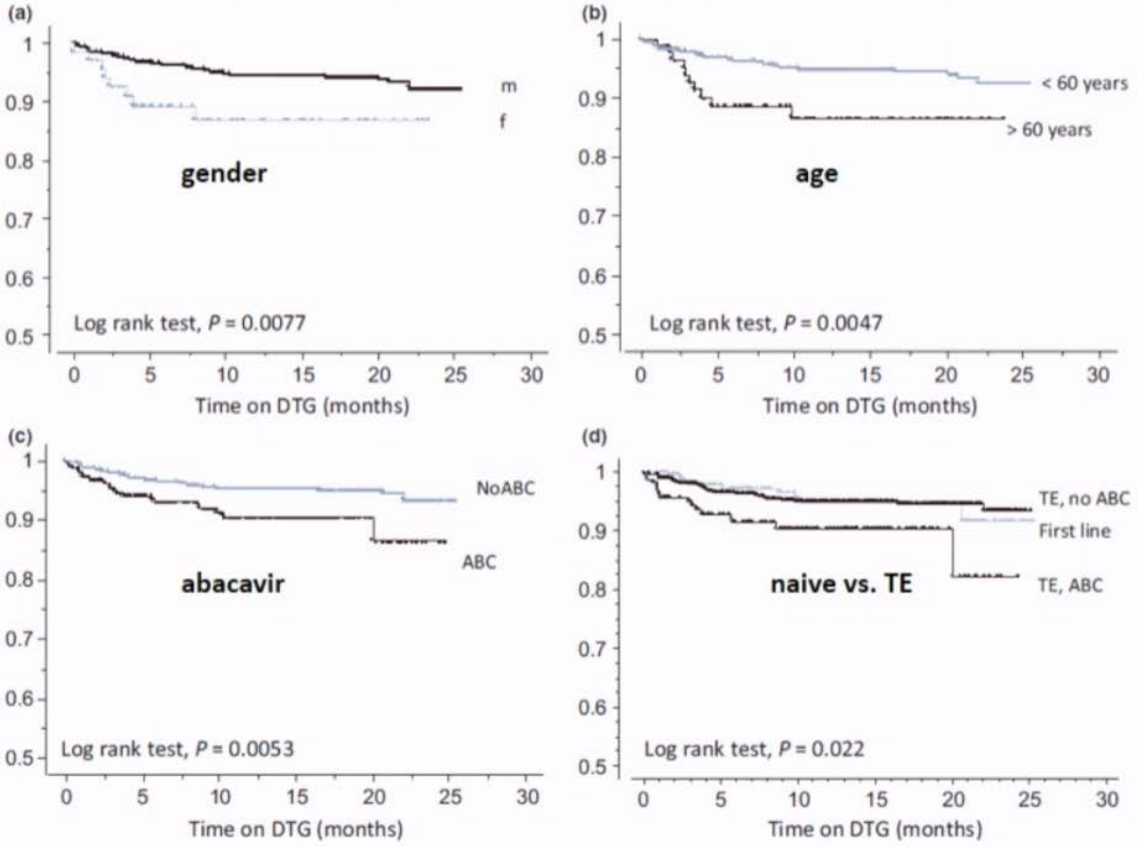
AEs leading to INSTI discontinuation

	Dolutegravir n=985	Elvitegravir n=287	Raltegravir n=678
Renal % (n)	0.2 % (2)	3.5 % (10)	0.0 % (0)
Gastrointestinal % (n)	0.7 % (7)	2.8 % (8)	0.9 % (6)
Hepatic % (n	0.1 % (1)	0.0 % (0)	0.1 % (1)
Skin % (n)	0.3 % (3)	0.7 % (2)	0.1 % (1)
Other % (n)	0.5 % (5)	1.4 % (4)	0.9 % (6)
Neuropsychiatric % (n)	5.0 % (49)	1.0 % (3)	2.1 % (14)
Neuropsychiatric Adverse Events*			
Insomnia, sleep disturbances	36	2	4
Poor concentration, slow thinking	8	0	0
Dizzyness	13	1	3
Headache, paraesthesia	16	1	6
Depression	7	0	1

* More than one symptom possible, as documented

Time on DTG (n=985)

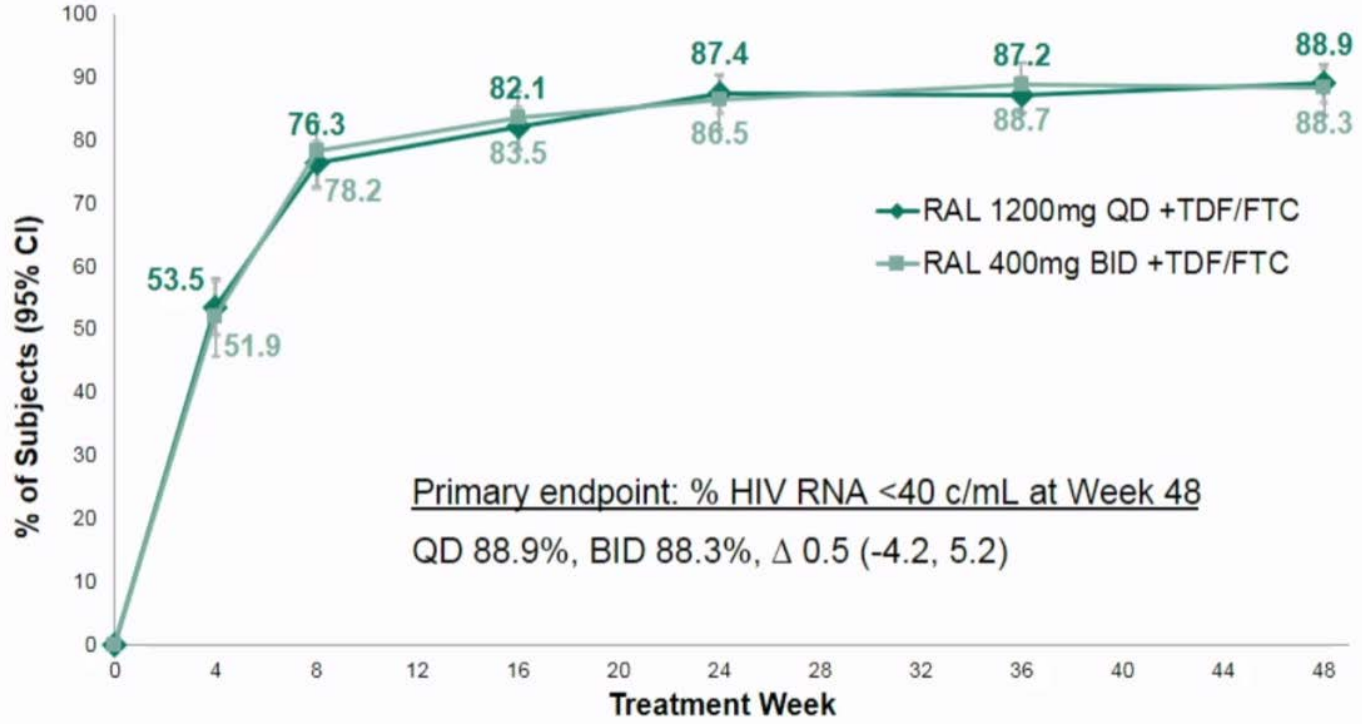
Neuropsychiatric AEs (all other events censored)



ONCEMRK: Multicenter, Double-blind, Randomized Controlled Trial

Primary Hypothesis: RAL 1200 mg QD is non-inferior to RAL 400 mg BID, each in combination with TDF/FTC, as assessed by the proportion of subjects achieving HIV RNA <40 c/mL at Week 48 (non-inferiority margin of 10 percentage points).

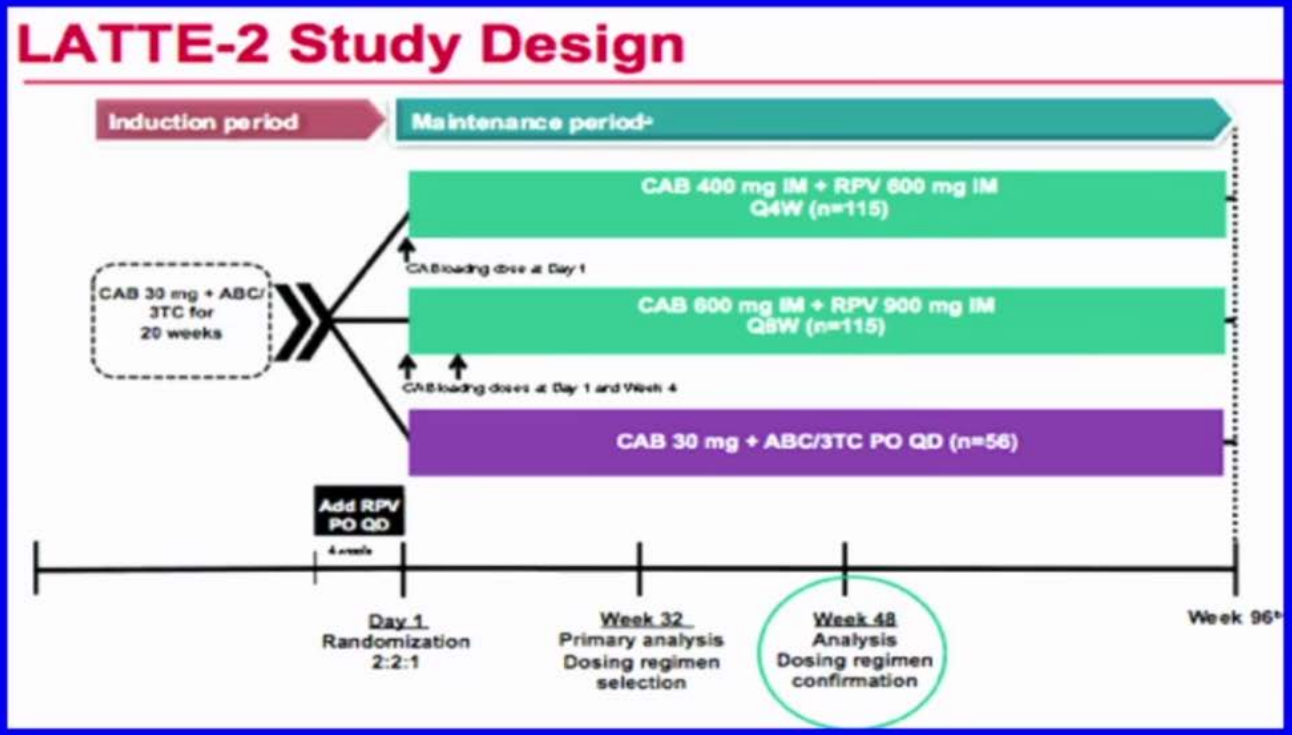
HIV RNA <40 copies/mL (NC=F; snapshot)



- CD4 increase (cells/mm^3), Week 48 (OF): QD 232, BID 234, Δ -2 (-31, 27)

LATTE-2: CAB + RPV IM Maintenance

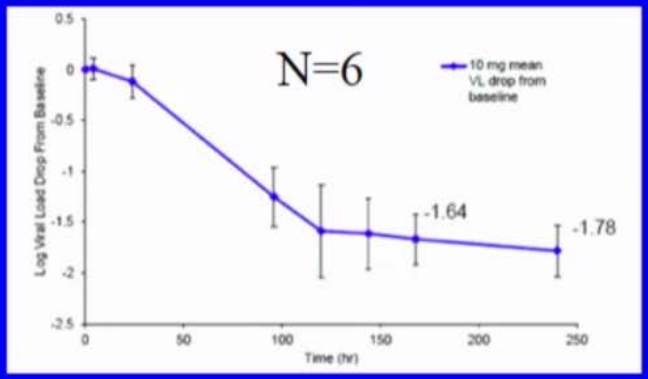
Phase 2b multicenter, parallel group, open-label study
Study population: Rx-naïve individuals (N=309)

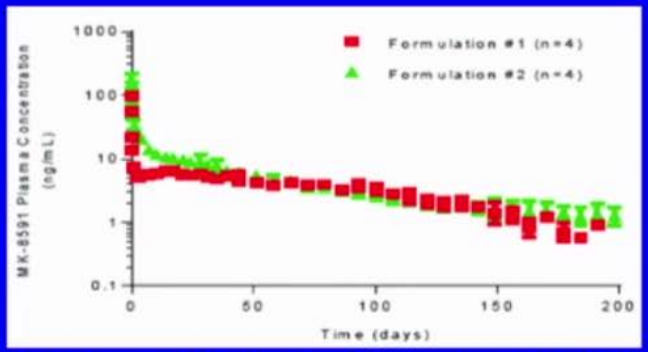


Margolis IAS 2016 #THAB0206LB

MK-8591 (EFdA)

- 4’-ethynyl-2-fluoro-2’-deoxyadenosine; EFdA
- Non-obligate chain terminator
- Inhibits RT by preventing translocation (NRTTI)
- Potent antiviral activity (PBMC EC50 = 0.2 nM) with broad coverage (HIV-1, HIV-2, MDR strains)





Friedman CROI 2016 #437LB; Grobler CROI 2016 #98

3. Access and cost

The UK National Health Service is refusing patients treatment, because of high prices

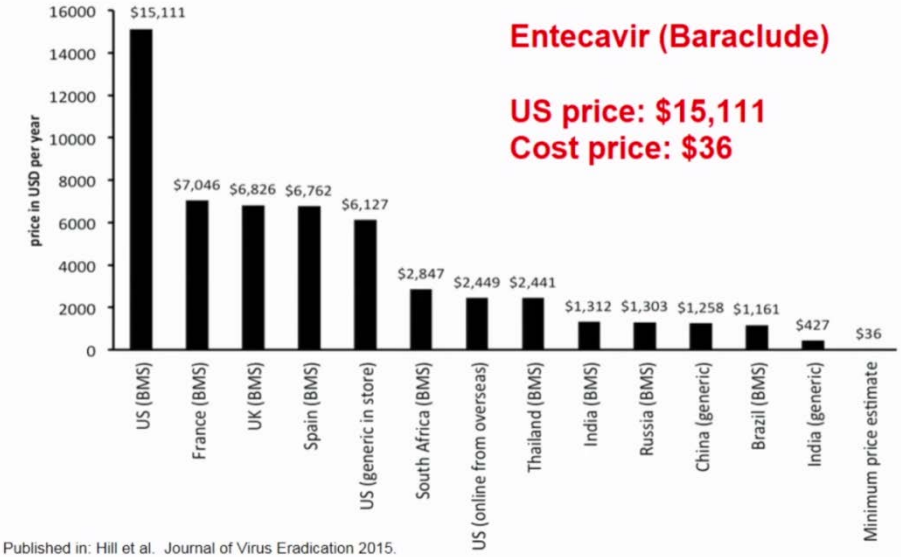
PrEP – TDF/FTC	£4800 per year
HCV DAAs	£30,000 to £100,000 per cure
Cancer Drugs Fund	Shut down – prices too high

HCV DAAs: Prices in USA and India versus Target

Drug	Current US price (lowest)	Current lowest Indian market price	Target price
Sofosbuvir	$49,680	$324	$62
Daclatasvir	$50,653	$153	$14
SOF+LDV	$56,700	$507	$96
SOF+VEL	$74,760	-	$181-216

Gotham D, Barber M, Fortunak J, Pozniak A, Hill A. Rapidly falling costs for new hepatitis C direct-acting antivirals (DAAs): potential for universal access. Abstract number A-792-0516-01639, presented at AIDS2016, Durban.

Entecavir for Hepatitis B cost per person/year by country



Entecavir (Baraclude)

US price: $15,111
Cost price: $36

Published in: Hill et al. Journal of Virus Eradication 2015.

Active Pharmaceutical Ingredient

Raw drug substance

Database www.indiainfodrive.com
exports of API from India to other
with costs per kilogram of API, for

From API cost/kg to target price

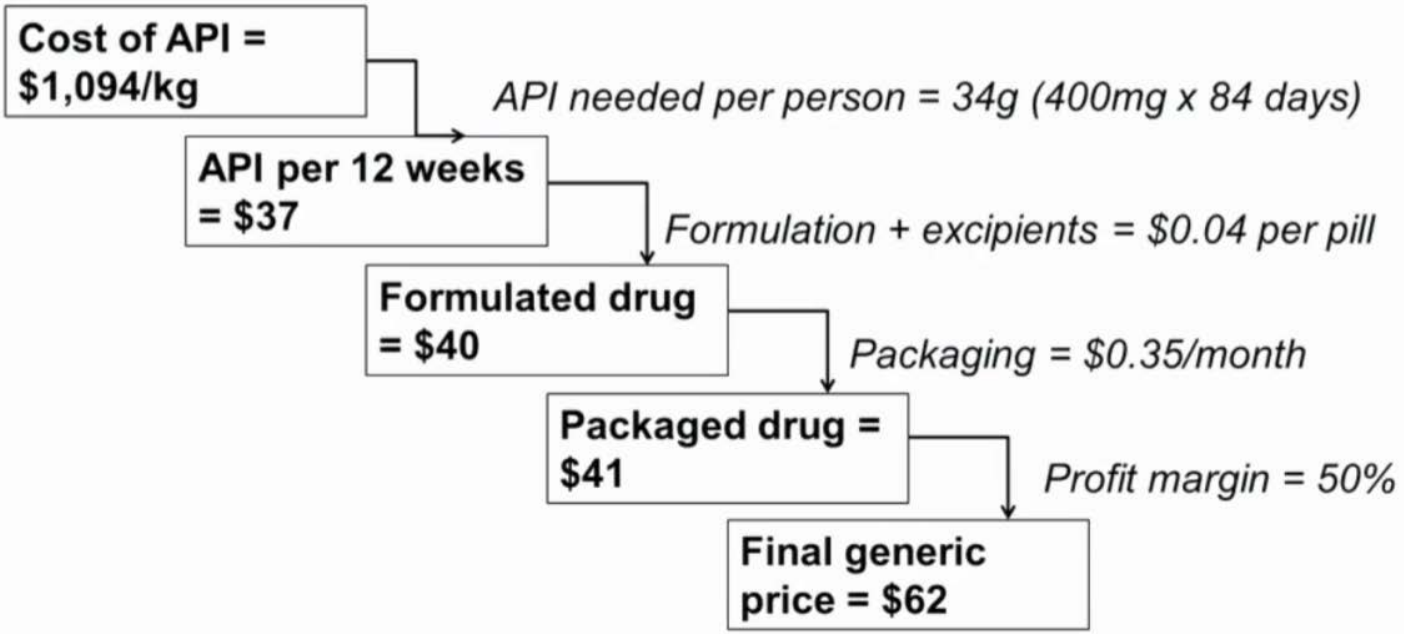
API price/kg x grams per treatment course

+ $0.04 / tablet for excipients and tableting,
+ $0.35/month for formulation
x 10-50% profit margin

(10% for mass-produced drugs e.g. HIV, TB)

Gotham D, Barber M, Fortunak J, Pozniak A, Hill A.
Abstract number A-792-0516-01639, presented at AIDS2016, Durban.

Target generic price of sofosbuvir (12 weeks)



Gotham D, Barber M, Fortunak J, Pozniak A, Hill A.
Abstract number A-792-0516-01639, presented at AIDS2016, Durban.

HIV: ARV Patent Expiry dates: 2016-2029

10 years (2016-2026) when many drugs are available as individual generics, but co-formulated versions are still on patent

2015: ZDV, 3TC, NVP, EFV, RTV – already generic
2016: ABC/3TC, LPV/r
2017: TDF/3TC, FTC, ATV/r, DRV/r
2018: ATV/r
2019: ETR, DRV/r

2025: Raltegravir
2026: TDF/FTC/EFV (Atripla), TDF/FTC/RPV (Complera),
2029: ABC/3TC/DTG (Triumeq), TAF/FTC/ELV/c

Medecins Sans Frontieres 2016: Untangling the web of ARV price reductions

Widespread access to generics

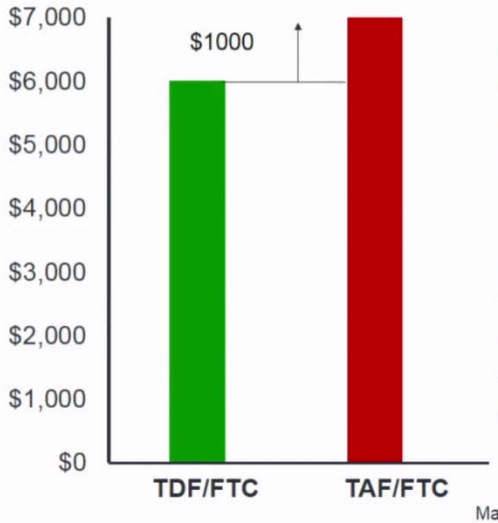
When patents have expired, drugs should be available worldwide, at close to the cost of production

However, few national health services know these costs

There is widespread over-charging. Pricing transparency is needed (WHO panel)

Lower costs for generics could drive down patented drug prices in the same therapeutic area

Value of patented drugs before generics have been approved

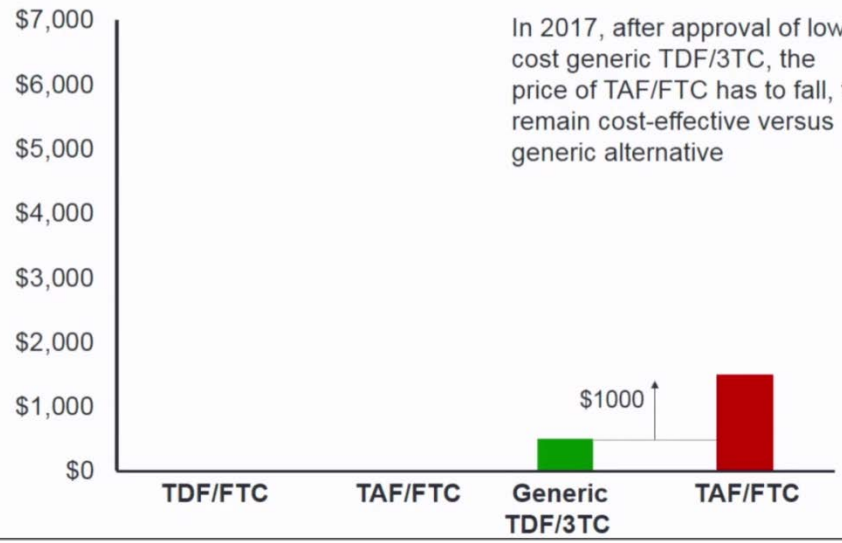


Pharmaceutical company negotiates additional value of new drug versus price of current branded version

For example:
Tenofovir alafenamide (TAF) versus
Tenofovr disoproxil fumarate (TDF)

Mayer K et al. Clin Infect. Dis 2016, 62: 915-918

Value of patented drugs after generics have been approved



In 2017, after approval of low-cost generic TDF/3TC, the price of TAF/FTC has to fall, to remain cost-effective versus generic alternative

Options if drugs still patented - Voluntary licenses

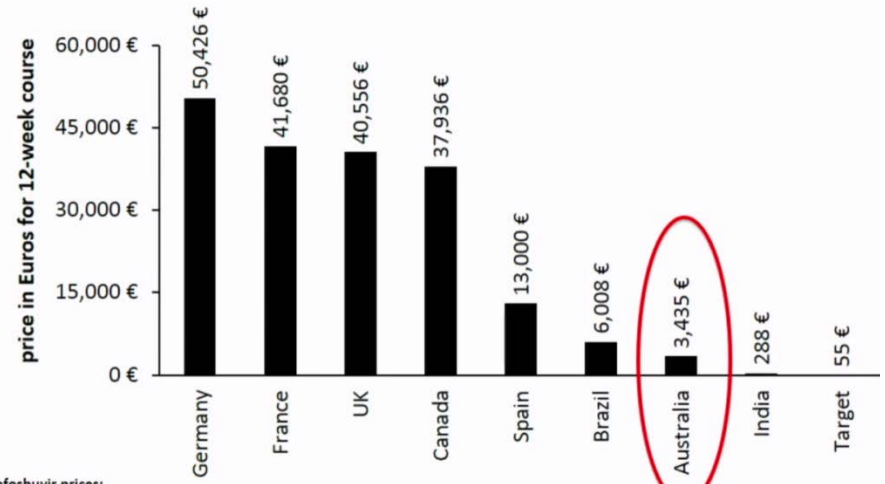
Some pharmaceutical companies allow cheap generics to be sold in certain low and middle income countries, with voluntary licenses. However:

1. China, South America, Russia and Eastern European countries are not included in most of these agreements. As a result, prices in these countries can be unaffordable

2. Other countries may have voluntary licenses but if the company does not register the drug for regulatory approval, then the drug cannot be accessed

3. Merck and AbbVie have no voluntary licenses for their Hepatitis C treatments.

Price of sofosbuvir by country (12 weeks)



Sofosbuvir prices:

1. Canada (Quebec): http://www.ramq.gouv.qc.ca/SiteCollectionDocuments/liste_med/liste_med_2016_10_03_fr.pdf
2. France: http://www.medecinsdumonde.org/actualites/presse/2016/09/29/mdm-soppose-au-brevet-sur-le-sovaldir-decision-le-5-octobre-2016
3. Germany: medizinfuchs.de
4. Spain: http://politica.elpais.com/politica/2016/04/05/actualidad/1459873421_480033.html?id_externo_rsoc=TW_CC
6. UK: British National Formulary 2016
7. Brazil: http://www.portaltransparencia.gov.br/despesasdiarias/empenho?documento=250005000012015NE801493
8. Australia: Based on total annual government expenditure (AU$200 million) and 40,000 treated in 2016
9. India: http://hepcasia.com/wp-content/uploads/2016/03/31-Jan-2016-Indian-generic-sofosbuvir.pdf

The Australian "All you can Treat" contract for Hepatitis C

Contract for $1 billion Australian dollars, over 5 years, with a group of pharmaceutical companies.

For €138 million/ year, unlimited treatment numbers
In 2016, 40,000 people will be treated (20% of epidemic)

Unit cost per DAA treatment = €3,450 / person

If this price is acceptable in Australia, we should have access to DAAs at the same prices in Europe, to acheive elimination of Hepatitis C across our region.

Adapted from "The New HCV treatment Era in Australia: Early Lessons"
Presented at: http://www.hepatitis.org.au/ehome/viralhepatitis2016/411320/

A new option for access to treatment: HIV and Hepatitis C buyers clubs

There are many companies willing to export generic PrEP and DAAs into Europe and North America

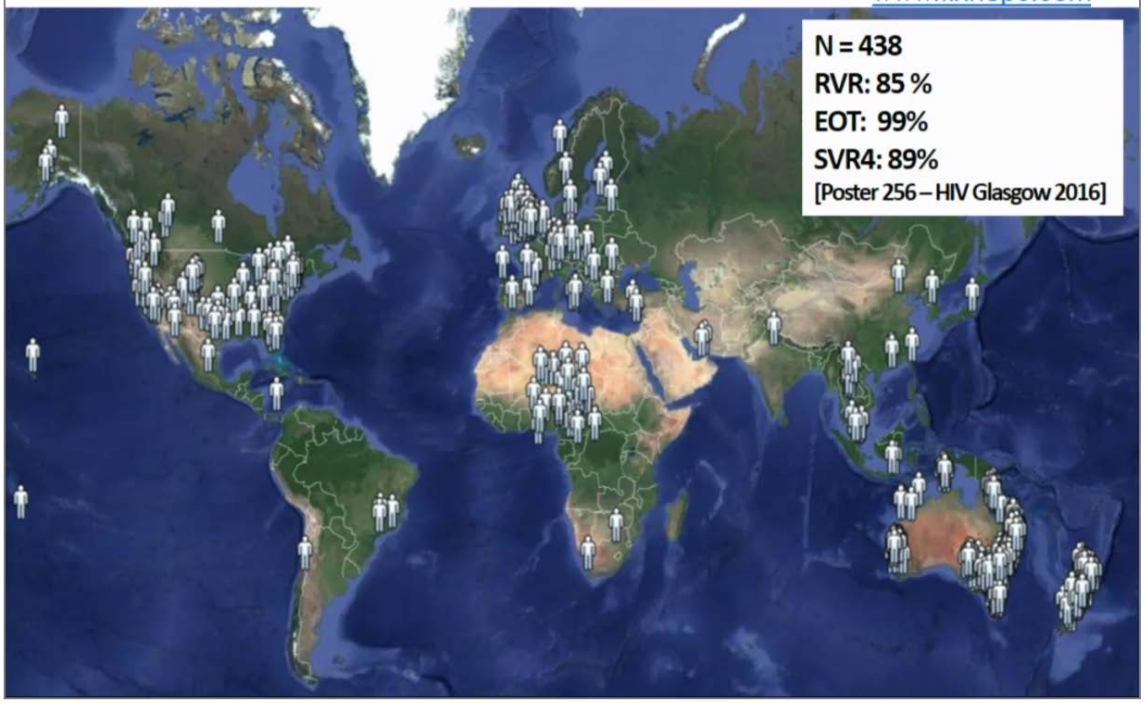
Several generic ARVs are already approved by the US Food and Drug Administration and the World Health Organization.

Generic PrEP or DAAs can be bought online in 10 minutes. Prices are falling rapidly.

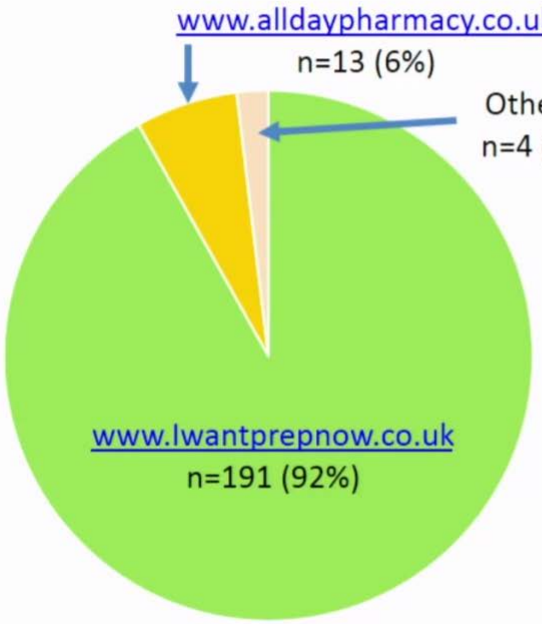
www.alldaychemist.com
www.iwantprepnow.co.uk
www.fixhepc.com
www.myhepc.info

FixHepC Buyer's Club

www.fixhepc.com



Dean Street Cohort: online suppliers of PreP



*Within www.Iwantprepnow.co.uk:

www.unitedpharmacies-uk.md n=131
www.alldaychemist.com n=37
www.Iwantprepnow.co.uk n=20
www.aids-drugs-online.com n=3

**Other suppliers (1 person each):
www.everydaypharmacy.co.uk
www.buylowdrugs.com
www.clearskypharmacy.biz
www.inhousepharmacy.vu

56 DEAN STREET
DEAN STREET express
Imperial College London
Chelsea and Westminster Hospital NHS
NHS Foundation Trust

The new "$90 $90 $90" in 2017

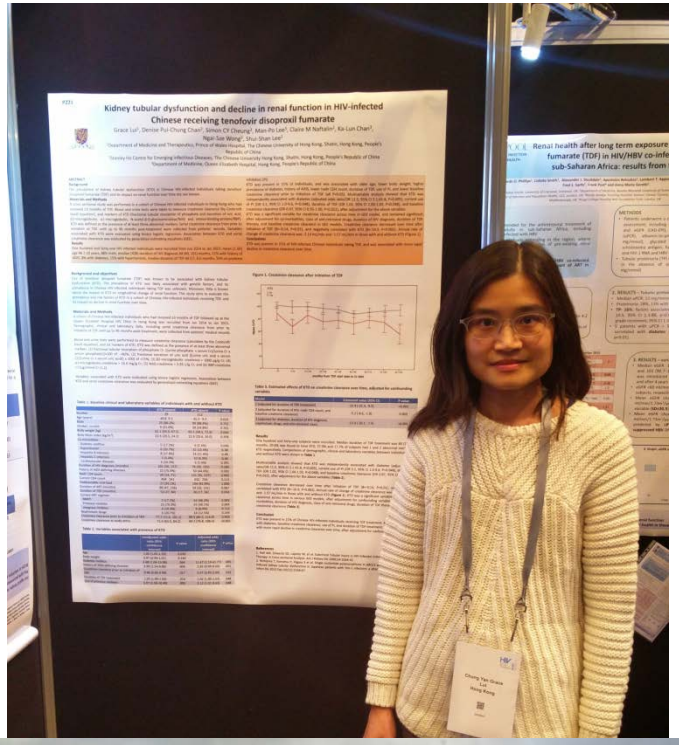
There should be standard prices to treat HIV, Hep B/C and TB

< $90 per year to treat HIV: TDF/3TC/EFV
< $90 per year to treat Hepatitis B: TDF/3TC or ETV
< $90 for first-line treatment for TB
< $90 for 12-weeks course of HCV DAAs: SOF/DCV

TDF/3TC, efavirenz, entecavir and most TB drugs will be generic worldwide in 2017. Prices should then fall in all countries, close to Indian / South African levels.

<$90 price to cure Hepatitis C will only be in low and middle income countries


PEOPLE MAKE GLASGOW
HIV Drug Therapy
2016
23 – 26 October 2016
SECC, Glasgow


Kidney tubular dysfunction and decline in renal function in HIV-infected Chinese receiving tenofovir disoproxil fumarate
Renal health after long term exposure
fumarate (TDF) in HIV/HBV co-infe
sub-Saharan Africa: results from