

# UK-CAB feedback: CROI 2017

**i-base**

Simon Collins

HIV i-Base

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# Key areas

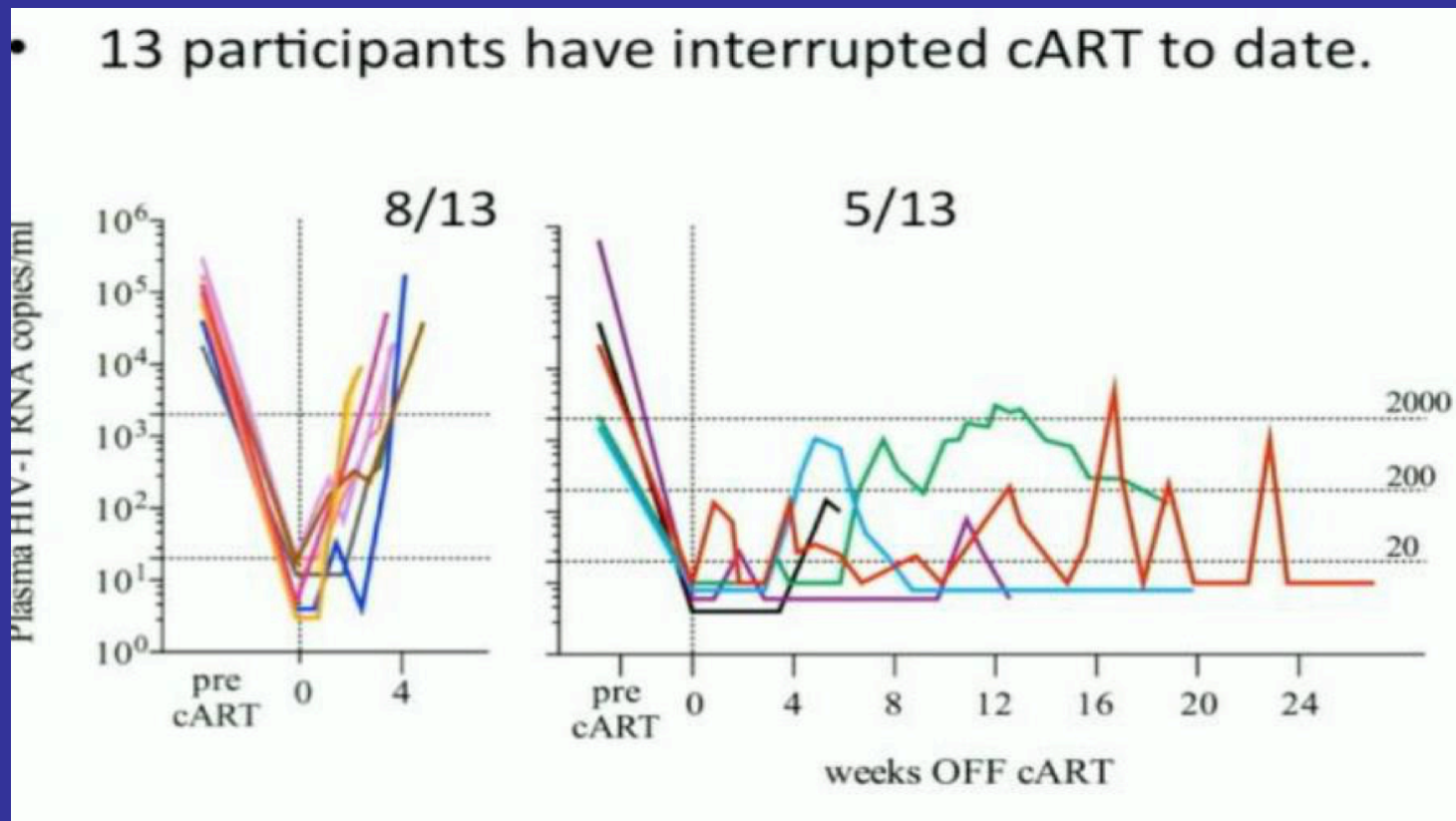
- Cure update
- New pipeline drugs
- ART strategies: monotherapy
- PrEP case
- “brain ageing” – COBRA
- HCV – DAA update
- CROI talks are all webcast
- BHIVA feedback is webcast

# Beatriz Mothe et al

- Roll-over study from dual vaccine
- n=24, ART within 3 mo of infection
- 15/24 boost vaccine + 3 x romidepsin infusions (HDACi – some side effects).
- Stop ART after the last vaccine
- 5/13 have controlled low-level viraemia
- 38% defined as response (up to 6 mo)

# Cure update?

Therapeutic vaccination: BCN02 – 35% response

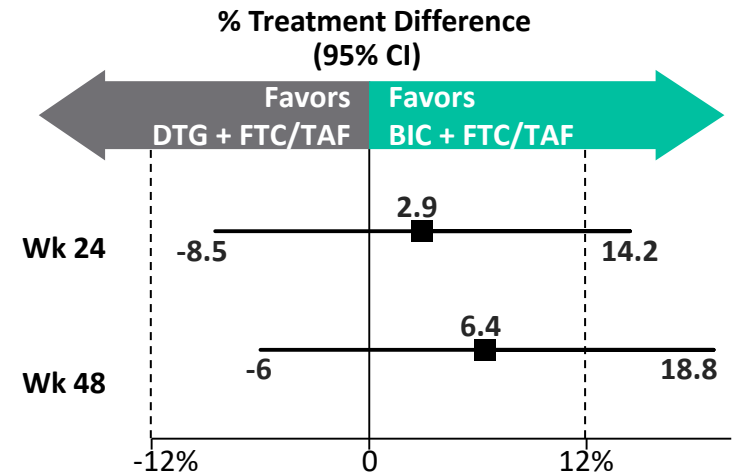
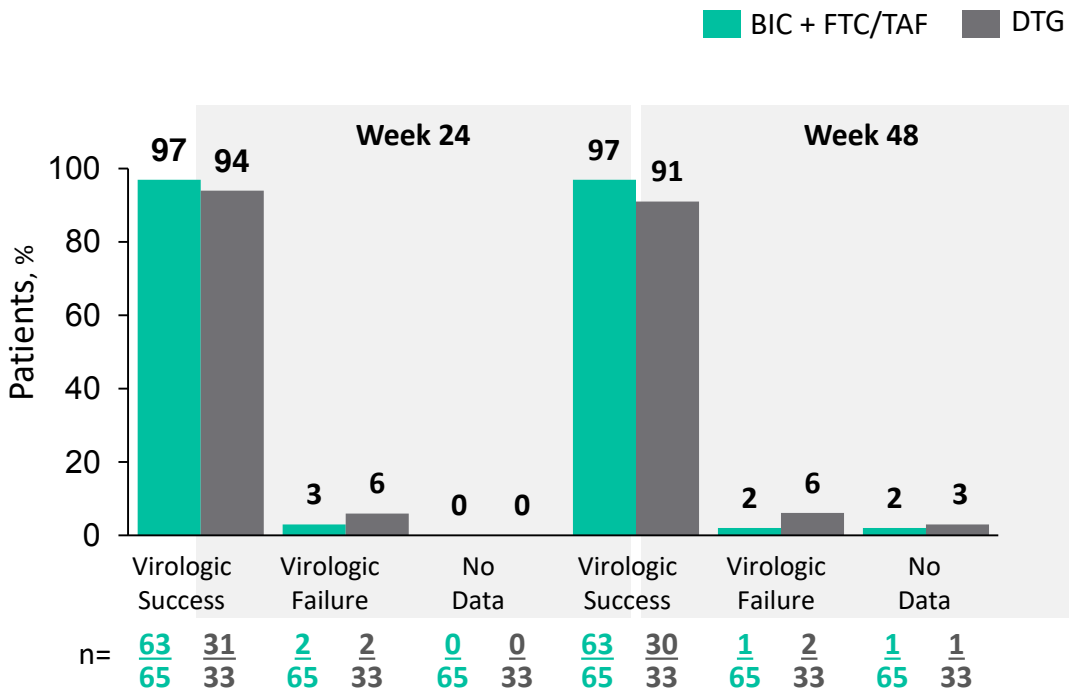


# New drugs

- bictegravir – integrase inhibitor Ph2
- doravirine – NNRTI Ph3
- nanoformulations: efavirenz, LPV/r
- Others – integrase, NRTI, mAbs etc

# Bictegravir 50 mg vs dolutegravir

## Similar viral load results



No resistance to study medications was detected in either arm

# Bictegravir vs dolutegravir

## similar side effects etc – small pill FDC

### Adverse Events

All Grades, ≥5% in either group	BIC + FTC/TAF n=65	DTG + FTC/TAF n=33
Diarrhea	12%	12%
Nausea	8%	12%
Headache	8%	3%
Upper respiratory tract infection	8%	0%
Fatigue	6%	6%
Arthralgia	6%	6%
Chlamydial infection	6%	3%
Back pain	6%	0%
Furuncle	5%	6%
Flatulence	2%	6%
Gastroenteritis	2%	6%
Costochondritis	0%	6%
Hemorrhoids	0%	6%
Pruritis	0%	6%

- 1 patient in the BIC + FTC/TAF group with a past history of urticaria and atopic dermatitis discontinued study drug after Week 24 due to urticaria

### G2-4 Lab events

≥5% in either group	BIC + FTC/TAF n=64*	DTG + FTC/TAF n=32*
Creatine kinase (CK)	13%	9%
AST	9%	3%
Hyperglycemia	8%	13%
ALT	6%	0%
LDL	6%	9%
Amylase	5%	6%
Hematuria	3%	6%
Glycosuria	2%	6%

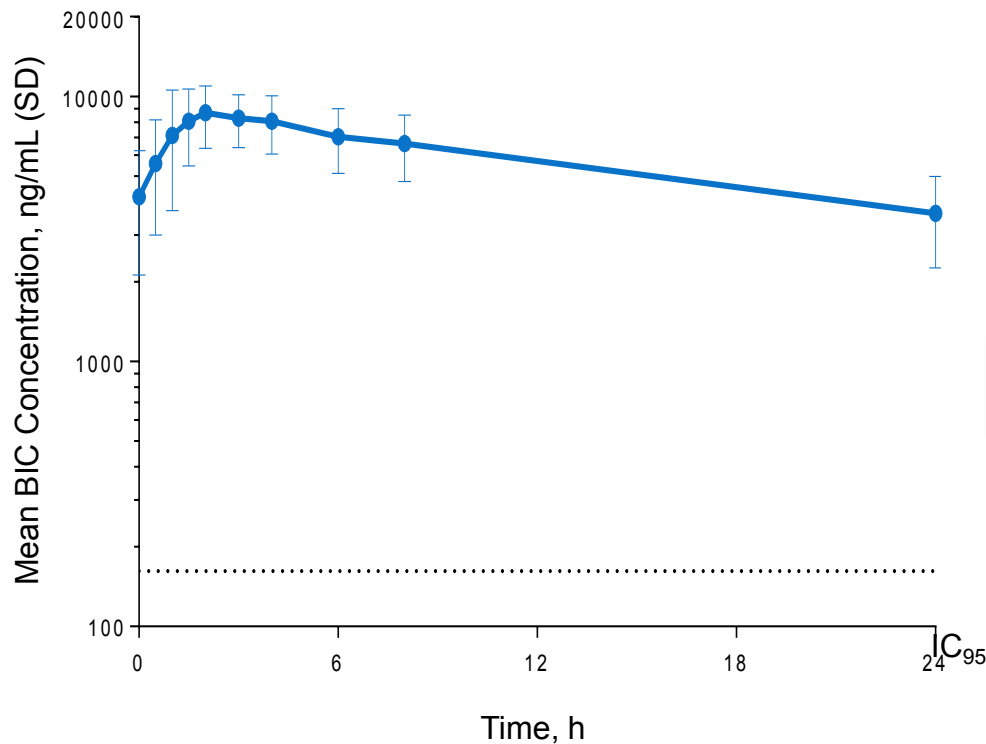
\*The number of patients randomized and dosed with at least 1 post-baseline laboratory assessment, excluding assessments not specified for all patients at any given visit.

# Bictegravir PK

## BIC Pharmacokinetic Profile HIV-infected Subjects

### Phase 2: BIC 75 mg + F/TAF 200/25 mg

Heather Zhang



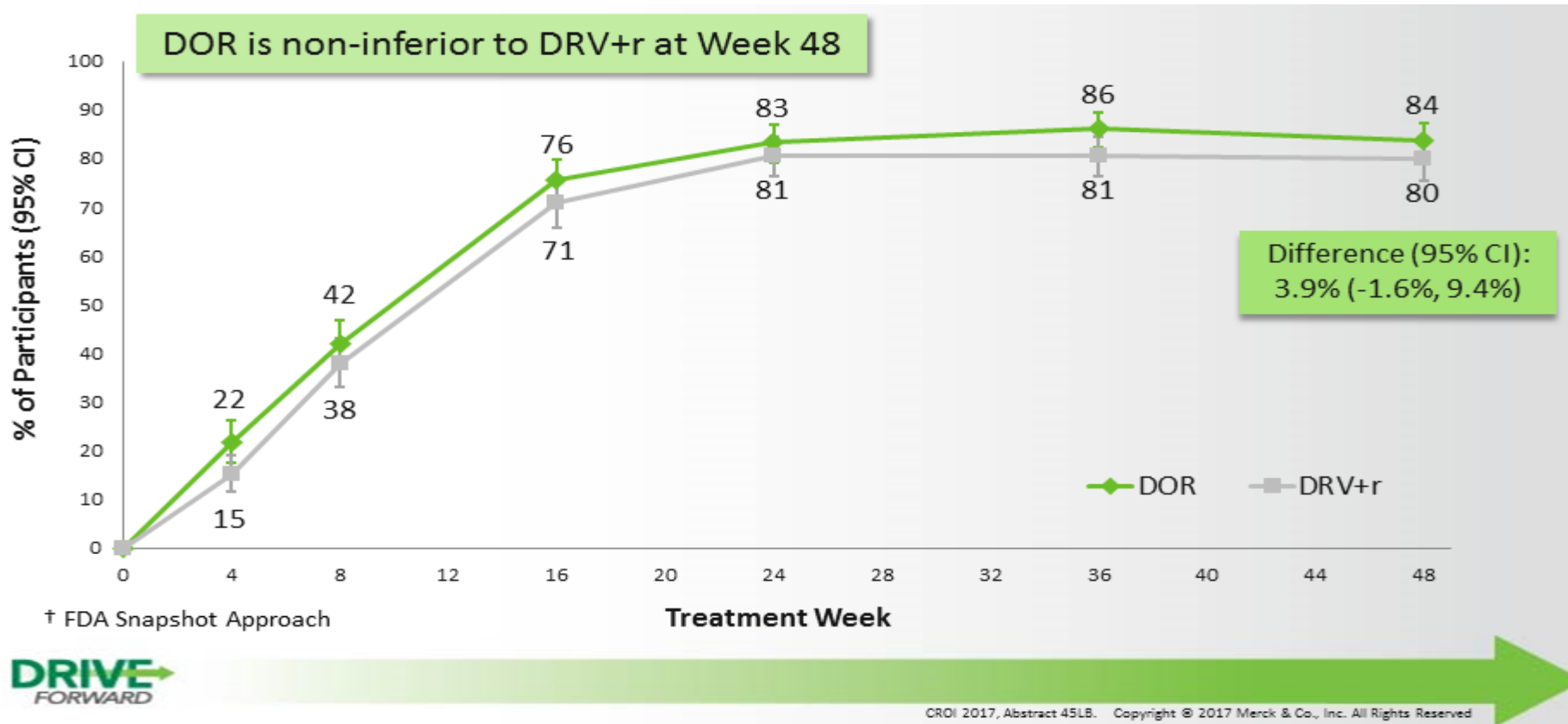
BIC PK Parameters N=23			
	AUC <sub>τ</sub> , h·ng/mL	C <sub>max</sub> , ng/mL	C <sub>τ</sub> , ng/mL
BIC 75 mg	140,000 (27)	9340 (27)	3510 (37)

\*Data presented as mean (%CV).



# Doravirine vs darunavir

Less GI side effects and lipids, coformulation



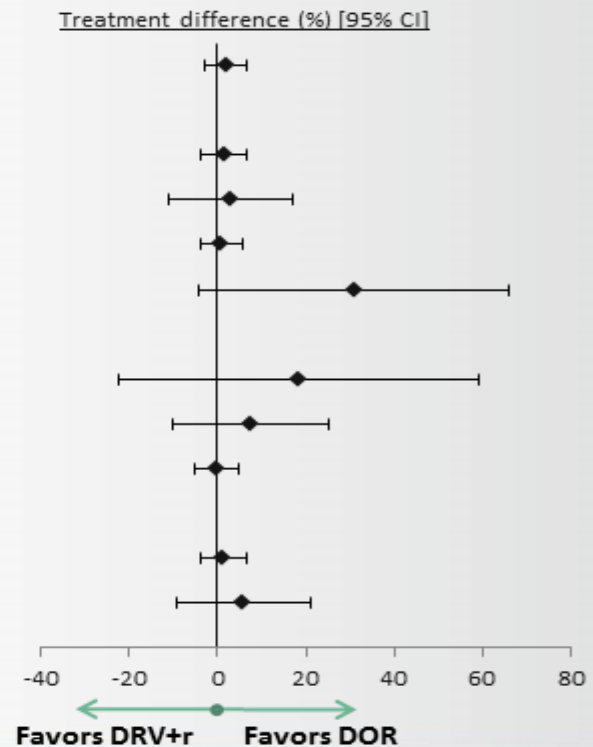
# Doravirine vs darunavir

## Sub group analysis

### Efficacy by Subgroup, Observed Failure<sup>†</sup> Approach

J. Molina (K. Squires) CROI 2017

	HIV-1 RNA <50 c/mL, % (N)	
	DOR	DRV+r
<b>All Participants</b>	<b>88 (364)</b>	<b>86 (355)</b>
<i>Baseline HIV-1 RNA, c/mL</i>		
≤100,000	90 (285)	89 (282)
>100,000	81 (79)	76 (72)
≤500,000	88 (347)	87 (342)
>500,000	82 (17)	50 (12)
<i>Baseline CD4+ T-cell Count, cells/mm<sup>3</sup></i>		
≤50	83 (6)	67 (18)
>50 and ≤200	83 (35)	74 (43)
>200	89 (323)	89 (294)
<i>NRTI Component</i>		
TDF/FTC	88 (316)	87 (312)
ABC/3TC	90 (48)	84 (43)



<sup>†</sup> Discontinuation due to lack of efficacy = failure; data missing for other reasons were excluded. N = number of participants in subgroup.

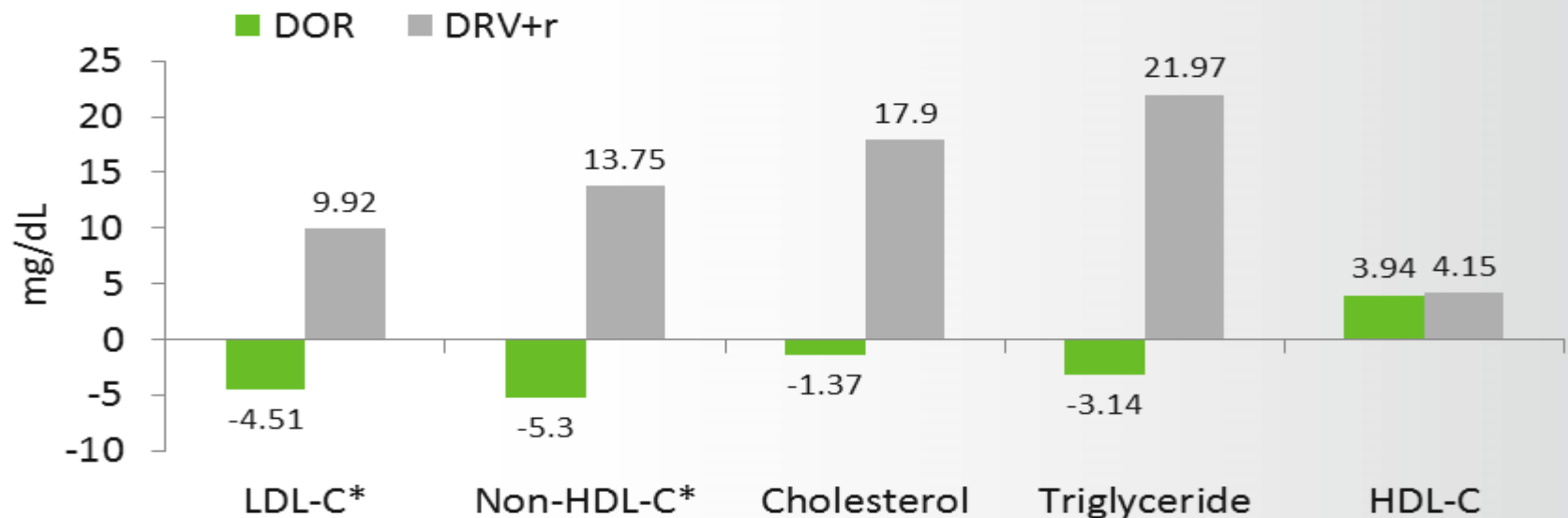


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# Doravirine vs darunavir

## Lipids

### Fasting Lipids, Change from Baseline at Week 48



\*  $P < 0.0001$  for DOR vs DRV+r. Statistical testing for other parameters was not prespecified.



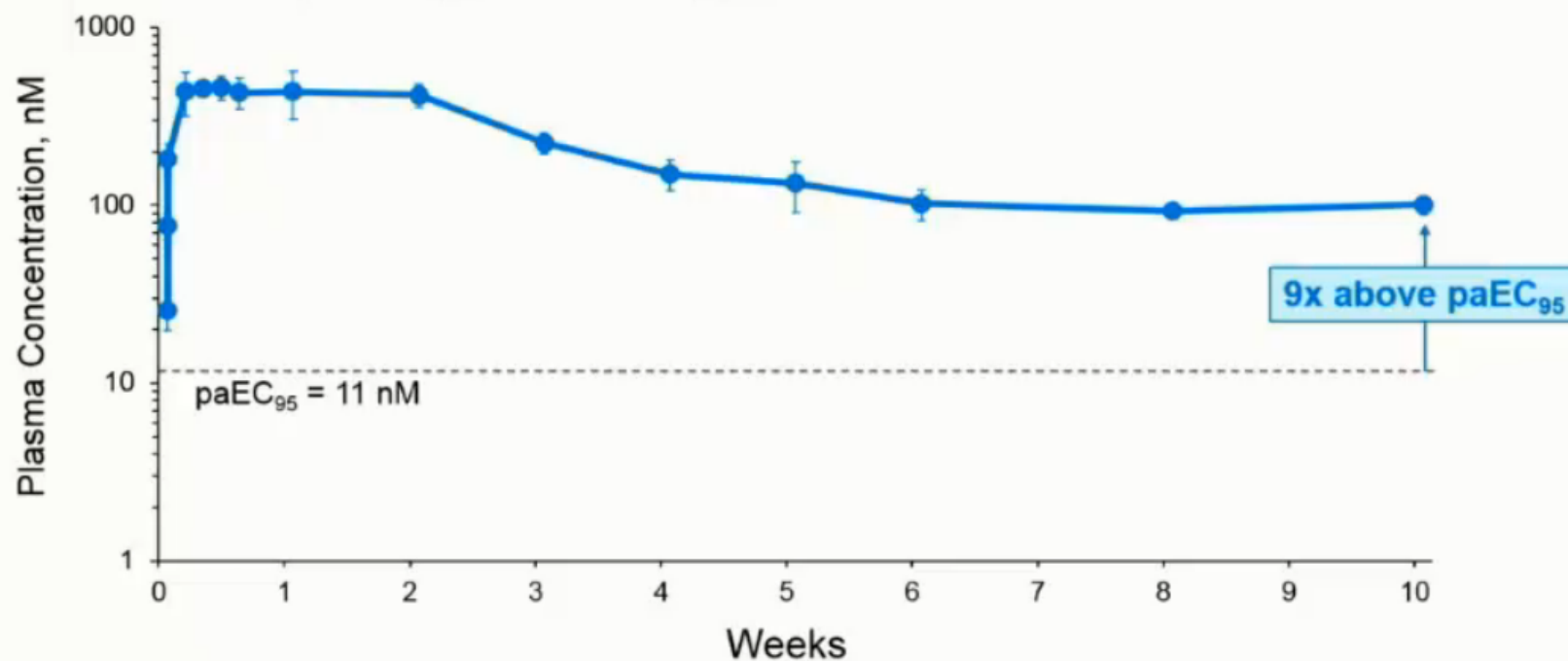
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# Other new compounds

- MK-8591 / EFdA (Abs 435)
- capsid inhibitor (Abs 38) - Gilead
- non-boosted PI (Abs 433)
- GS-9882 – integrase – early stage
- GS-9131 – NRTI – early stage
- Monoclonal antibodies:  
PRO 140 (abs 437), Ibalizumab (abs 438, 449LB), VRC01 (abs 760)

## GS-CA1 Pharmacokinetics in Rats Extended Release Formulation

- Single subcutaneous injection maintains plasma concentrations well above  $paEC_{95}$  for >10 wks
- Potential for a monthly dosing interval or longer in humans

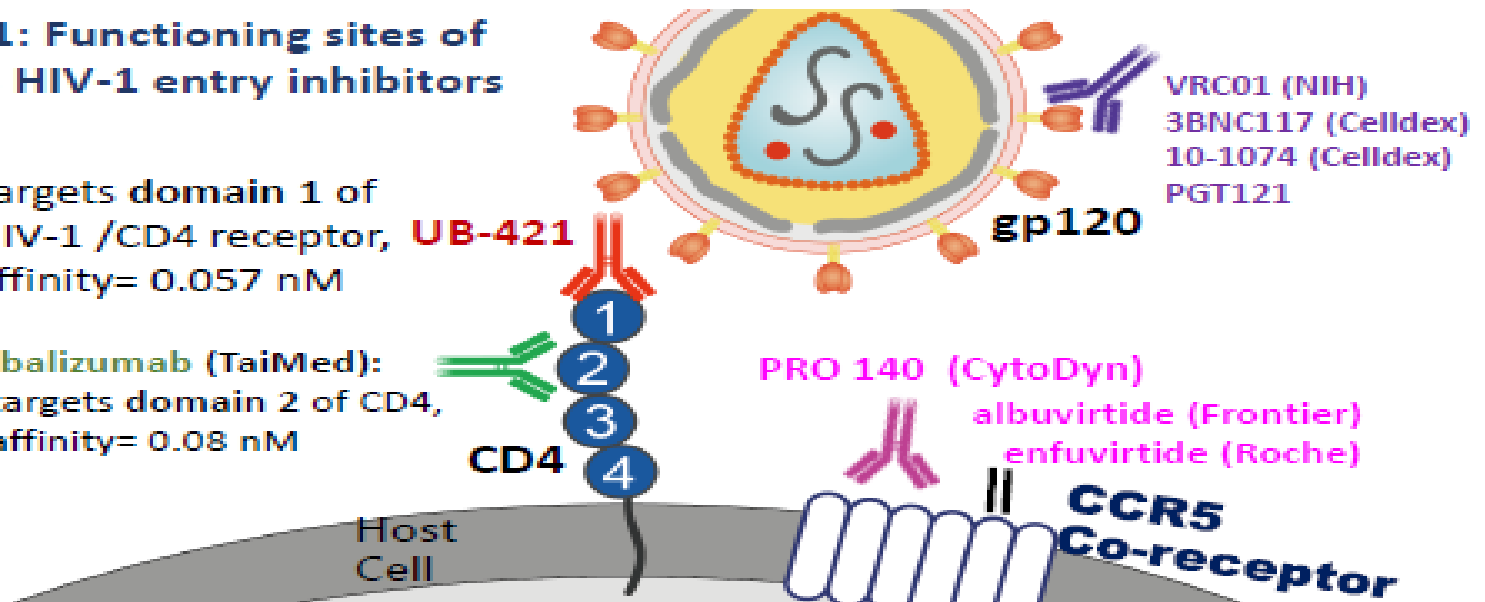


# Functioning sites of various HIV-1 entry inhibitors

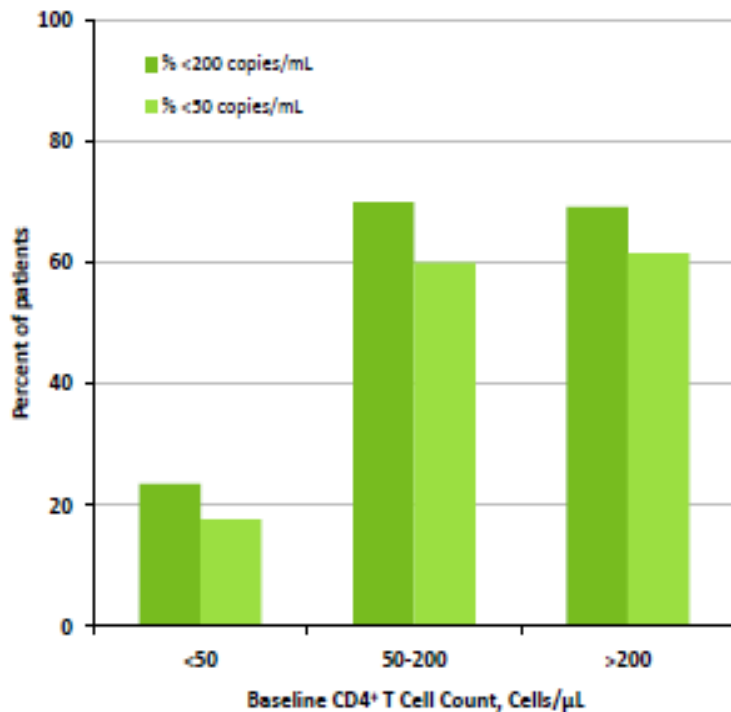
**Figure 1: Functioning sites of various HIV-1 entry inhibitors**

Targets domain 1 of HIV-1 /CD4 receptor, **UB-421**  
affinity= 0.057 nM

**Ibalizumab (TaiMed):**  
targets domain 2 of CD4,  
affinity= 0.08 nM



# TMB-301: Ibalizumab in patients with multi-drug resistant HIV-1 infection – 24 week data



- Mean VL decrease 1.6 log<sub>10</sub> from baseline
- 43% with undetectable VL <50 cp/ml
- 10 discontinuations
  - 1 drug-related IRIS
  - 4 deaths
  - 3 consent withdrawals
  - 1 lost to follow up
- Rolling over to expanded access & FDA application

# New strategies

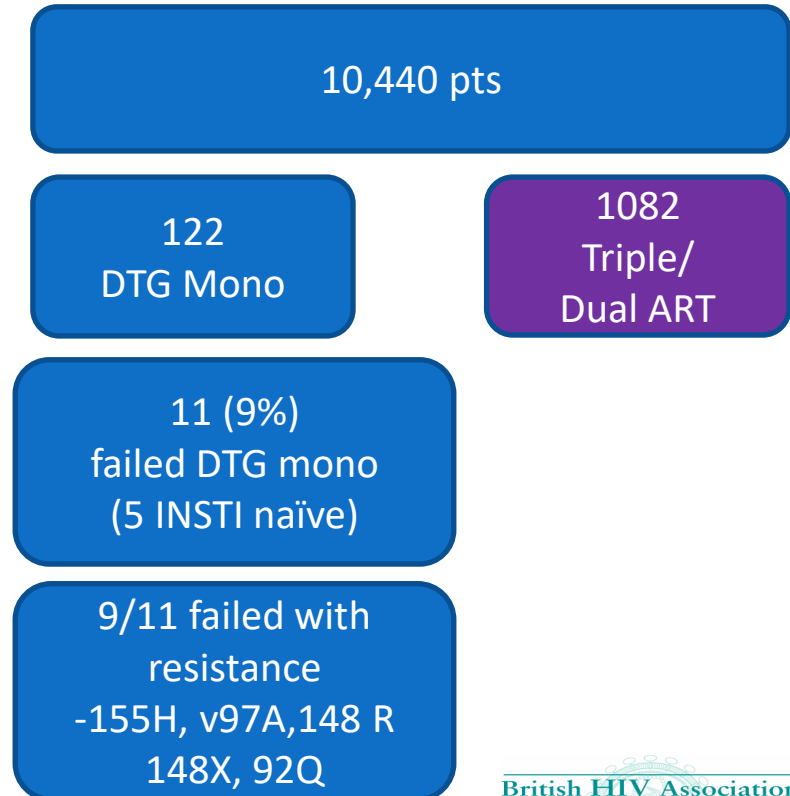
- dolutegravir monotherapy
- dolutegravir crushing
- Dual: dolutegravir + rilpivirine
- Dual: cabotegravir+ rilpivirine



# Pathways for resistance in those failing DTG mono-therapy

Blanco J

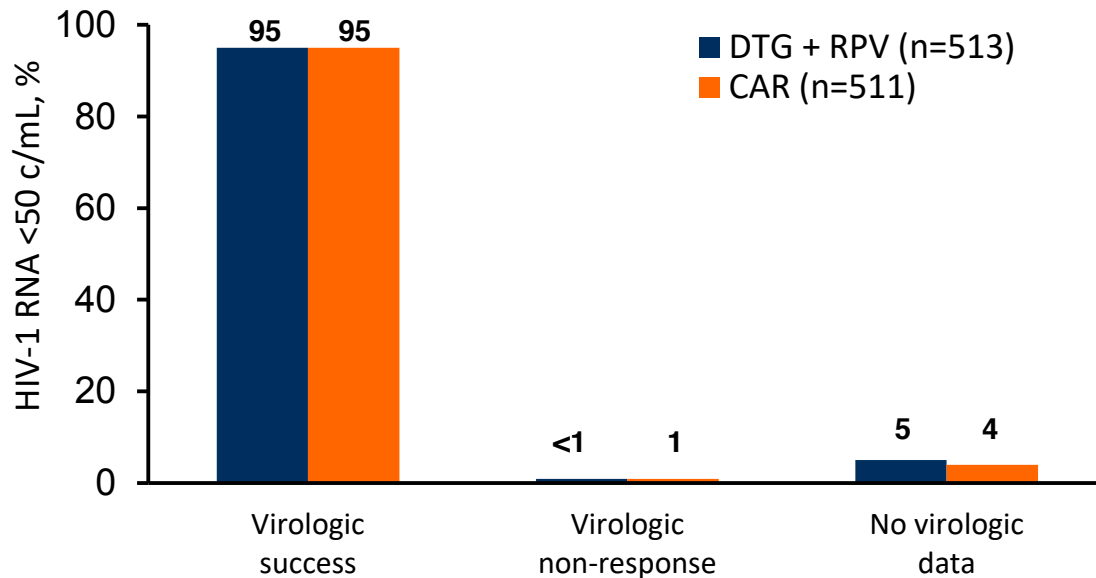
- Aim:
  - To assess rate of failure with or without resistance in 3 large cohorts with complex DDI/comorbidity/toxicity
  - Describe resistance and outcc for failing pts
- Pts from 3 centres, had to be VL<50 at switch,
- Exclusion : prior INSTI failure or no available resistance test
- Adherence was variable
- Most switched to DRV/r /triple



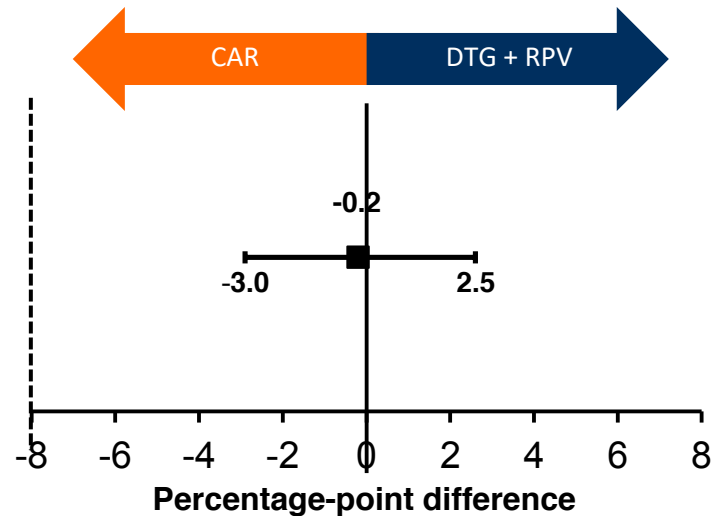
# Dolutegravir + rilpivirine switch

## Cost vs 2RTIs?

### Virologic outcomes



### Adjusted treatment difference (95% CI)<sup>a</sup>



DTG + RPV is **non-inferior** to CAR with respect to snapshot in the ITT-E population (<50 c/mL) at Week 48

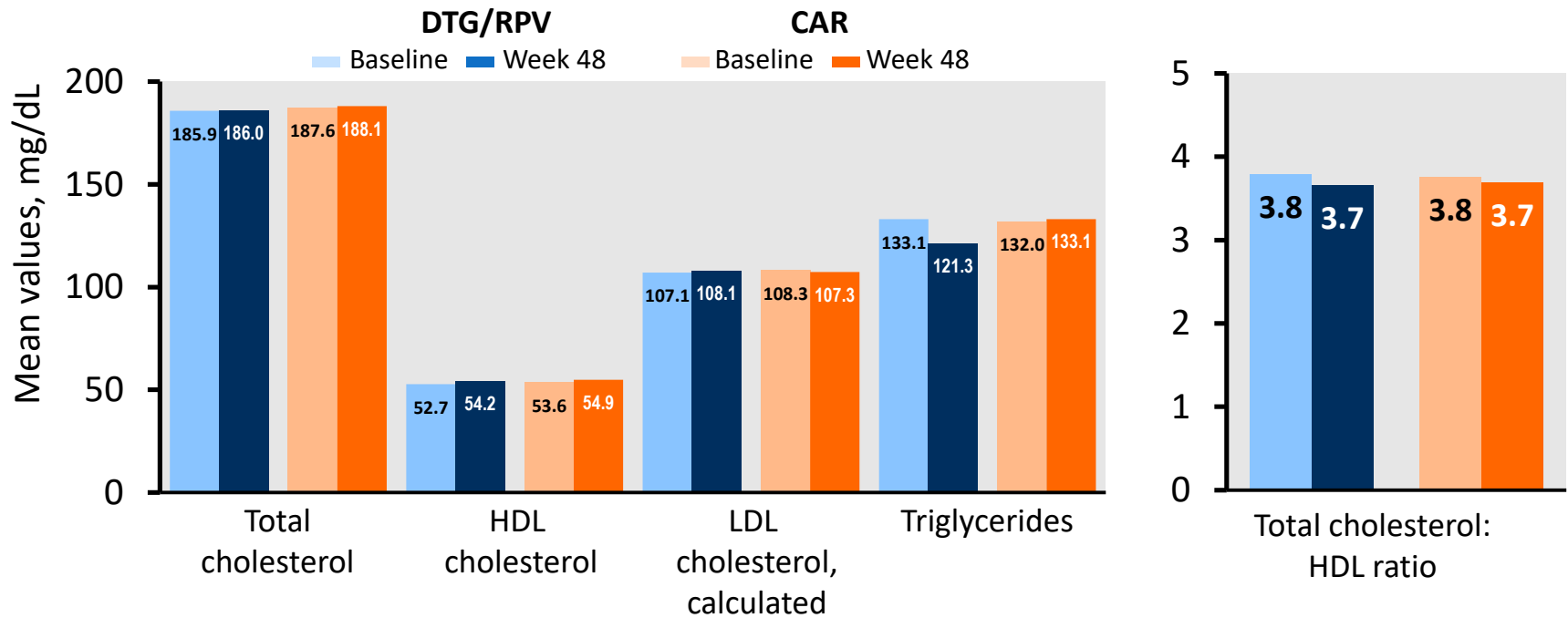
<sup>a</sup>Adjusted for age and baseline 3<sup>rd</sup> agent.

# Dolutegravir + rilpivirine switch

## Cost vs 2RTIs?

### Change in Serum Lipids at Week 48

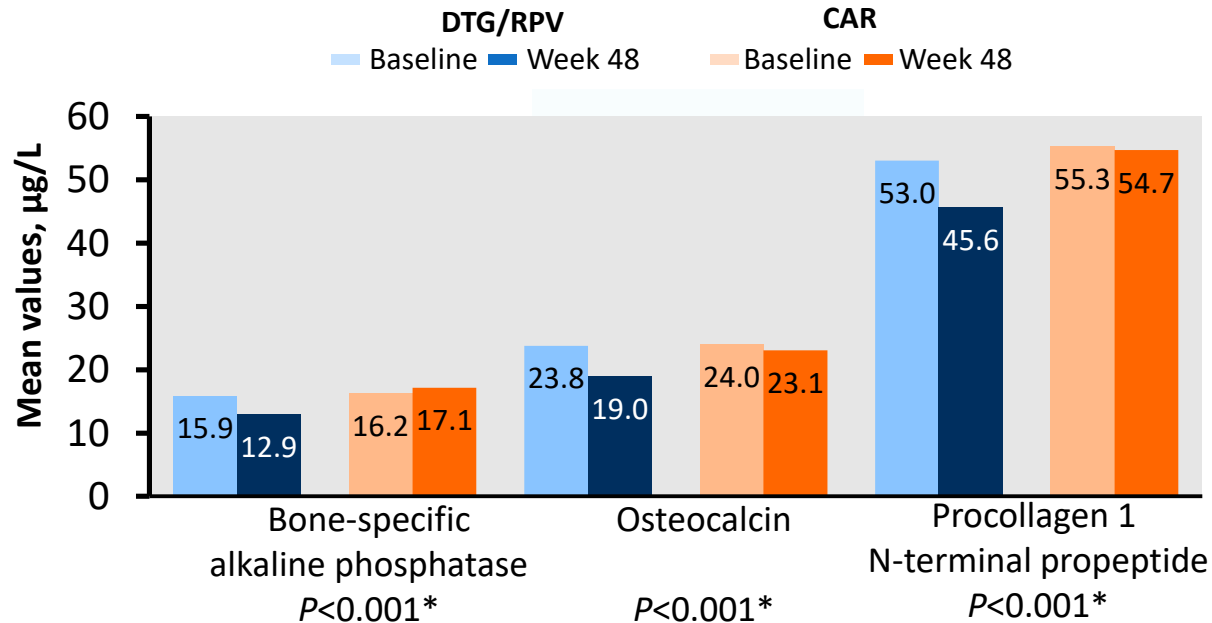
Pooled Data Early Switch Phase



# Dolutegravir + rilpivirine switch

## Change in Bone Markers at Week 48

Pooled Data Early Switch Phase



\* Adjusted for baseline third agent, age, sex, body mass index, smoking status, and baseline biomarker level. Statistical model uses log-transformed data.

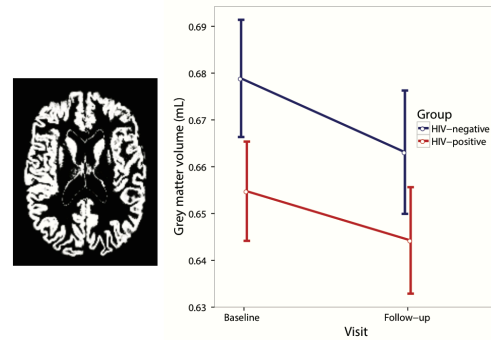
# PrEP case: success or failure?

- 50 yo gay man, adherent
- Very high risk: 38-75 partners pcm
- 3-5 partners a day, ChemSex etc
- Fever after 8 months PrEP
- Ag/Ab+ but RNA/DNA neg
- Stopped PrEP, VL 0 wk 1, 10,000 wk2
- Ethics of reporting, adherence etc

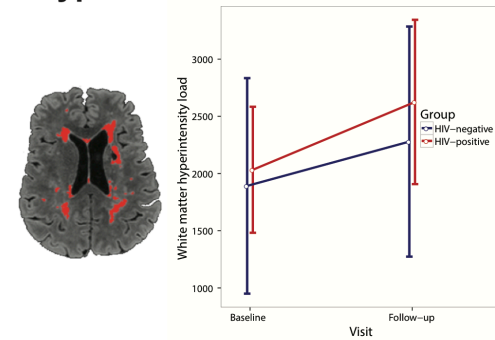
# COBRA – Abs 352LB

- Are neurological changes on ART important/different to HIV negative?
- Well matched HIV negative control group
- Longitudinal results
- Lower baseline levels
- Similar rate of decline on ART

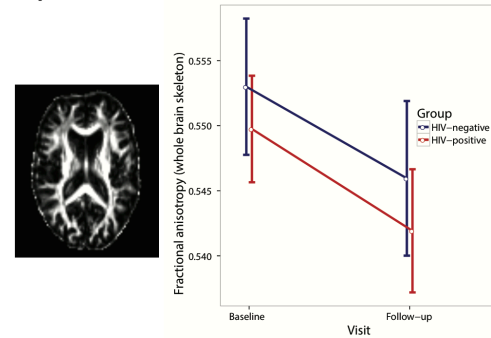
**A) T1 - Grey matter volume**



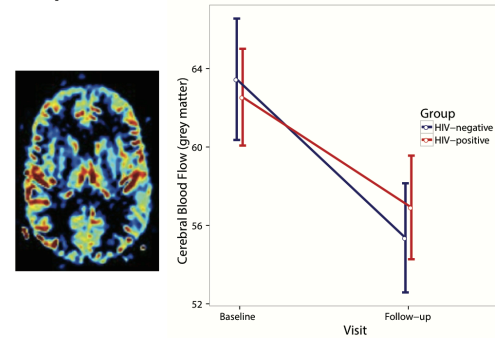
**B) FLAIR - White Matter Hyperintensities**



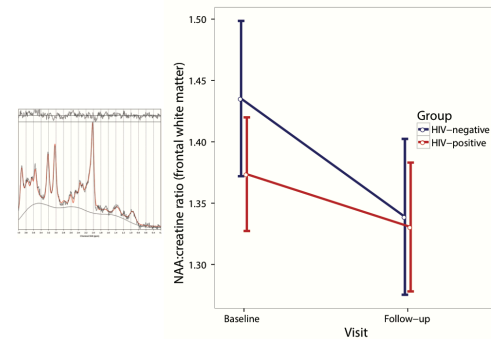
**C) DTI - White Matter structure**



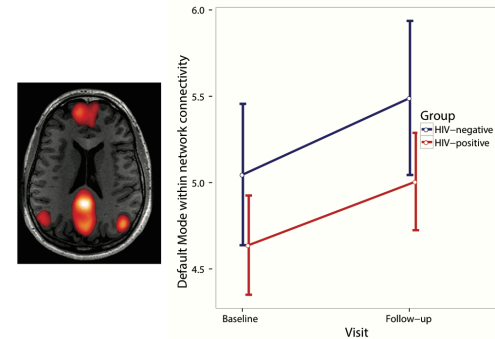
**D) ASL - Cerebral blood flow**



**E) MRS - Neural metabolites**



**F) Resting state fMRI - Functional network connectivity**



# DAAAs for HCV

## Substantial decline in Acute HCV post DAA rollout in the Netherlands

(Rjinders, et al O137LB)

### 2014

A-HCV n = 93

PYFU n = 8290

**11.2/1000 PYFU (95% CI 9-14)**

**1.1% per year**

### 2016

A-HCV n = 49

PYFU n = 8961

**5.5/1000 PYFU (95% CI 4-7)**

**0,55% per year**



**IRR 0.49 (95% CI 0.34 – 0.69)**

Jan-Dec 2014 11.2/1000

Jan-Jun 2016 6.9/1000

July-Dec 2016 4.0/1000





# DAAAs for HCV

- By 2017, 75% of gay men with coinfection will be treated
- Incidence of acute HCV halved 2014-2016
- Not from behaviour change reducing risk – similar STIs

# Generic DAAs

## Generic DAAs via Buyers Clubs (A Hill, et al P569)

Table 1: Baseline Characteristics

Patients	SOF & SOF/RBV N=100	SOF/DCV N=545	SOF/LDV N=502
% Male	79 % (79/100)	57 % (321/545)	57 % (288/502)
% Cirrhosis	16 % (16/100)	20 % (111/545)	16 % (78/502)
% GT 1	35 % (35/100)	31 % (168/545)	87 % (439/502)
% GT 3	46 % (46/100)	58 % (314/545)	4 % (19/502)
+ RBV	65 % (65/100)	7 % (81/545)	5 % (57/502)
12 weeks or less*	41 % (41/100)	66 % (363/545)	79 % (398/502)
24 weeks or more*	38 % (38/100)	21 % (114/545)	11 % (55/502)

Figure 3: SVR4 responses by genotype

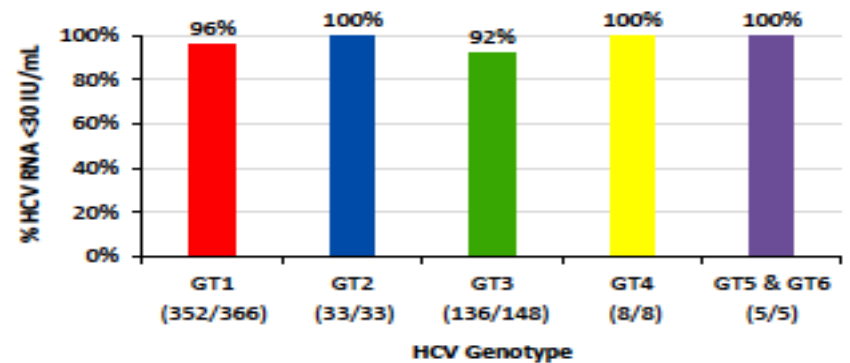
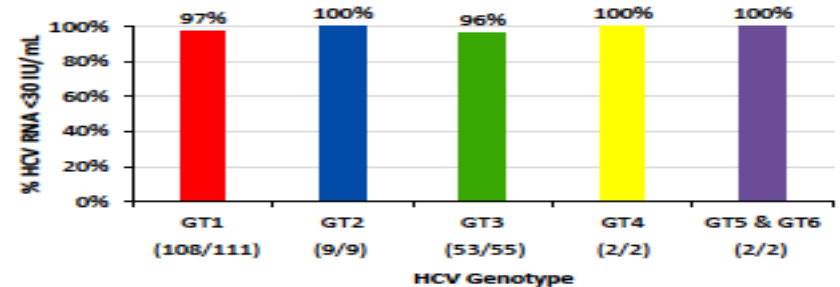


Figure 4: SVR12 responses by genotype\*



The logo for the British HIV Association (BHIVA) is centered at the top of the slide. It features the text "British HIV Association" in a teal serif font, with "BHIVA" in a larger, bold teal serif font below it. The text is flanked by two horizontal teal lines. In the background, there is a faint, circular emblem with intricate details, possibly a coat of arms or a historical seal.

British HIV Association  
**BHIVA**

Thanks to researchers for use of slides and  
BHIVA compilation from 2017 BHIVA “Best of  
CROI” feedback meetings.

Four talks+ Q&A are webcast at:  
[www.bhiva.org](http://www.bhiva.org)