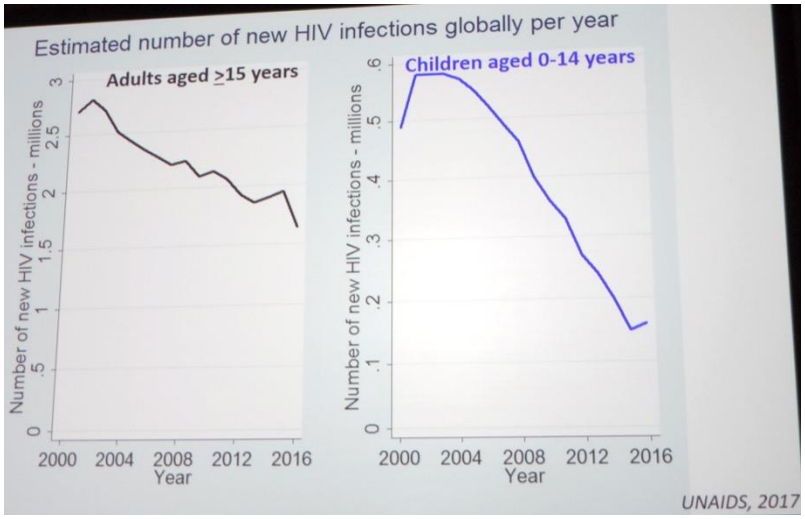
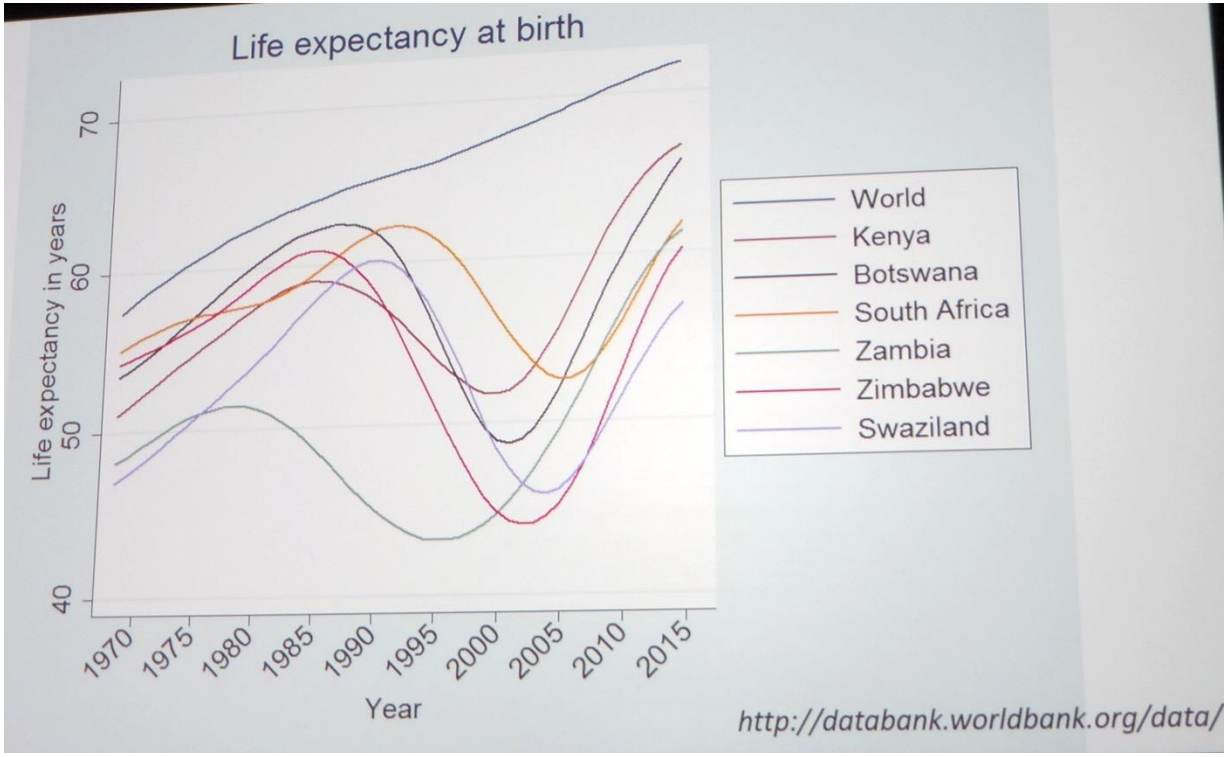
CROI 2018, Boston

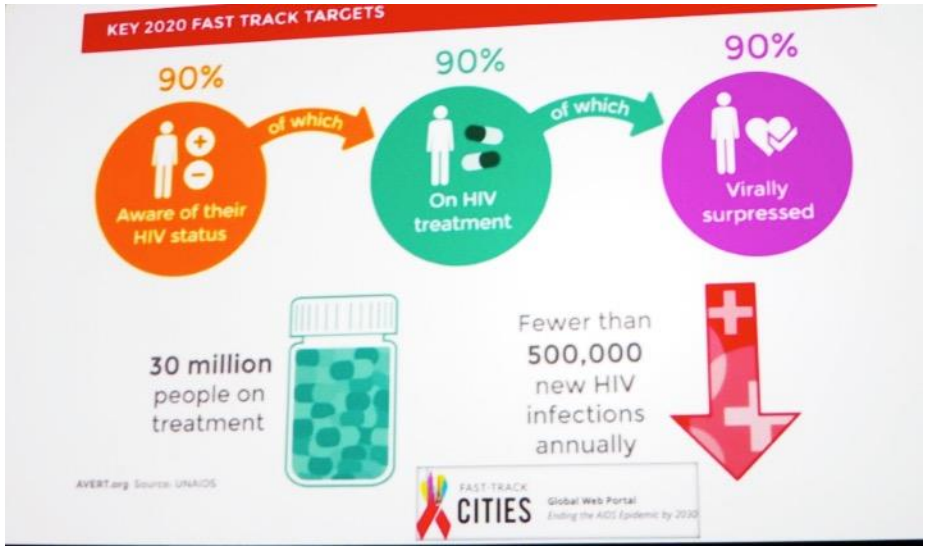
EPIDEMIOLOGIE

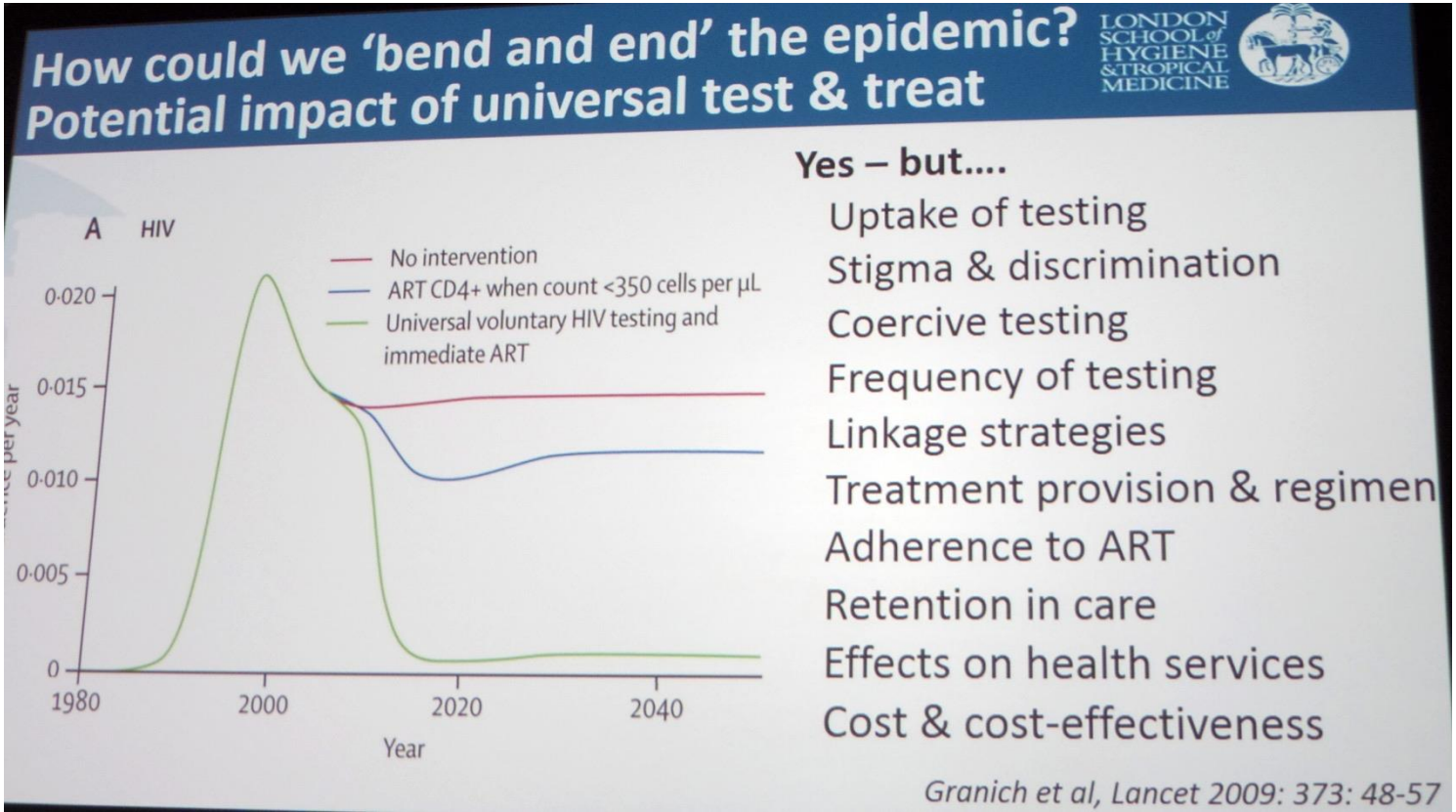
To end the Epidemics ?



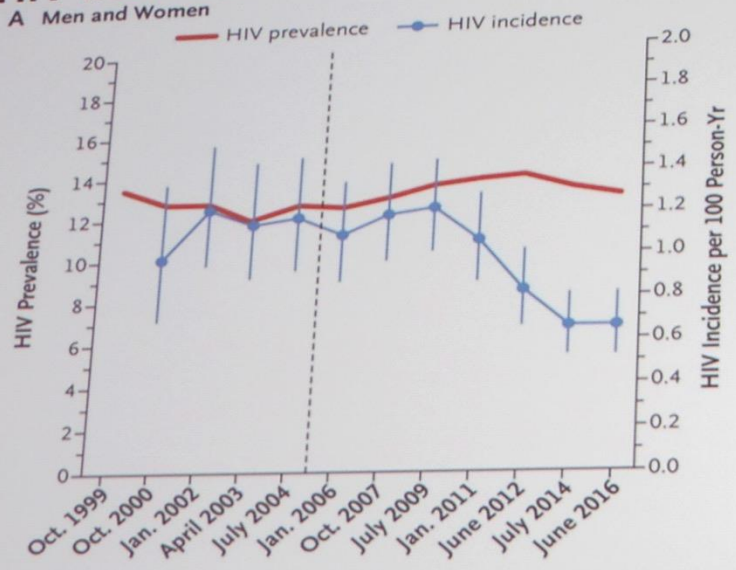


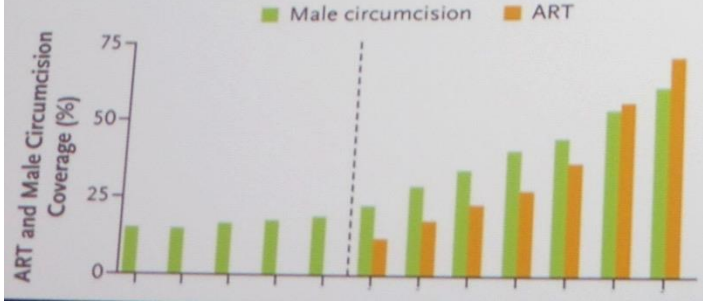
H.A. Weiss

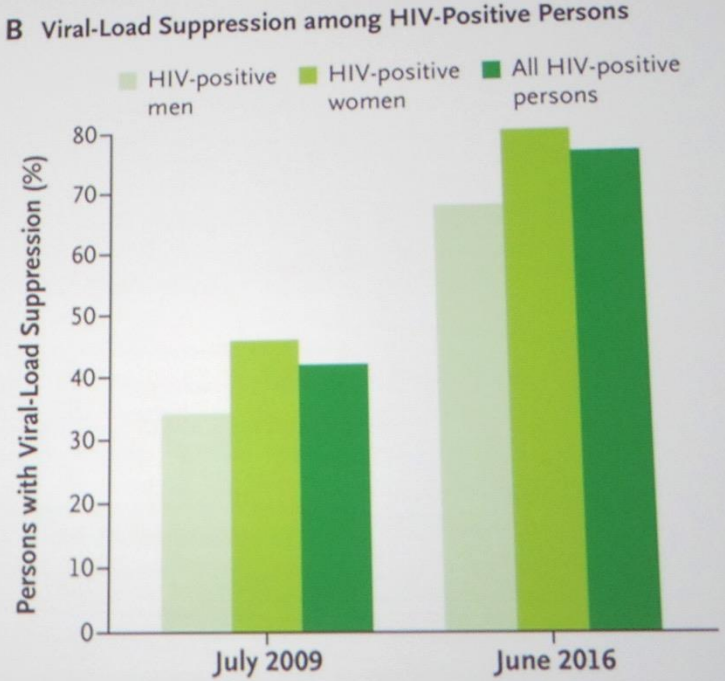

KEY 2020 FAST TRACK TARGETS
90%
Aware of their HIV status
of which
90%
On HIV treatment
of which
90%
Virally surpressed
30 million people on treatment
Fewer than 500,000 new HIV infections annually
AVERT.org Source: UNAIDS
FAST-TRACK CITIES
Global Web Portal


How could we 'bend and end' the epidemic?
Potential impact of universal test & treat
LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE
A HIV
No intervention
ART CD4+ when count <350 cells per µL
Universal voluntary HIV testing and immediate ART
0·020
0·015
0·010
0·005
0
1980
2000
2020
2040
Year
Yes – but....
Uptake of testing
Stigma & discrimination
Coercive testing
Frequency of testing
Linkage strategies
Treatment provision & regimen
Adherence to ART
Retention in care
Effects on health services
Cost & cost-effectiveness
Granich et al, Lancet 2009: 373: 48-57

HIV Incidence and Prevalence in the Rakai Community Cohort Study, 1999–2016

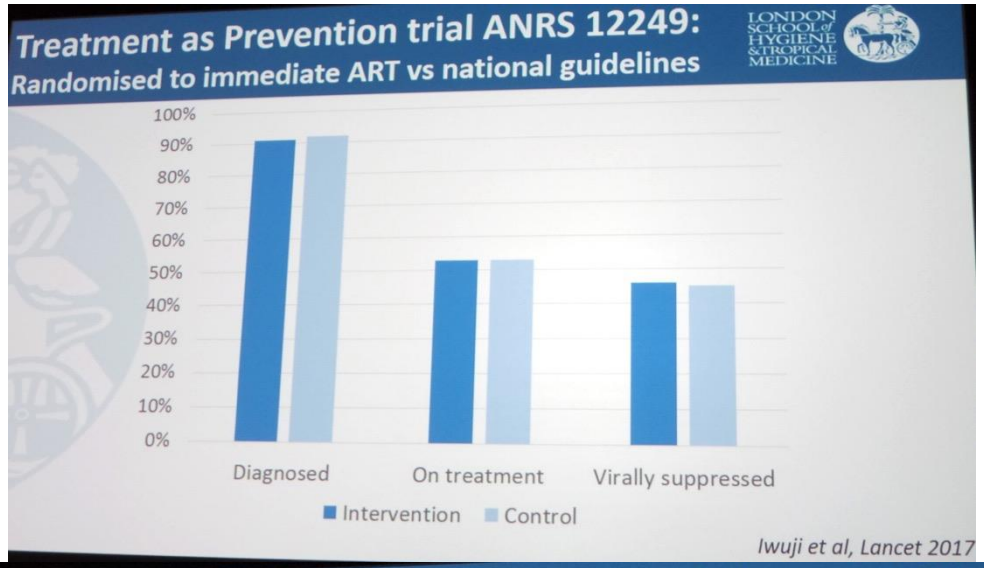


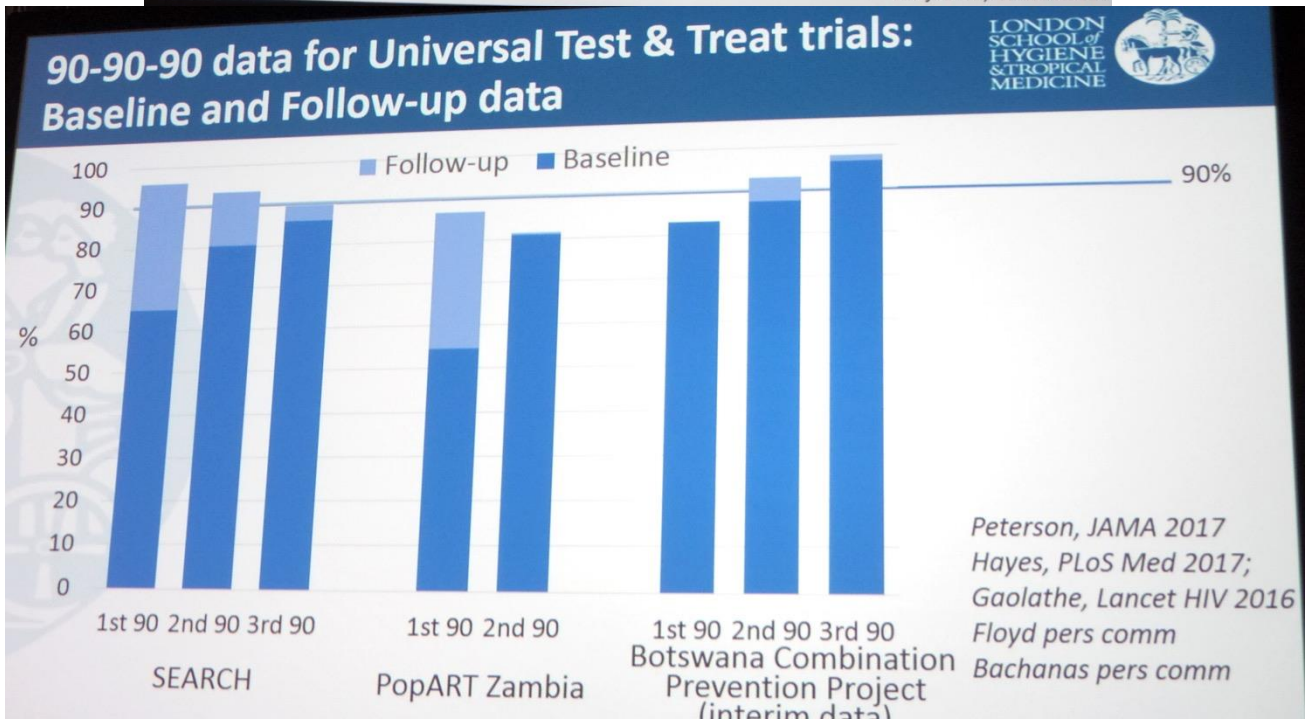




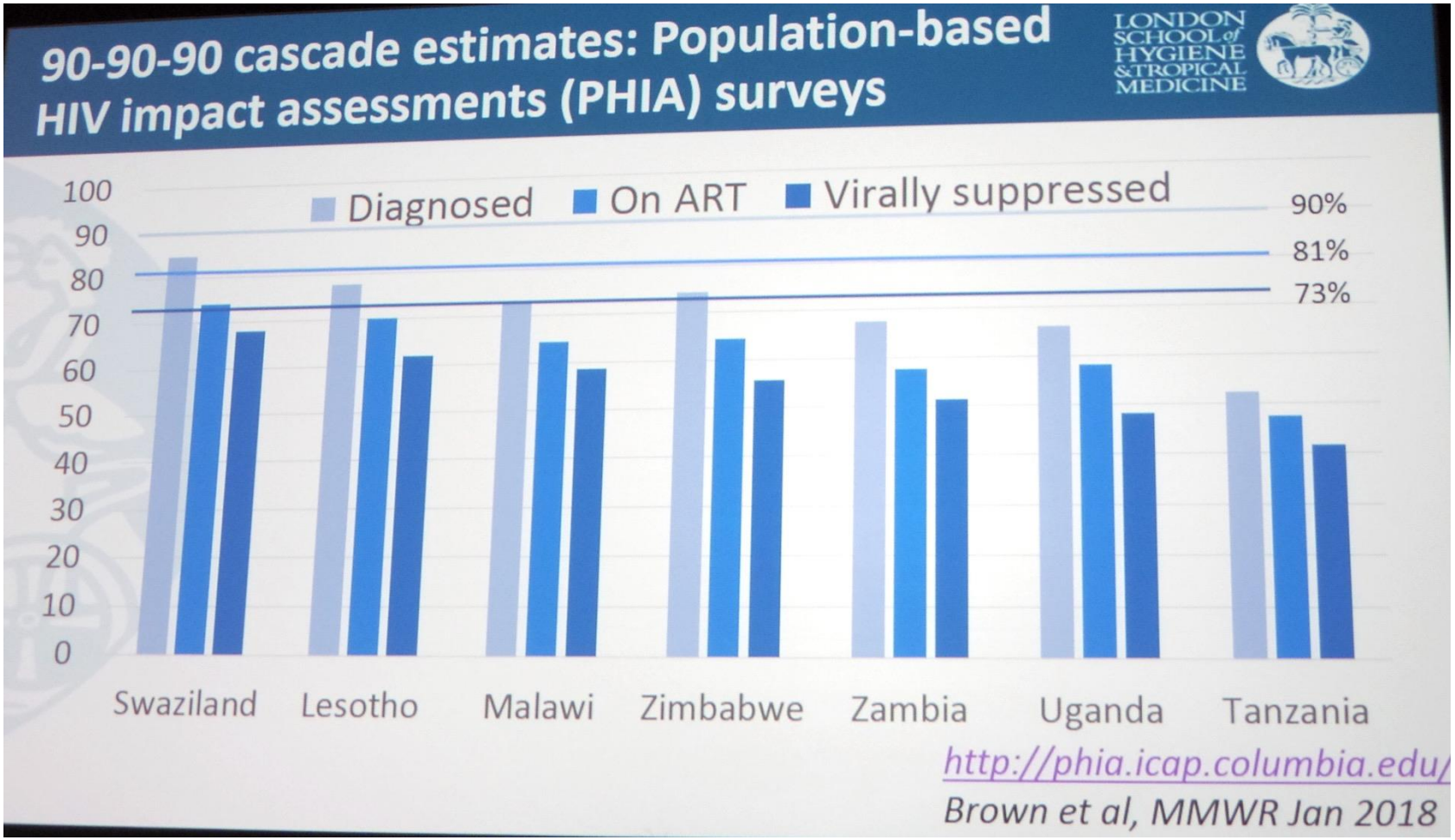
Grabowski MK et al. N Engl J Med 2017;377:2154-2166.

TasP dans la vraie vie

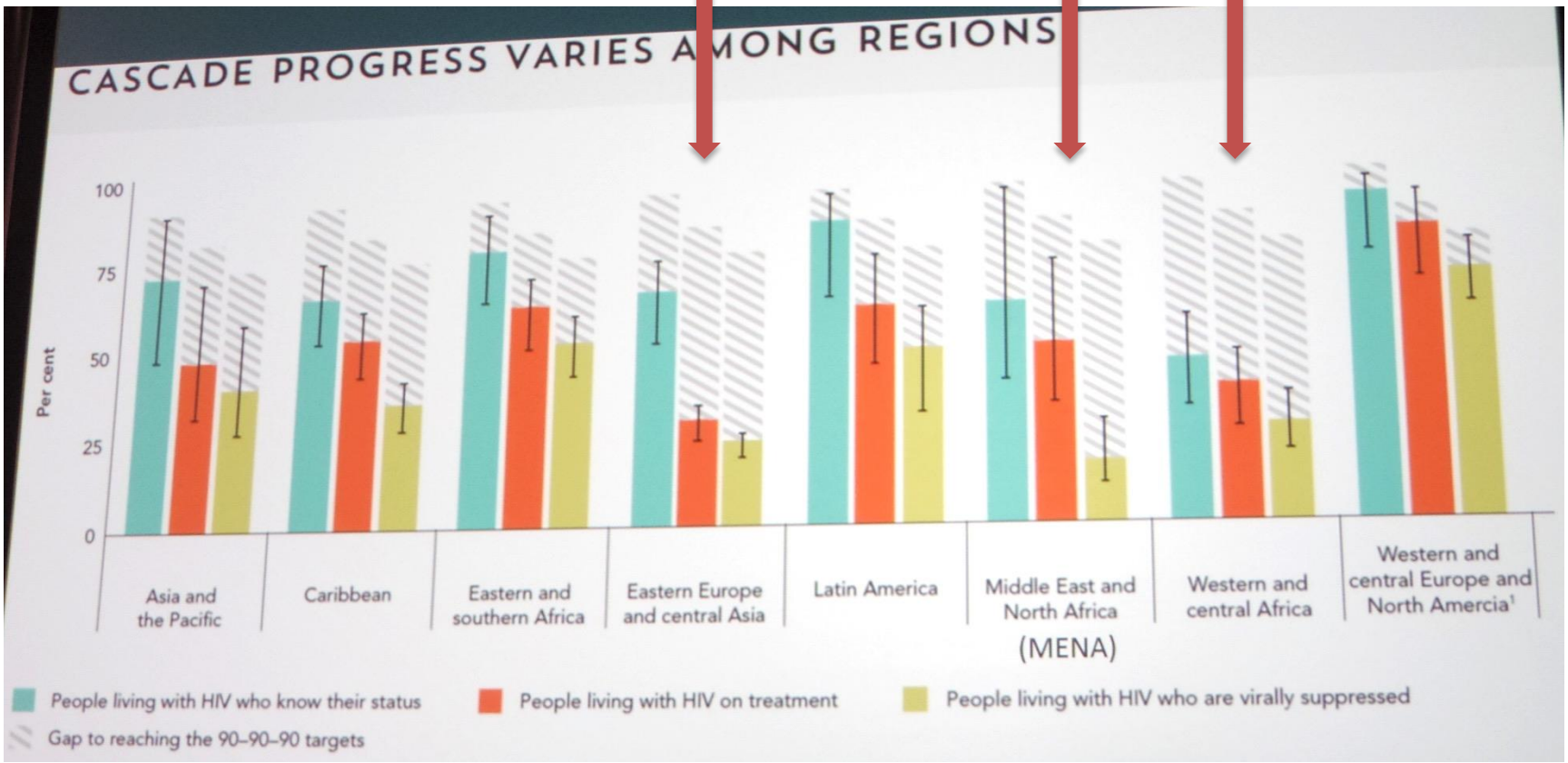




Des progrès nationaux



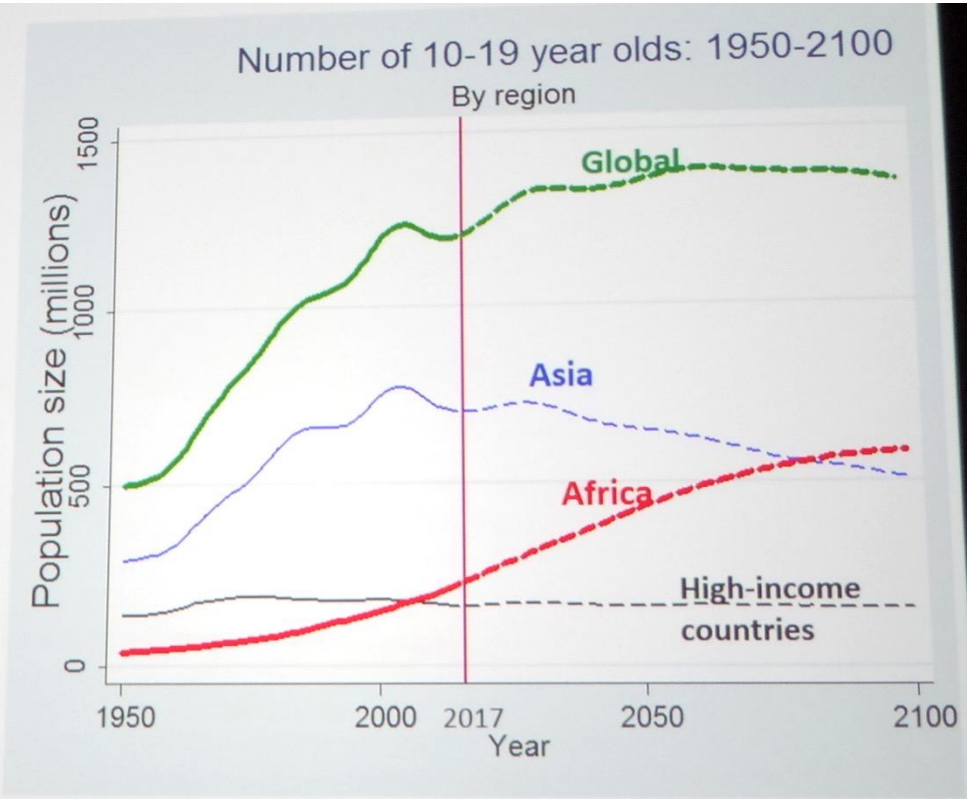
Des retards régionaux



Et les adolescents

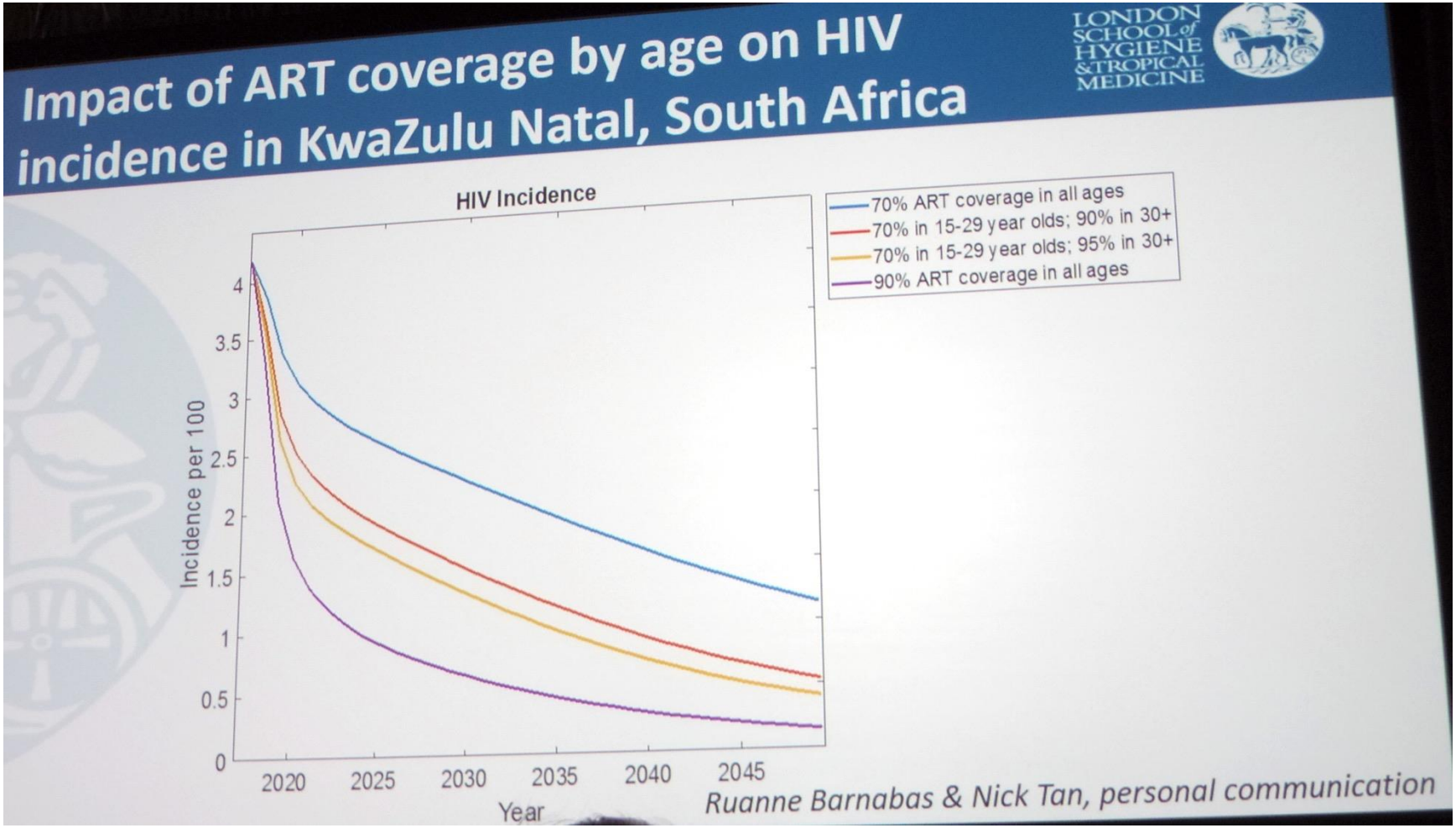
- *HIV is the leading cause of death among adolescents in sub-Saharan Africa*
  - *the second cause globally*

- *The number of adolescents will increase in coming decades globally and in SSA*



WHO Global Health Estimates; Health for the World's Adolescents
UN Dept Economics & Social Affairs; Population Division; World Population Prospects 2015

projections



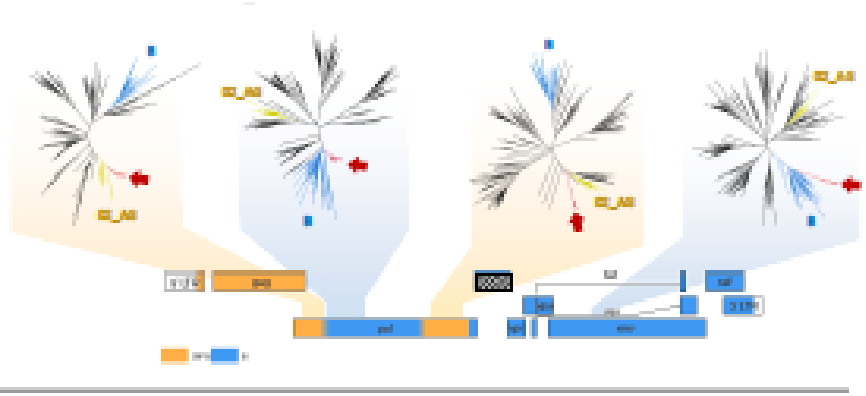
CROI

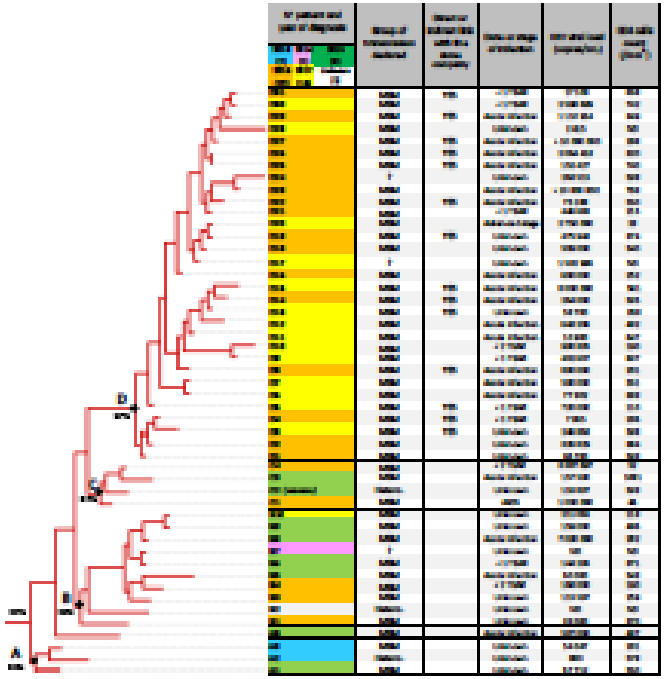
POSTER
#958

A new B/CRF02 circulating recombinant spreading quickly in Paris area, France

Marc Wirden[1], Fabienne De Oliveira[2] ,Alexandre Storto[3], Magali Bouvier-Alias[4], Karine Grenet[5], Marie-Laure Chaix[6], Philippe Simon[5], Eric Froguel[5], Thuy T. Nguyen[1], Cathia Soulié[1], Vincent Calvez[1], Jean-Christophe Plantier[2], Diane Descamps[3], Anne-Geneviève Marcelin[1], Benoit Visseaux[3]*, ANRS AC-11 Resistance Study Group.

1-Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique (IPLESP); AP-HP Pitié-Salpêtrière Hospital, Paris, France ; 2-Normandie Univ, UNIROUEN, EA2656, CHU de Rouen, Laboratoire de virologie associé au Centre National de Référence du VIH, F-76000; 3- IAME, UMR 1137, Univ Paris Diderot, Sorbonne Paris Cité; INSERM; AP-HP, Hôpital Bichat, Virologie, Paris, France ; 4- Hôpital Henri Mondor, Créteil, France ; 5- Grand Hôpital de l'Est Francilien, Jossigny, France ; 6- INSERM U941, Université Paris Diderot, APHP, Service de Virologie, CHU Saint Louis, CNR VIH, Paris, France ;; * -Presenting author





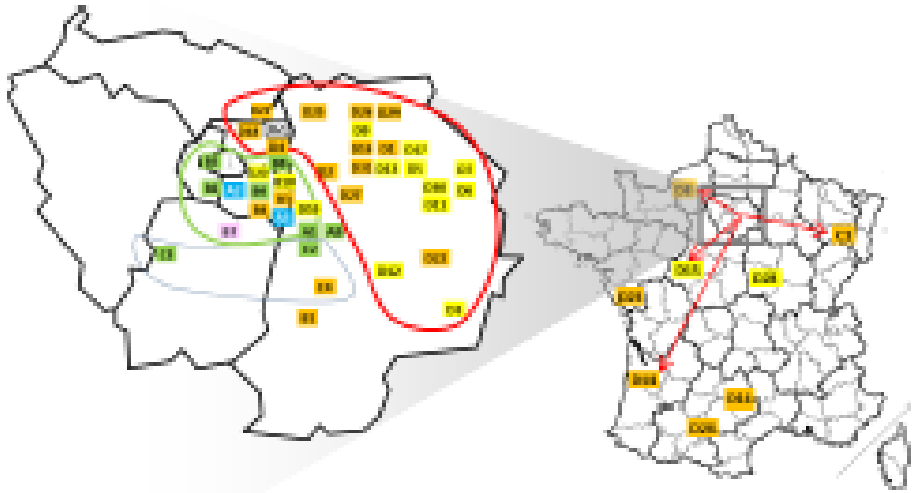
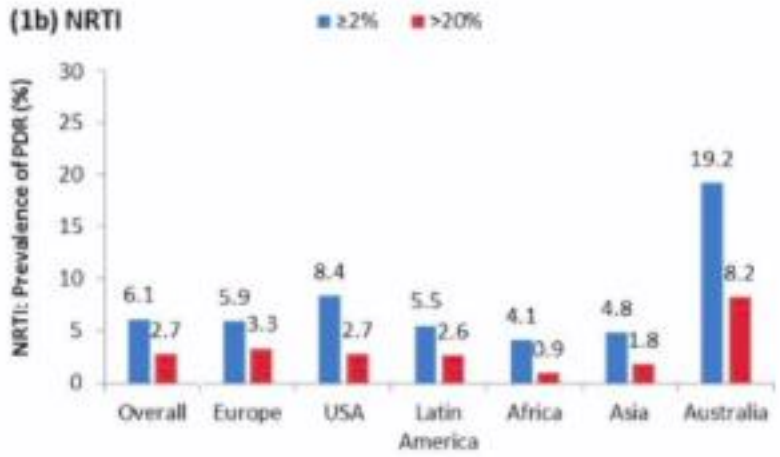


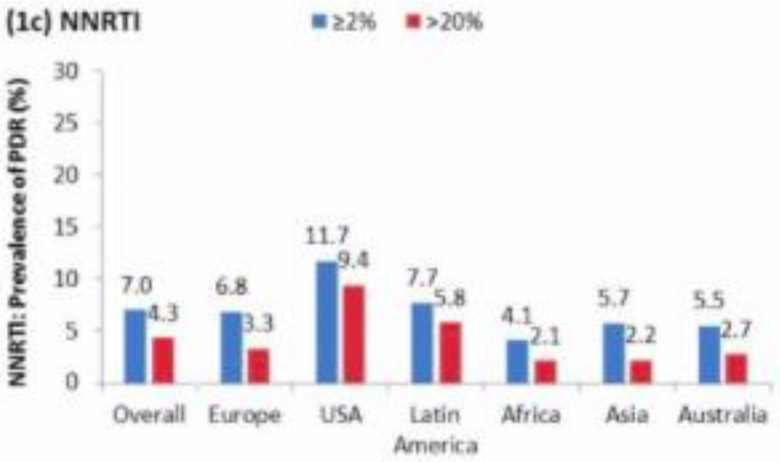
Figure 3. Geographic distribution of the town of residence for all patient identified as infected by the new recombinant form. The color correspond to the year of diagnosis (see Figure 2 for legend). The red arrows indicate a geographical displacement after the probable date of infection.

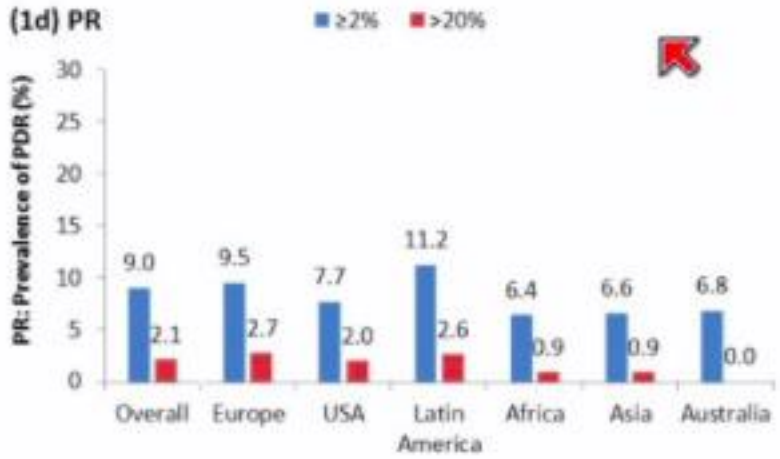
M. Wirden, 958

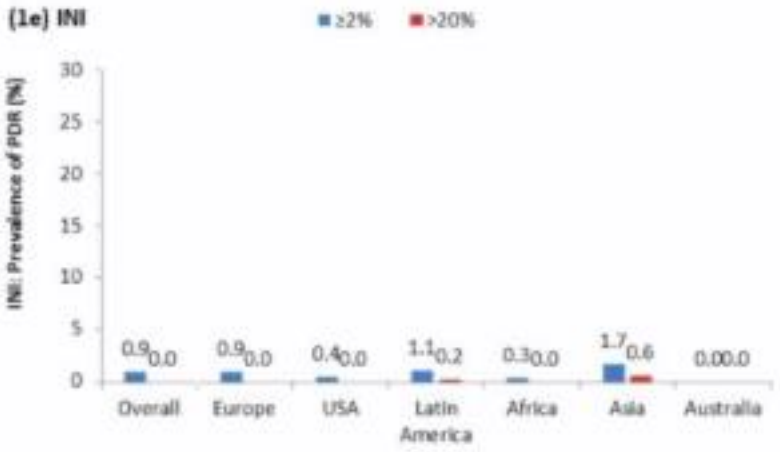
VIROLOGIE, TRAITEMENTS ARV

Baseline resistance in the START trial, 2009-2013









Baxter J, et al. 25th CROI, Boston, MA; March 4-7, 2018. Abst 527

Poster 529

High prevalence of NNRTI and INI-resistant polymorphic virus in primary HIV infection

ML Chaix[1,2], M Grude[3], H Delagrèverie[1,2], C Roussel[4], H Pere[5], H Le Guillou-Guillemette[6], J Dina[7], A Signori-Schmuck[8], MJ Carles[9], L Morand-Joubert[10], J Izopet[11], L Meyer[12], L Assoumou[3], D Descamps[13] on behalf the AC11 ANRS Resistance Group

1- INSERM U941, Université Paris Diderot, Sorbonne Paris Cité, CNR VIH, 2 -AP-HP, Laboratoire de Virologie, Hôpital Saint-Louis, Paris, 3- Sorbonne Universités, UPMC Univ Paris 06, INSERM, Institut Pierre Louis d'épidémiologie et de Santé Publique (IPLESP UMRS 1136), 4- Laboratoire de Virologie, CHU Amiens, 5-AP-HP, Service de Virologie, HEGP, Paris , 6- AP-HP, Service de Virologie, Hôpital Tenon, Paris , 7- Laboratoire de Virologie, CHU Caen, 8- Laboratoire de Virologie, CHU Grenoble, 9 - Laboratoire de Virologie, CHU Nimes, 10 Laboratoire de Virologie, CHU Saint Antoine, Paris, 11 -Department of Virology, Federative Institute of Biology, CHU Toulouse, Department of Physiopathology Toulouse Purpan, Inserm Unit U563, Toulouse 12- University Paris Sud, INSERM CESP U1018, APHP Bicêtre Hospital, Paris, 13- INSERM UMR1137, Université Paris Diderot Sorbonne Paris Cité, AP-HP, Laboratoire de Virologie, Hôpital Bichat-Claude Bernard, CNR VIH Paris, France

Marie-Laure Chaix, MD, PhD
Université Paris Diderot
Paris, France
E-mail: marie-laure.chaix@aphp.fr

Objective

Results

Table 1. Population Characteristics at baseline

Men (n. %)	1009	90 %
Age, median, IQR (years)	36	[28, 45]
Risk Group (n. %)		
Homosexual	789	74%
Heterosexual	199	19%
Others or unknown	77	7%
CD4/mm3, median, IQR	479	[329, 636]
HIV-1 RNA (log_{10} copies/ml), median, IQR	5.5	[4.7, 6.4]
Subtype		
B	638	57%
Non B	483	43%

Table 2. RAMs according to the Stanford list and the ANRS algorithm 2017

At least 1 RAM using WHO list	**10.8%**
At least 1 NRTI RAM using Stanford list	5.0%
At least 1 NNRTI RAM using Stanford list	4.0%
At least 1 PI RAM using Stanford list	2.9%
At least 1 RAM using Stanford + ANRS (2017)	**18.6%**
At least 1 NNRTI RAM using Stanford list + ANRS (2017)	12.7%
At least 1 II RAM (ANRS 2017)	5.3%
At least 1 Doravirine RAM	0.9%

Figure1. Frequency of transmitted drug resistant mutations to NRTI, NNRTI, PI and INI according to the year of inclusion

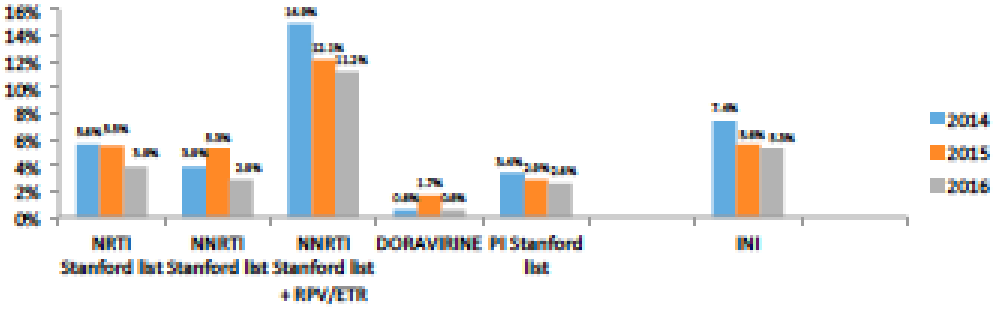
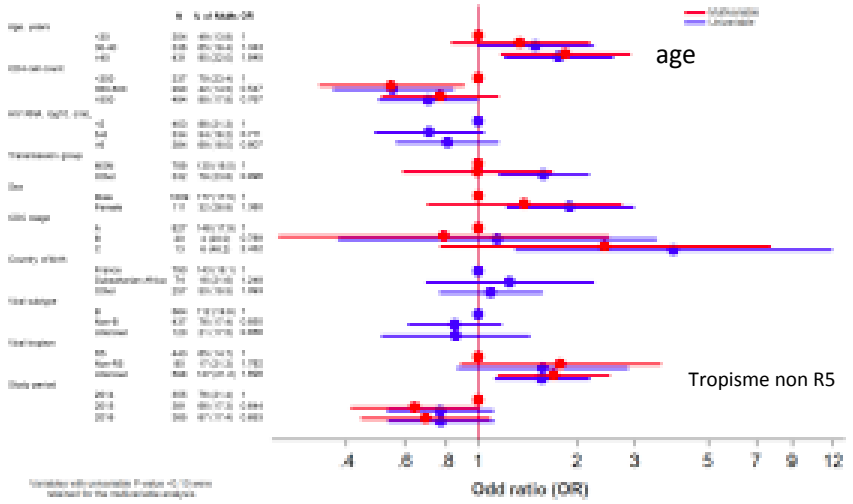


Table 3. Univariate and multivariable analysis, risk factor for RAMs (Satnford+ ANRS)

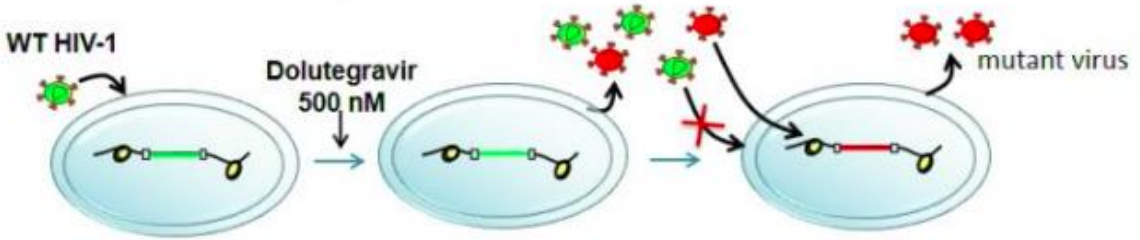


ML Chaix, 529

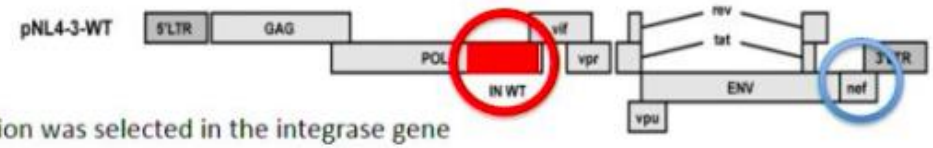
Virus résistant DTG sans mutation sur l'intégrase

Unintegrated viral DNA involved in Dolutegravir resistance ?

Mbio, 2017 I. Malet, F. Subra, C. Richetta, H. Leh, C. Charpentier, G. Collin, D. Descamps, E. Deprez, V. Calvez, AG. Marcelin, O. Delelis



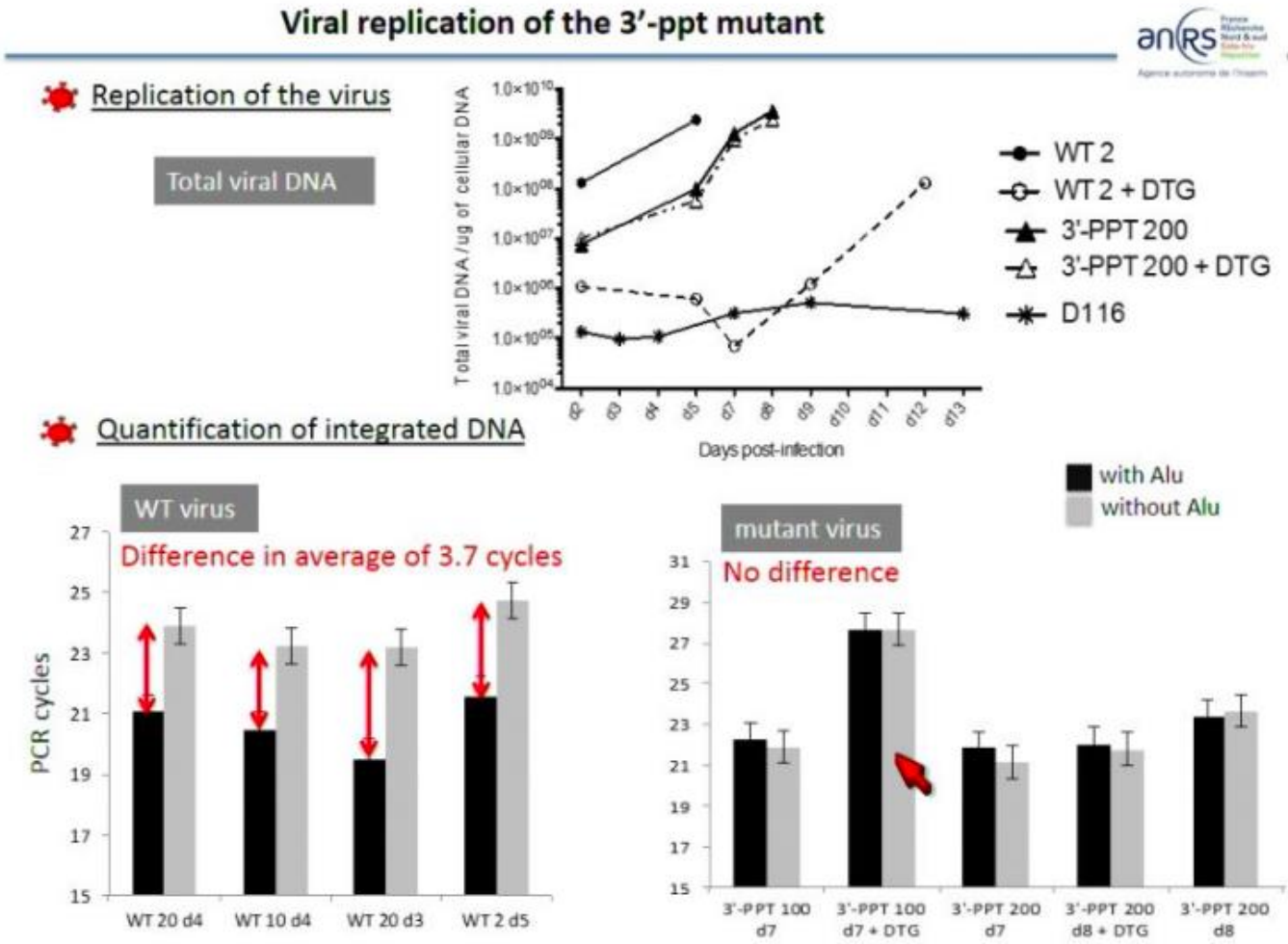
Analysis of the mutant Laï virus



- No mutation was selected in the integrase gene
- Sequencing allowed to highlight the presence of mutations in the 3'PPT region included in the nef gene as shown below

WT sequence	C		G	G	G	G	G	G
Mutated sequence	T		G	C	A	G	T	Δ

Virus résistant DTG sans mutation sur l'intégrase



O Delelis, 544

Conclusions and perspectives

Conclusions

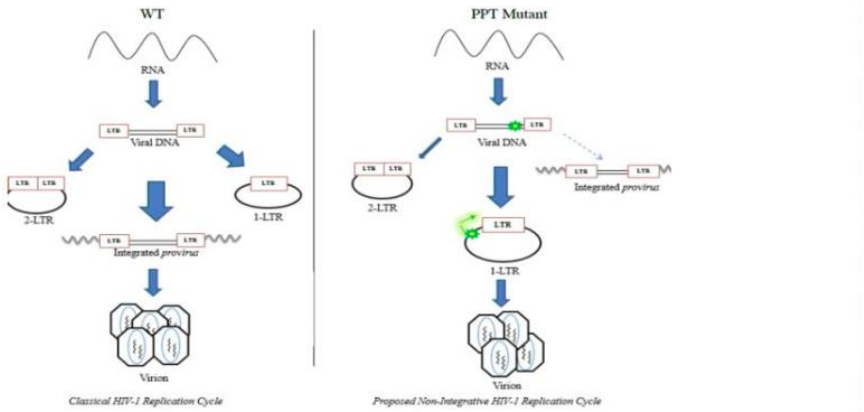
A mutant highly resistant to integrase inhibitors

- Selected mutations in the 3'-PPT region, not in the integrase gene
- Efficient replication with or without a high DTG concentration
- No integrated viral DNA was detected
- We do not observe an accumulation of 2-LTR circles
- We observe a strong accumulation of 1-LTR circles

Further perspectives

- Wijting and colleagues (JID, 2018) report the case of one patient failing DTG with similar mutations in the 3'-PPT region with no mutation in the integrase gene
- Study the mechanism implicated in 1-LTR circles accumulation ?
- Could the accumulation of 1-LTR circles explain the replication of the mutant virus?
- Could the mutation lead to a stronger expression of episomal forms?

Unintegrated viral DNA involved in Dolutegravir resistance ? Poster 544



I. Malet, V. Calvez, AG.Marcelin
F. Subra, C. Richetta, H. Leh, E. Deprez
C. Charpentier, G. Collin, D. Descamps

Hôpital Pitié-Salpétrière.
LBPA, ENS-Paris Saclay.
Hôpital Bichat.

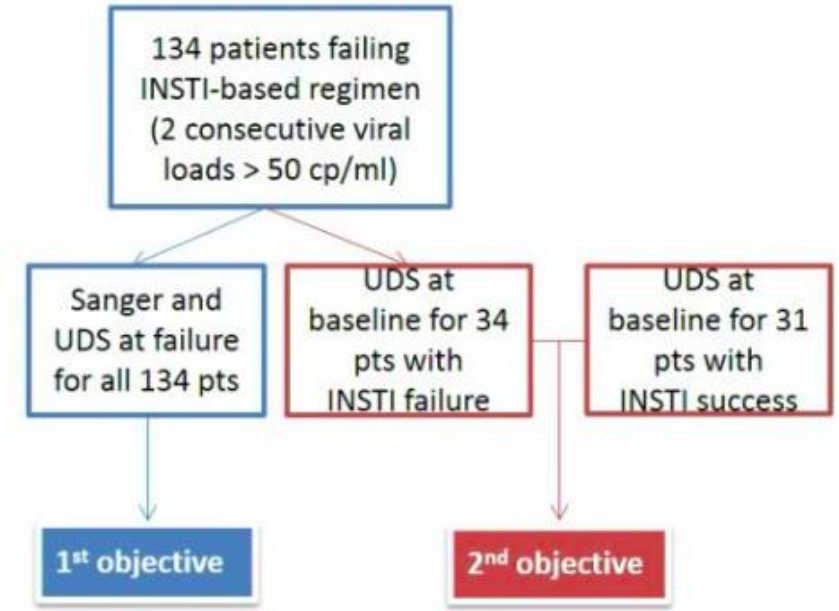
O Delelis, 544

Impact des variants minoritaires résistants à l'intégrase

1) Methods

- Sanger and UDS-Illumina (Miseq)
- Smartgene IDNS® : Data analysis (cut-off 1% and cut-off 5%)
- Resistance interpretation: ANRS algorithm V27 (updated 2017)

2) Study design



INSTIs at failure (n =134)	
RAL	65
EVG	20
DTG	49
HIV-1 viral load (cp/ml)	459 (IQR = 130-4687)
INSTI history	naïve (66%)
Time to failure , median, IQR (months)	6 (3-15)

Characteristics	Failure (n=34)	Success (n=31)
RAL	11	3
EVG	10	15
DTG	13	13
Duration with suppressed viral load, median , IQR (months)	-	15 (12-21)

T.T. Nguyen

Impact des variants minoritaires résistants à l'intégrase

More Resistant Mutations Detected at Failure by UDS

1) *Majority resistant variants (MaRVs) at failure detected by Sanger and UDS*

- At least 1 INSTI MaRV in 40% of patients
- No difference in effective INSTI C_{trough} at failure between patients with at least 1 MaRV and those with no MaRV

2) *Minority resistant variants (MiRVs) at failure detected only by UDS*

- Added MiRVs: in 9% (cut-off 5%) and in 18% (cut-off 1%)
- Resistance interpretation changes in 7% and 13%, respectively (S => I/R or I => R)

Sequencing Techniques	Frequency of detected mutations	Detected mutations (in n patients)													
		T66A/I	L74M/I	E92Q	T97A	E138A/K	G140A/C/S	Y143C/H/R	S147G	Q148H/R	S153F	N155H	E157Q	S230G/R	R263K
Sanger	-	**3**	9	**4**	6	**4**	7	6	**4**	12	0	**24**	3	**0**	0
UDS	>20%	**4**	9	**5**	6	**4**	7	6	**4**	12	0	**25**	3	**1**	0
	5-20%	1	0	2	2	2	0	1	0	1	1	0	0	0	1
	1-5%	5	0	1	1	2	1	2	2	1	0	2	0	1	1
Total UDS	-	10	9	8	9	8	8	9	6	14	1	27	3	2	2

T.T. Nguyen

Impact des variants minoritaires résistants à l'intégrase

Impact of MiRVs ?

3) MiRVs at baseline in patients with VF (n=34) and in those with VS (n=31)

- No difference in prevalence of baseline MiRVs in patients with VF (14.7%) and VS (12.9%)
- 34 patients with VF: 17 carried MaRVs at failure but not previously found at baseline.
- MiRVs at baseline in VF patients: not emerged at failure.

Patients	Treatment at failure	Last viral load at baseline (cp/ml)	Viral load at failure (cp/ml)	MiRVs at baseline	MaRVs at failure	INSTI C_{trough} at failure (ng/ml)-Interpretation
VF	ETR/RAL BID	775	1000	S147G (1.8%)	N155H (100%)	91-Effective
VS	EVG/c/FTC/TDF	1515	-	Q148H (13.1%)	-	-

⇒ **No emergence of MiRVs and no impact of baseline MiRVs on INSTI response**

T.T. Nguyen

Impact des variants minoritaires résistants à l'intégrase

MÉDECINE SORBONNE UNIVERSITÉ

Instituts thématiques Inserm
Institut national de la santé et de la recherche médicale

anrs France REcherche Nord & sud Sida-hiv Hépatites
Agence autonome de l'Inserm

4) Conclusions

- More INSTI resistant mutations at failure detected by UDS compared to Sanger.
- No association between baseline INSTI MiRVs and risk of INSTI failure.
- MiRVs if present at baseline in patients failing INSTI did not emerge as MaRVs at failure.

5) Questions

- Could pre-existing MiRVs **facilitate** the selection of other MaRVs at failure ?
- Could a not fully active backbone and persistence of viremia under INSTIs **ease** the emergence of variants from minority to majority ?
- Existence of new resistant mutation profiles ? (Analyses ongoing)
- Other mechanism of resistance to INSTI ?

This study was funded by ANRS.

T.T. Nguyen

Sélection de mutants résistants (BIC) sur virus préexposés aux InsTI ?

Bictegravir (BIC) has a favorable resistance profile

- BIC is a novel, unboosted, once daily INSTI recently approved in US as STR with F/TAF
- In clinical trials no emergent resistance in 1271 naïve and suppressed patients treated with B/F/TAF
- Cell culture experiments *ex vivo*
  - Breakthrough resistance selections: no breakthrough of BIC or DTG compared to rapid EVG breakthrough
  - Dose escalation resistance selections with BIC: R263K ± M50I (<3-fold change)
  - BIC has an improved resistance profile compared to other INSTIs

IN Genotype	Fold Change vs WT			
	BIC	DTG	EVG	RAL
E92Q	1.2	1.6	60	18
T97A	0.7	0.9	10	1.8
F121Y	0.4	0.6	16	9.2
Y143C	0.9	0.9	2.2	4.3
Y143R	1.4	1.4	2.2	16
Q148H	0.7	0.8	8.7	4.3
Q148K	0.8	0.7	108	43
Q148R	0.7	0.7	117	40
N155H	1.4	1.5	41	17
R263K	1.7	1.7	4.5	1.2

IN Genotype	Fold Change vs WT			
	BIC	DTG	EVG	RAL
T97A, N155H	1.0	1.5	95	53
E138K, Q148R	1.7	2.2	>150	54
G140A, Q148R	2.0	2.2	>150	88
G140S, Q148H	2.5	5.6	>150	>143
G140S, Q148H, G163K	2.5	5.7	>150	>143
L74M, G140C, Q148R	8.4	9.1	>150	>143
T97A, G140S, Q148H	4.4	15	>150	>143
E138K, G140S, Q148H	2.5	5.3	>150	>143
E138A, G140S, Q148H	7.2	10	>150	>143
E138K, G140A, Q148K	19	63	>150	>143

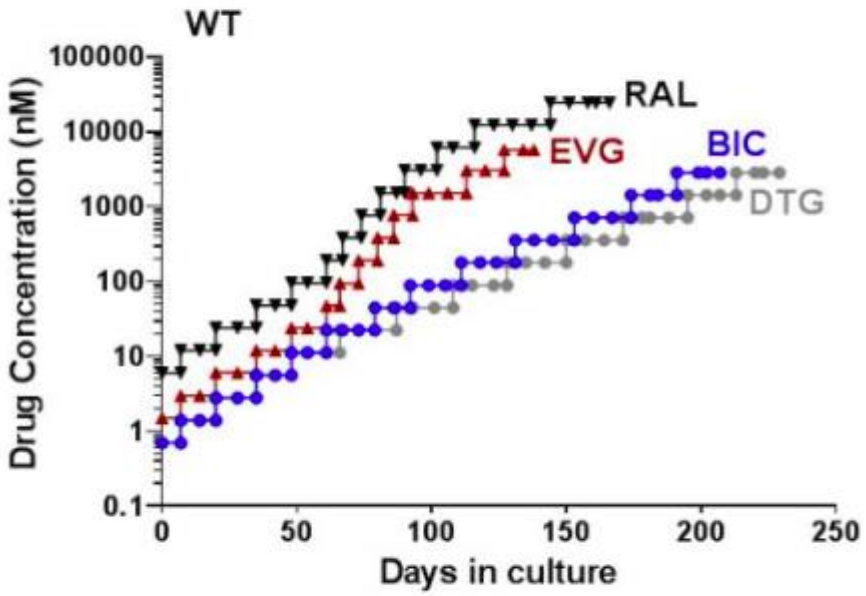
Tsiang et al, Antimicrobial Agents and Chemotherapy, 2006 and data on file

2

K Andreatta, 546

Sélection de mutants résistants (BIC) sur virus préexposés aux InsTI ?

Dose escalation resistance selections with wild-type HIV-1



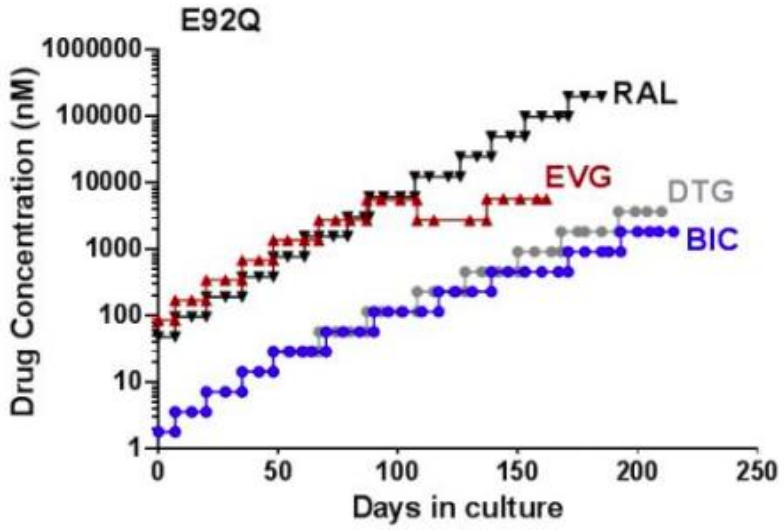
Selecting Drug	IN Genotype at Final Passage (Frequency, NGS)	Fold Change vs WT			
		BIC	DTG	EVG	RAL
None	Wild-type [starting virus]	1.0	1.0	1.0	1.0
RAL	Q148K (98%) G118D (21%) E138K (3%)	0.8	0.8	71	47
EVG	Q148K (61%) E138K (55) T66I (50%) Q148R (23%) Q146L (12%) E92V (5%)	2.9	3.3	>145	61
DTG	S153Y (99%)	2.0	1.9	2.9	1.4
BIC	S153F (100%)	1.4	1.7	2.8	1.4

NGS=Next Generation Sequencing

K Andreatta, 546

Sélection de mutants résistants (BIC) sur virus préexposés aux InsTI ?

INSTI selections with HIV-1 E92Q mutant



*E92Q+G140E has very low replication capacity, did not grow in a multi-cycle assay, and may not be viable in vivo

Selecting Drug	IN Genotype at Final Passage (Frequency, NGS)	Fold Change vs WT			
		BIC	DTG	EVG	RAL
None	E92Q [starting virus]	1.2	1.5	33	5.5
RAL	E92Q (>99%) G140A (62%) L74M (14%)	1.2	1.8	63	27
EVG	E92Q (>99%)	1.1	1.5	22	5.3
DTG	E92Q (>99%) S147G (5%) E157K (2%)	1.1	1.4	26	4.9
BIC	E92Q (>99%) G140E (58%) V151I (7%)	0.9	1.7	25	9.4
Site-Directed Mutant	G140E	1.1	0.9	2.4	1.0
Site-Directed Mutant	E92Q + G140E *Replication Capacity = 0.6%	>104	>232	>114	>105

K Andreatta, 546

Sélection de mutants résistants (BIC) sur virus préexposés aux InsTI ?

Conclusions

- Further defined BIC resistance from WT HIV-1
  - Two patterns of low-level resistance after extended culture with BIC
    - R263K ± M50I (<3-fold reduced susceptibility)
    - S153F or S153Y (≤2-fold reduced susceptibility)
- Slow or no development of additional IN resistance substitutions after BIC selections from INSTI-R HIV-1

Selection condition	INSTI-R Substitutions at Final Time points (Fold Change)				
	WT	E92Q	Q148R	N155H	R263K
BIC	S153F (1.4)	E92Q, G140G/E, V151V/I (0.9)*	Q148R, G140G/E, E157E/K (0.6)	N155H (1.3)	R263K (1.7)
DTG	S153Y (1.9)	E92Q, S147S/G, E157E/K (1.4)	Q148R, E138K (1.4)	N155H, S147S/N (1.4)	R263K, E157E/K (1.8)

* E92Q+G140E has high-level INSTI-R but very low replication capacity

Poster 546 Andreatta et al.
Poster 549 Brenner et al.

Implications

- Slow development of resistance by BIC in HIV-1 ± INSTI-R confirms BIC's high barrier to resistance and supports future studies of B/F/TAF in patients with preexisting drug resistance

6

K Andreatta, 546

Durability of Initial Regimens when Starting ART with -200 CD4 and >5 log10 HIV-RNA (ICONA), 1127 Participants

Figure 1. Cumulative probability of TF according to the anchor drug of the initial ART regimen.

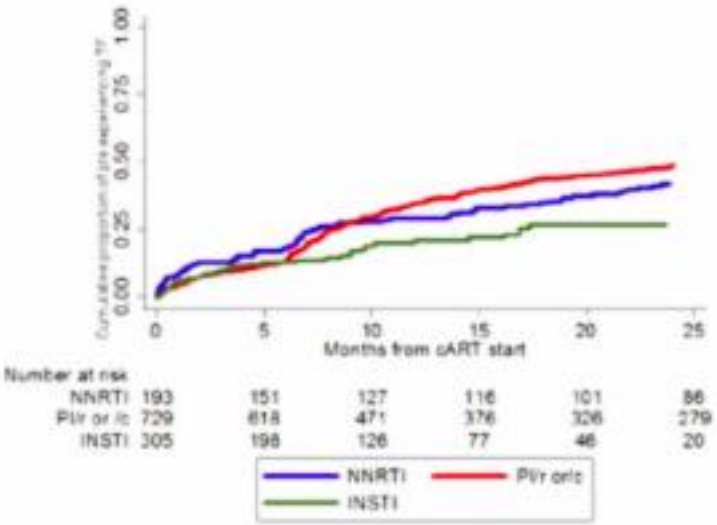
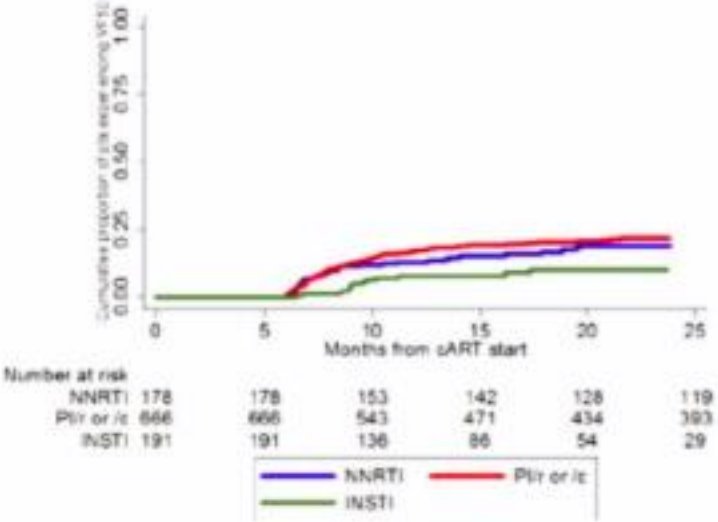


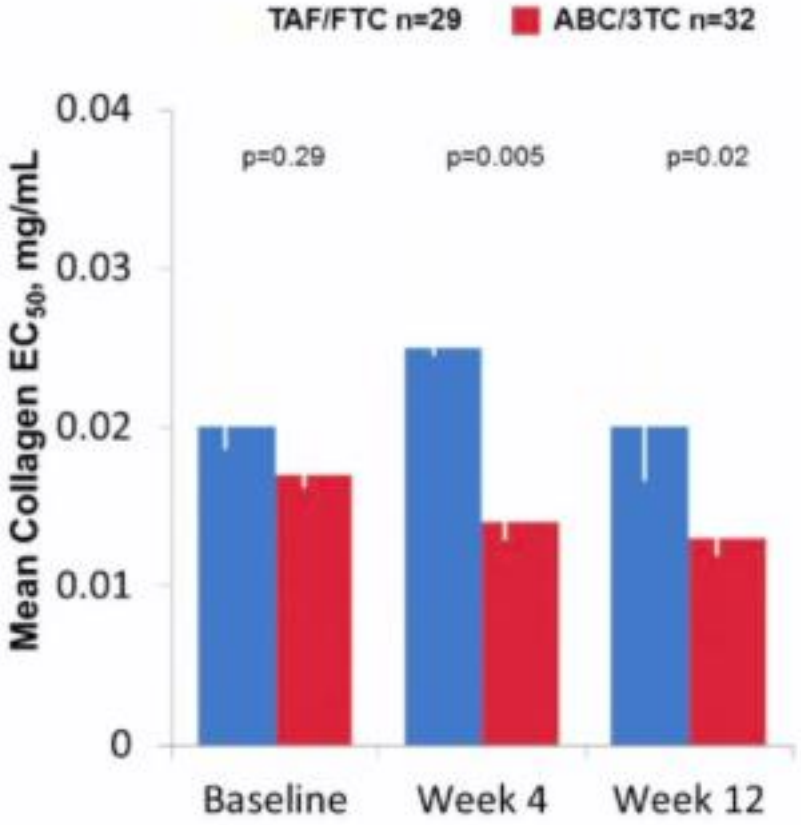
Figure 2. Cumulative probability of VF according to the anchor drug of the initial ART regimen.

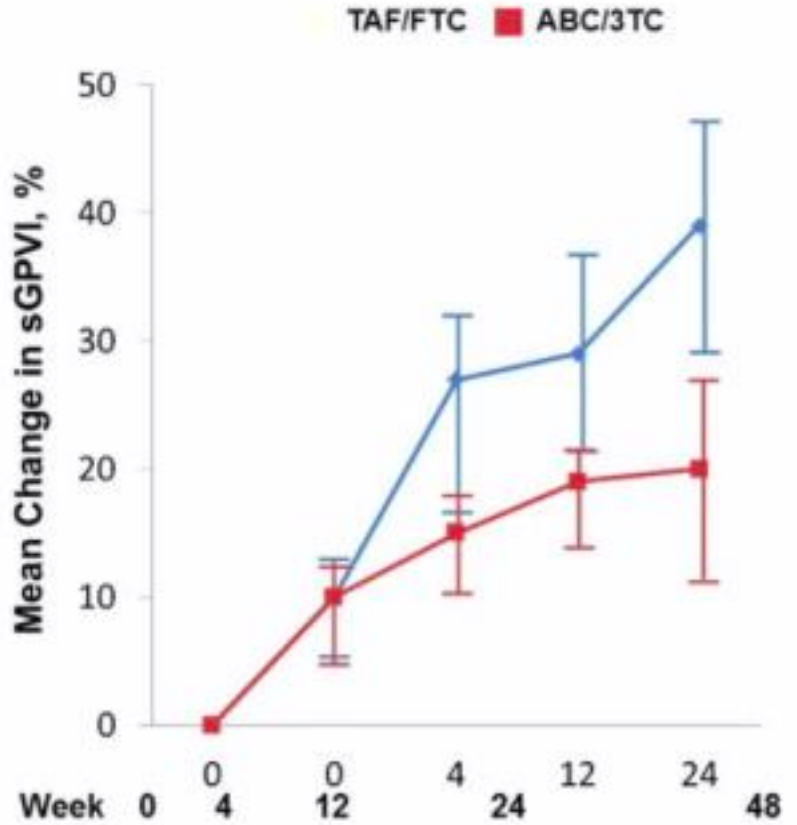


Anchor drug class (alternative 2)				
NNRTI	0.62 (0.50-0.78)	<0.001	0.65 (0.52-0.82)	<0.001
bPI	1.00		1.00	
INSTI	0.72 (0.54-0.95)	0.019	0.69 (0.52-0.92)	0.012

Association not maintained if baseline viral load >500,0000
Viral load >500,0000 only factor associated with virological failure

GS1717: Platelet Reactivity in Response to Collagen and Plasma Soluble Glycoprotein VI





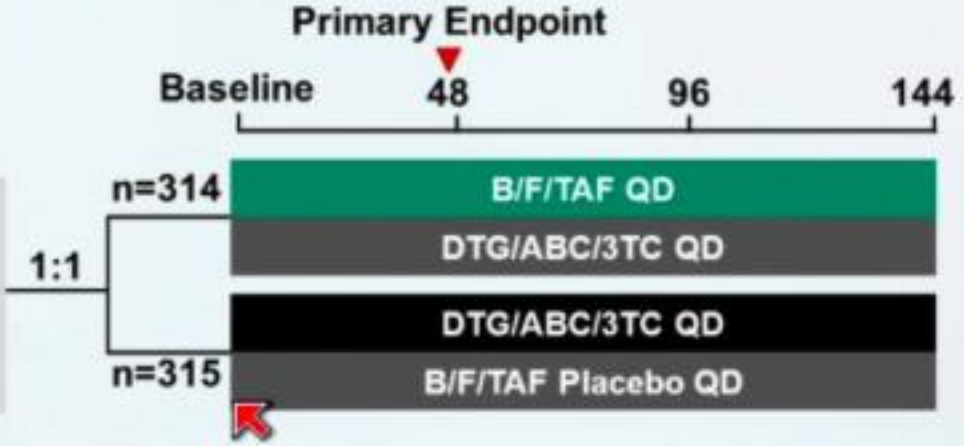
Mallon P, et al. 25th CROI, Boston, MA, March 4-7, 2018. Abst. 50.

Pooled Week 48 Efficacy and Baseline Resistance: B/F/TAF in Treatment-Naive Patients

B/F/TAF Treatment-Naïve Study Designs

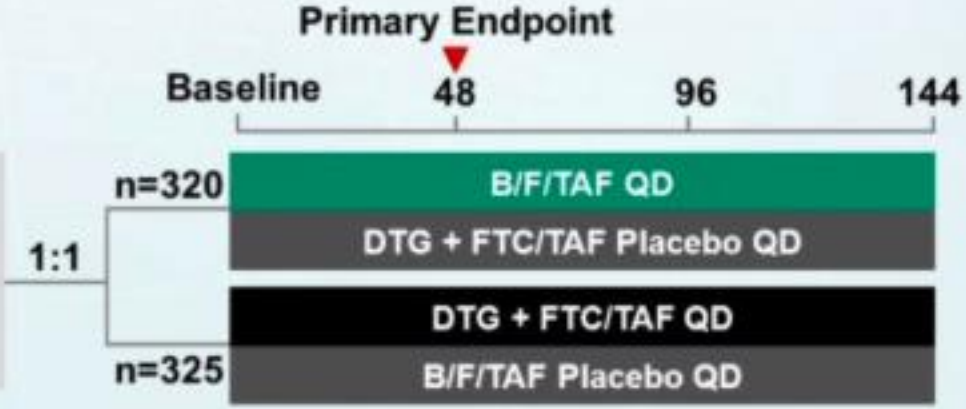
Study 1489

Treatment-Naïve Adults
- HIV-1 RNA ≥ 500 c/mL
- $eGFR_{CG}$ ≥ 50 mL/min
- HLA B*5701 negative



Study 1490

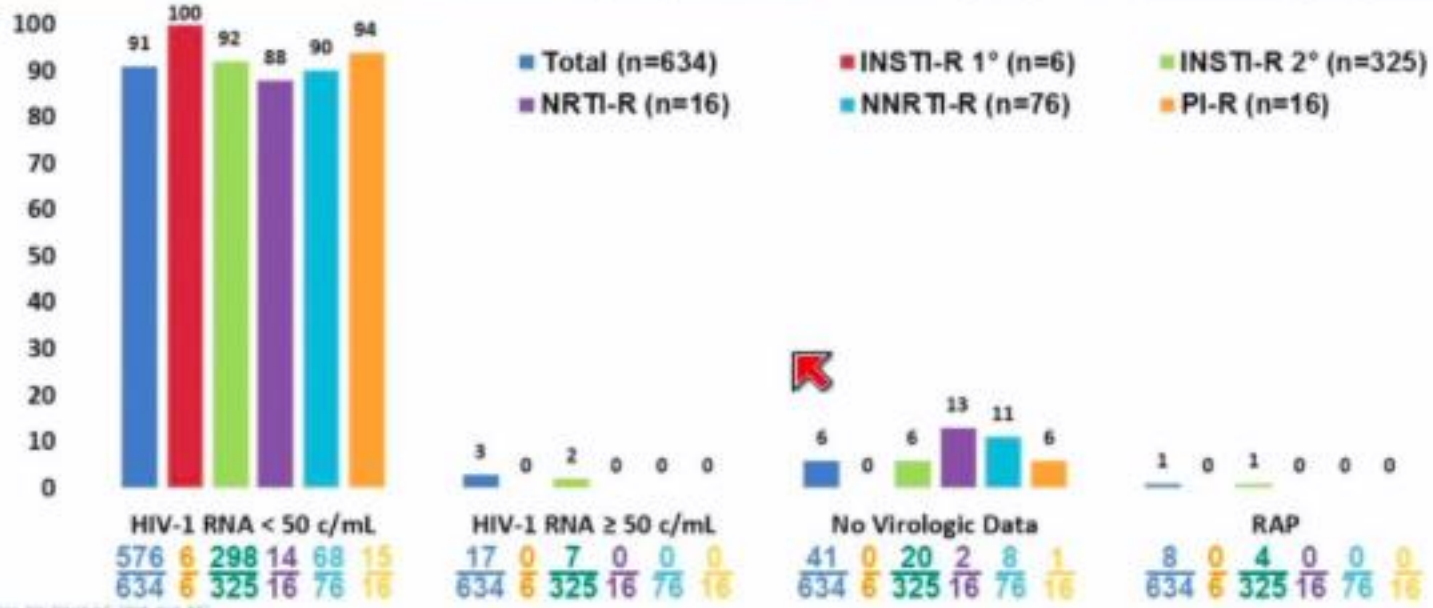
Treatment-Naïve Adults
- HIV-1 RNA ≥ 500 copies/mL
- $eGFR_{CG}$ ≥ 30 mL/min



White K, et al. 25th CROI. Boston, MA. March 4-7, 2018. Abst 532

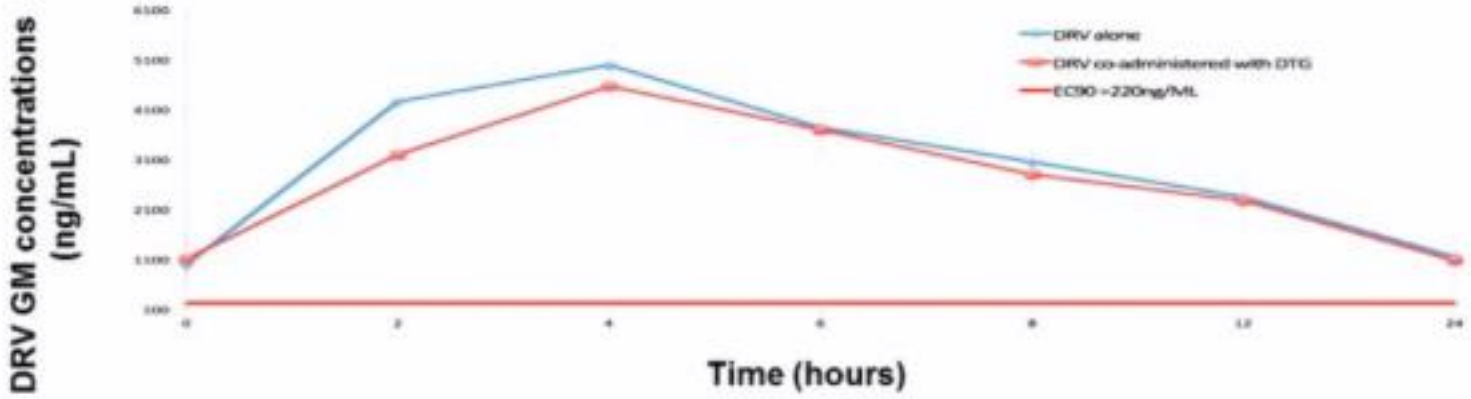
B/F/TAF in Treatment-Naive Patients: Resistance

	B/F/TAF n=634	DTG/ABC/3TC n=315	DTG+F/TAF n=325
Primary INSTI-R	6 (1.0%)	4 (1.3%)	6 (1.9%)
T97A	5 (0.8%)	4 (1.3%)	6 (1.9%)
Q148H	1 (0.2%)	0	0
Primary NRTI-R[a]	16% (2.5%)	5 (1.6%)	5 (1.5%)
Primary NNRTI-R	76 (12%)	51 (16%)	41 (13%)

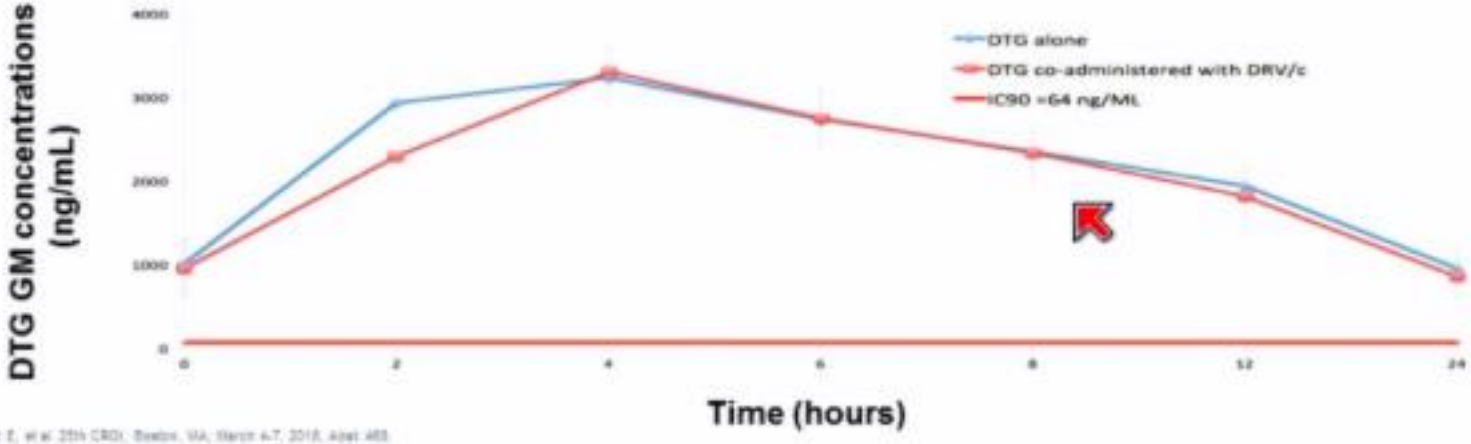


No Significant DTG + DRV/c Interaction

GM Darunavir (DRV) Concentrations Over 24 Hours With and Without DTG

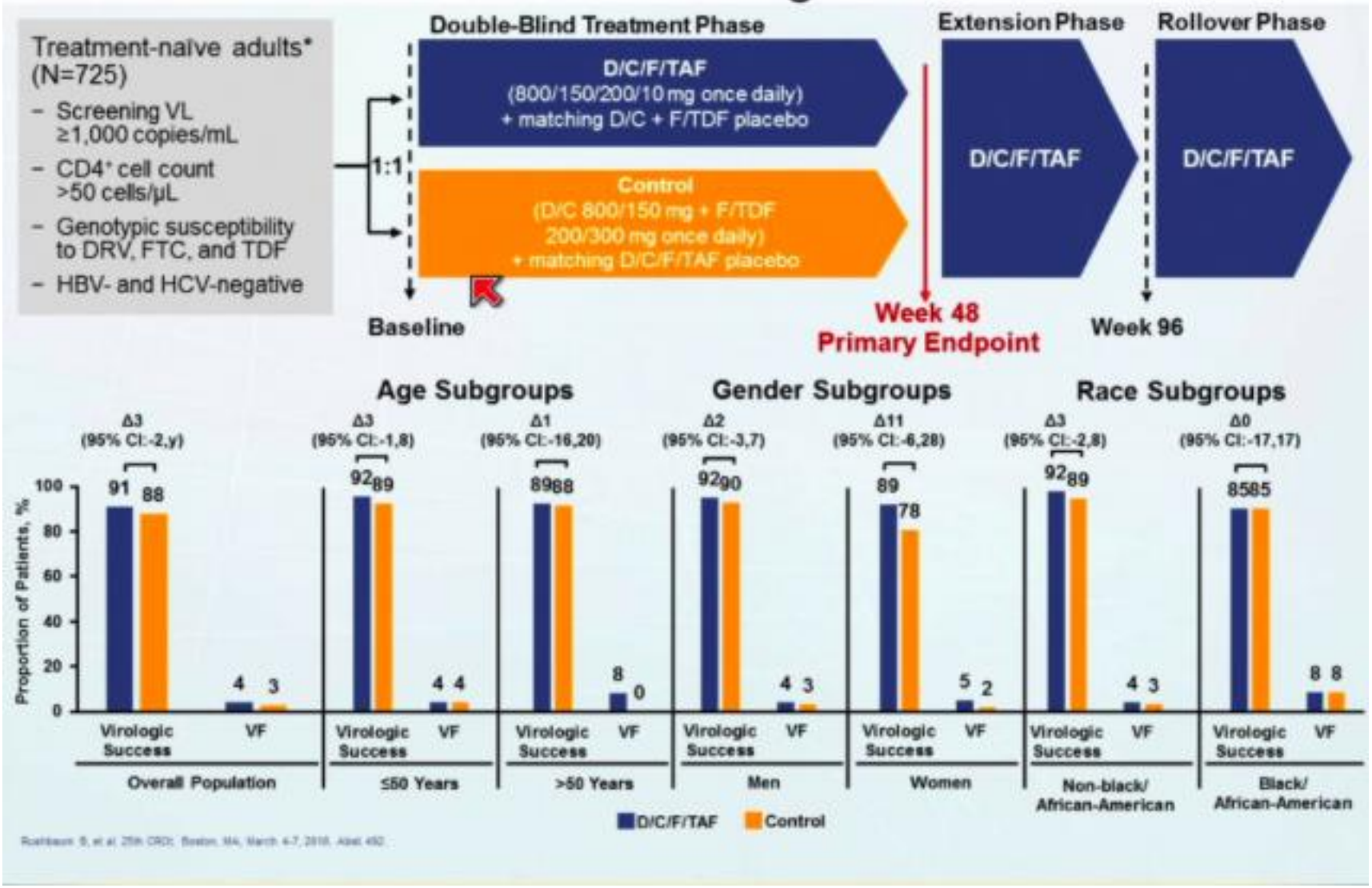


GM Dolutegravir (DTG) Concentrations Over 24 Hours With and Without DRV/c



Dorr E, et al. 25th CROI. Boston, MA. March 4-7, 2018. Abst 483.

AMBER Study: Analyses of D/C/F/TAF in HIV-1 Treatment-Naïve Patients – Design and VR at Week 48

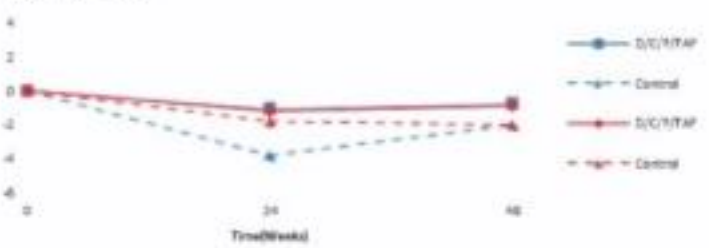


Similar Safety of D/C/F/TAF By Naive Subgroup

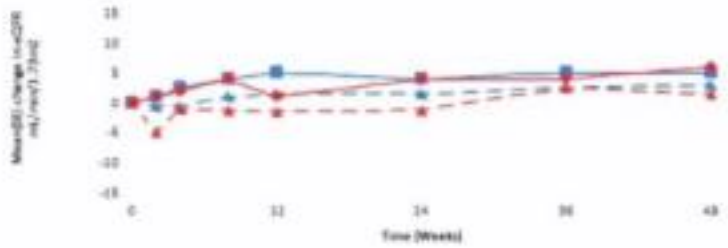
Mean Change in $eGFR_{cystC}$ and BMD From Baseline to Week 48*and BMD

A. Age subgroups

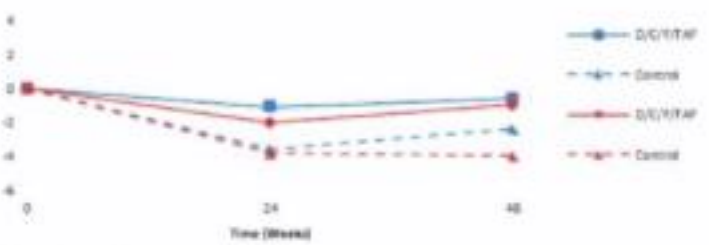
Lumbar spine



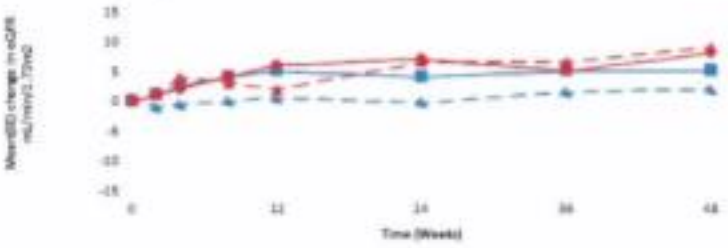
B. Gender subgroups



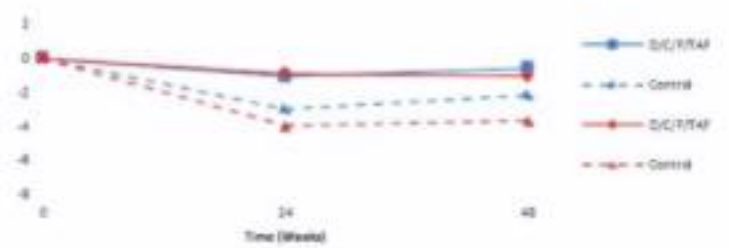
Lumbar spine



C. Race subgroups



Lumbar spine

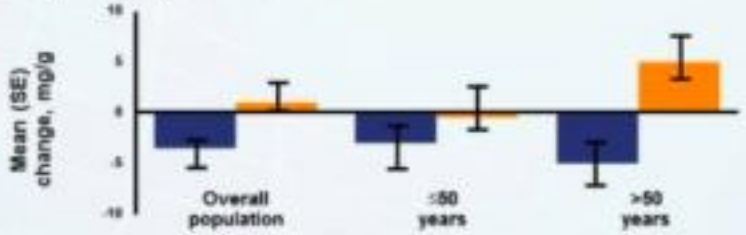


Ruane P, et al. 25th CROI. Boston, MA. March 4-7, 2018. Abst 492.

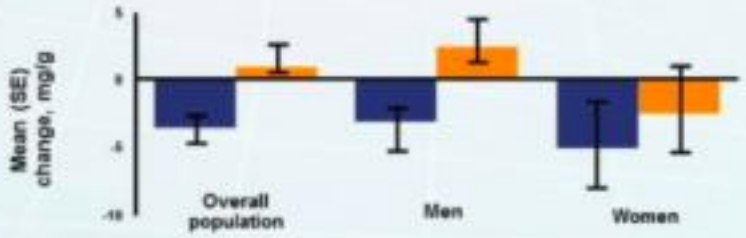
Similar Safety of D/C/F/TAF by Switch Subgroup

Urine albumin: creatinine ratio

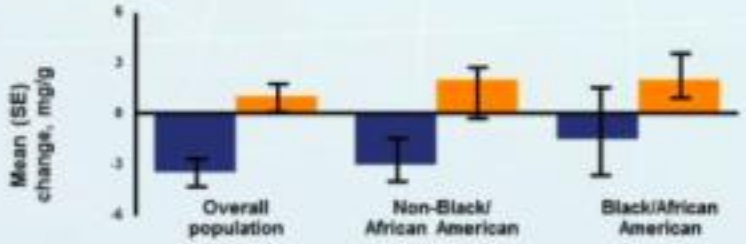
D. Age subgroups



E. Gender subgroups

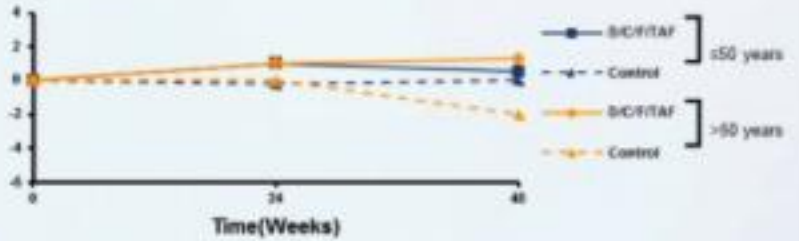


F. Race subgroups

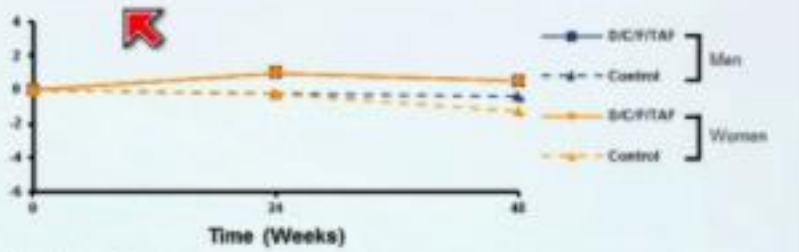


Lumbar BMD

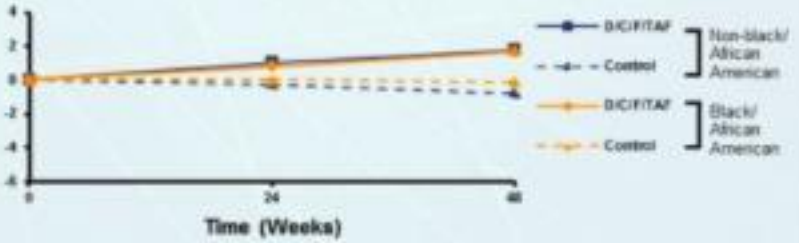
Lumbar spine



Lumbar spine



Lumbar spine



Rushbaum B, et al. 25th CROI. Boston, MA. March 4-7, 2018. Abst 492.

DRIVE-AHEAD Study: DOR/3TC/TDF versus EFV/FTC/TDF

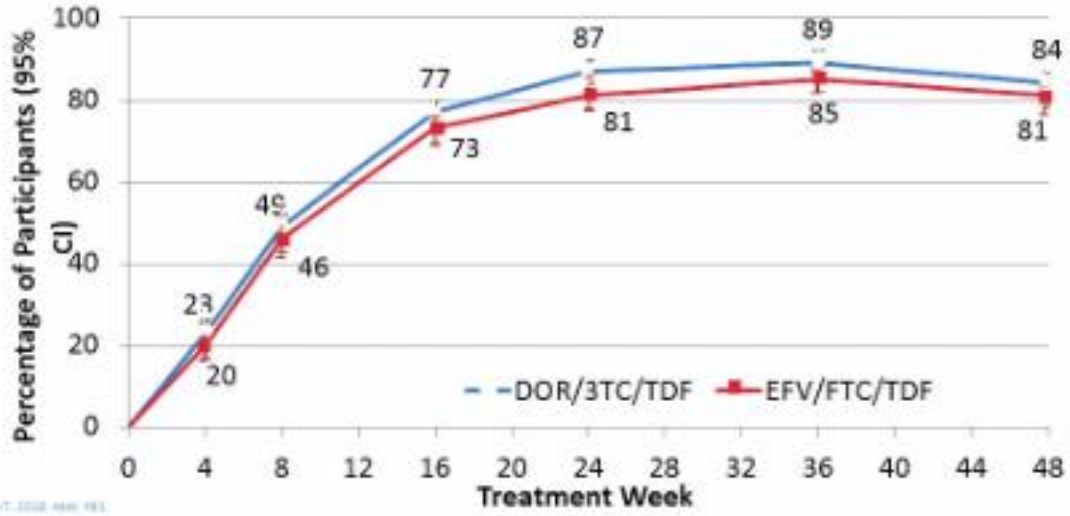
Key Entry Criteria:

- HIV-1 RNA≥1,000 copies/mL within 45 days before Day 1
- Antiretroviral-naïve
- No genotypic resistance to any study drugs
- Stratification factors: screening HIV-1 RNA level (≤100,000 copies/mL); chronic hepatitis B or C infection (yes/no)

Group 1 N=340	DOR 100 mg/3TC 300 mg/TDF 300 mg QD + Placebo	14-Day Follow-Up
Group 2 N=340	EFV 600 mg/FTC 200 mg/TDF 300 mg QD + Placebo	14-Day Follow-Up

Primary Analysis Time Point

At Week 96, eligible patients may opt to continue for an additional 96 weeks (study extension phase)

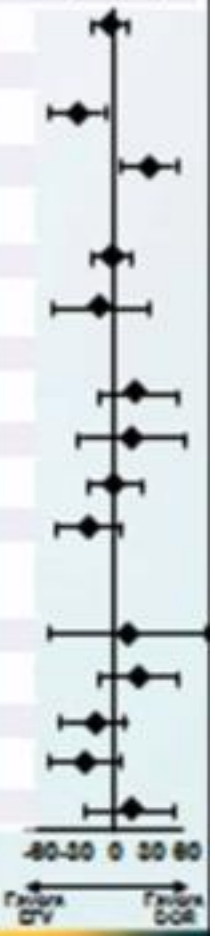


Drive Ahead: Sub Group Analysis

HIV-1 RNA <50 copies/mL

	% of Participants (N)		Difference
	DOR/3TC/TDF	EFV/FTC/TDF	(95%CL)
All Participants	88.7 (346)	88.8 (331)	
Baseline HIV-1 RNA			
≤100,000 copies/mL	90.6 (277)	91.1 (258)	
>100,000 copies/mL	81.2 (69)	80.8 (73)	
≤500,000 copies/mL	89.3 (337)	89.8 (314)	
>500,000 copies/mL	66.7 (9)	70.6 (17)	
Baseline CD4+ T Cell Count			
≤50/mm³	62.5 (8)	66.7 (9)	
>50 and ≤200/mm³	70.6 (34)	88.2 (34)	
>200/mm³	91.4 (304)	89.6 (288)	
Viral Subtype			
Subtype B	87.8 (222)	89.4 (226)	
Subtype Non-B	90.2 (122)	87.6 (105)	
HBV or HCV Co-Infection			
Positive	88.9 (9)	100 (8)	
Negative	88.7 (337)	88.5 (323)	

	% of Participants (N)		Difference
	DOR/3TC/TDF	EFV/FTC/TDF	(95%CL)
All Participants	88.7 (346)	88.8 (331)	
Age			
≤Median (31y)	83.4 (175)	92.0 (187)	
>Median (31Y)	94.2 (171)	84.7 (144)	
Gender			
Male	88.6 (290)	88.3 (283)	
Female	89.3 (56)	91.7 (48)	
Race/Ethnicity			
Asian	96.6 (58)	90.0 (60)	
Black	85.7 (63)	81.0 (63)	
White	89.8 (166)	89.6 (154)	
Hispanic/Latino	85.4 (123)	91.8 (110)	
HBV or HCV Co-Infection			
Africa	85.3 (34)	81.5 (27)	
Asia/Pacific	96.6 (58)	89.5 (57)	
Europe	90.4 (83)	92.9 (85)	
Latin America	86.5 (89)	93.8 (80)	
North America	85.4 (82)	81.7 (82)	



DRIVE-AHEAD Study: Clinical Adverse Events

	Male		Female	
	DOR/3TC/TDF N=305	EFV/FTC/TDF N=311	DOR/3TC/TDF N=59	EFV/FTC/TDF N=53
One or more AEs	83.6	91.0	78.0	88.7
Drug-related AEs	32.1	65.3	25.4	49.1
Serious AEs	3.6	5.8	3.4	5.7
Discontinued due to AE	3.0	6.4	3.4	7.5
Most Common AEs				
Abnormal dreams	5.2	13.2	1.7	1.9
Dizziness	9.2	38.6	6.8	28.3
Headache	12.5	12.9	15.3	9.4
Diarrhea	11.8	14.8	5.1	5.7
Nausea	7.5	10.6	8.5	11.3
Nasopharyngitis	11.5	9.0	6.8	5.7
Rash	4.9	12.5	3.4	9.4

ANDES Study: DRV/R/3TC FDC Vs DRV/r –TDF-3TC for HIV-1 Treatment-Naïve Patients: Week 48 Results

	Global (n=145)	Triple Therapy (n=70)	Double Therapy (n=75)
	33.1±9.9 30 (25.5-39.5)	32.5±8.4 30 (26-38)	33.7±11.1 30 (24-92)
Males	131 (91%)	61 (88%)	70 (93%)
Hispanic/Latino	102 (71%)	49 (71%)	53 (71%)
MSM/Bisexual	101 (73%)	48 (71%)	53 (76%)
CDC Stage B	11 (8%)	5 (7%)	6 (8%)
Viral Load (log)	4.5 (4.0-5.0)	4.5 (3.9-5.0)	4.6 (4.1-5.1)
CD4 Count	383 (286-562)	366.5 (275-544)	419 (290-564)
CD4 %	19 (14-25)	19 (14-25)	19 (14-25)
VL > 100000 c/mL (Baseline)	35 (24%)	15 (22%)	20 (27%)

FUNDACIÓN HUÉSPED

ID *489*

DRV/R FDC plus 3TC for HIV-1 treatment naive patients: Week 48 results of the ANDES study

Authors:, Maria I. Figueroa[1], Omar G. Sued[1], Ana M. Gun[1], Waldo H. Belloso[2], Diego M. Cecchini[3], Gustavo Lopardo[4], Daniel Pryluka[5], Maria J. Rolon[1], Valeria I. Fink[1], Santiago Perez Lloret[6], **Pedro Cahn**[1]
[1]Fundación Huésped, [2]Hospital Italiano, [3]Hospital Argerich,[4]Centro de Estudios Infectológicos,, [5]Consultorio Infectológico,, [6]University of Buenos Aires, all in Buenos Aires, Argentina

ESTUDIO ANDES

Table 1. Demographics at screening

* All patients were on CDC stage A or B			

Figure 1. Proportion of patients with plasma HIV-1 RNA less than 50 copies/ml.

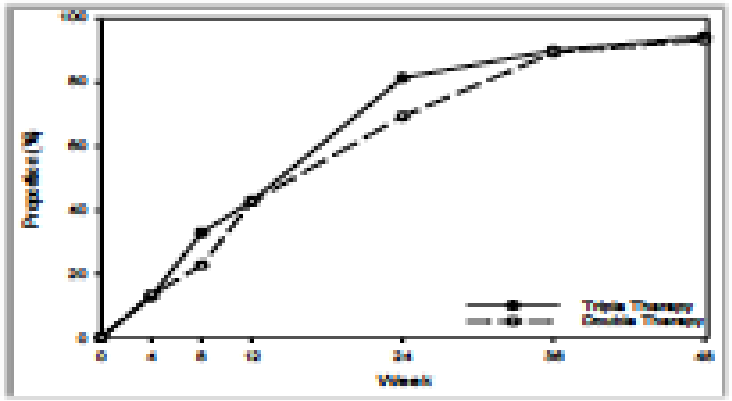


Figure 2 :CD4 count Increase (means ± standard error of the mean)

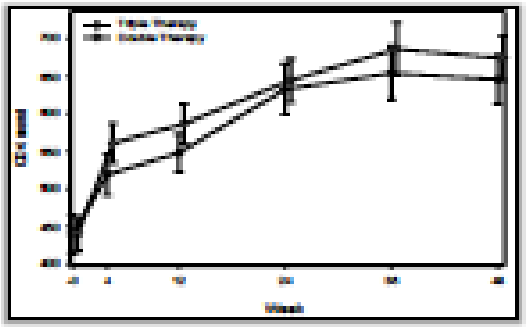


Table 2. Efficacy analysis

P Cahn, 489

503

Who wants to switch? Gauging interest in potential new antiretroviral therapies

Jan Ostermann[1,2], Caroline Derrick[1], Amy Hobbie[2], Andrew Weinhold[2], Noor Al-Shareef[2], Valerie Yelverton[1,2], Sharon Weissman[1], Helmut Albrecht[1], Nathan Thielman[2]
[1] University of South Carolina, Columbia, SC, USA, [2] Duke University, Durham, NC, USA, [3] Hochschule Neubrandenburg, Germany

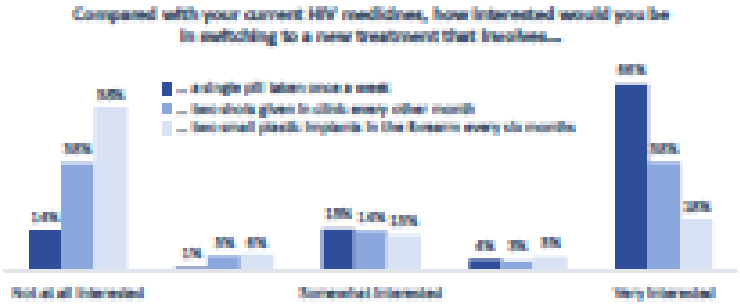


Figure 3. Interest in switching to novel drug delivery modalities

RESULTS

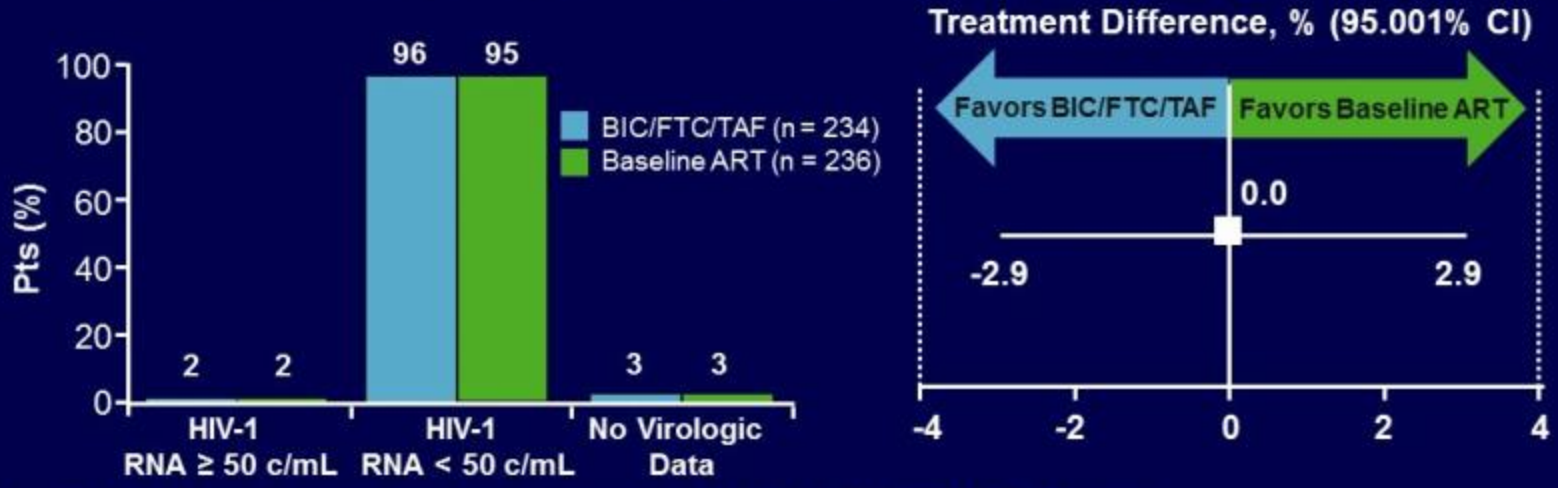
Table 1 / Figure 2. Characteristics of the study cohort (N=263) and corresponding distributions of levels of interest in switching to novel drug delivery modalities (%). Bars in the figure correspond to the categories shown in the table (categorical variables only; * indicates continuous variable).

J Ostermann, 503

Switch B/F/TAF

Switch From Suppressive PI- or INSTI-Based ART to BIC/FTC/TAF in Women

- Open-label, randomized, active-controlled phase III trial in 470 women with viral suppression for ≥ 6 mos on EVG/COBI/FTC/(TAF or TDF) or ATV + RTV + FTC/TDF
  - Primary endpoint: Wk 48 HIV-1 RNA ≥ 50 c/mL (FDA snapshot; noninferior. margin 4%)

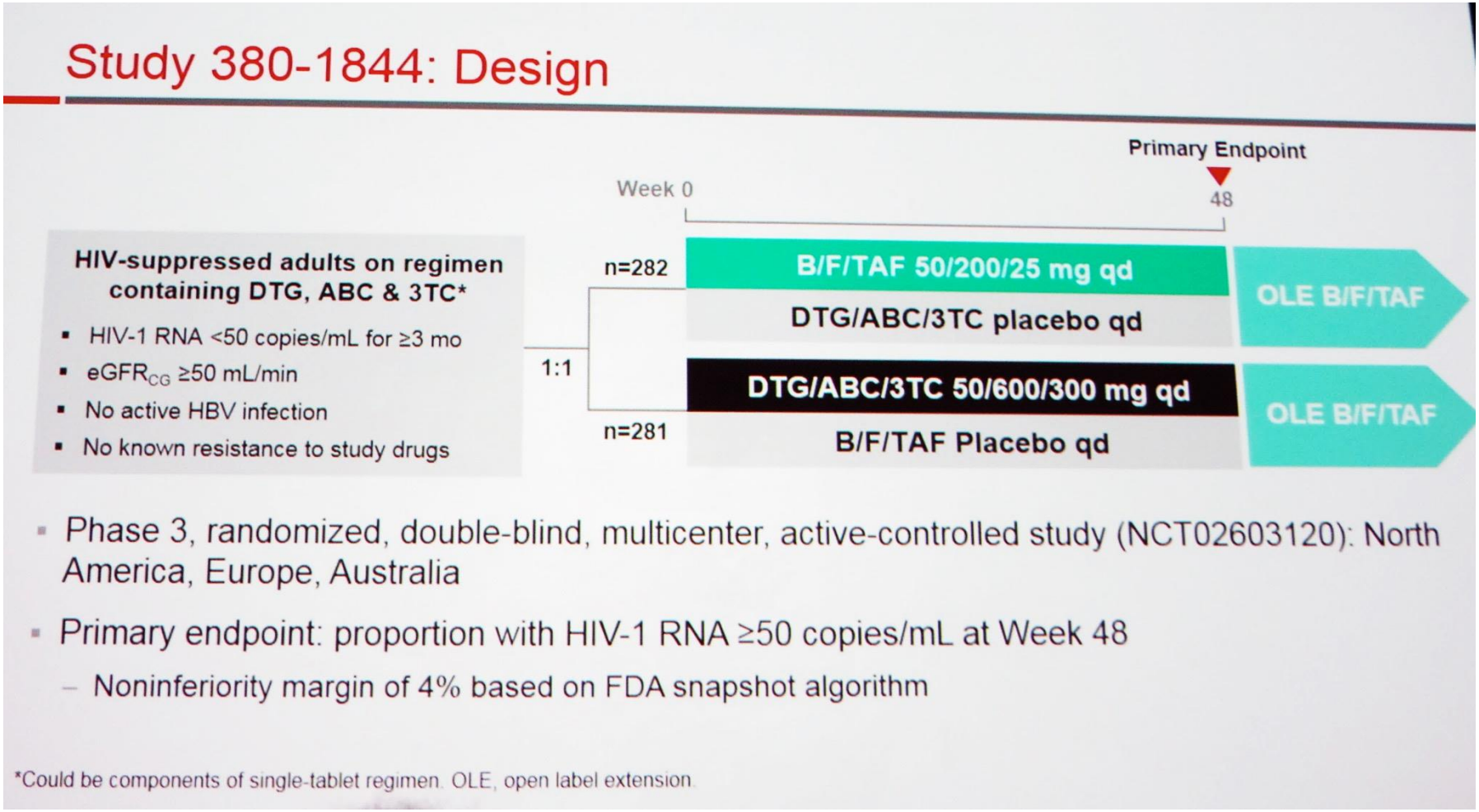


- No treatment-emergent resistance detected in BIC/FTC/TAF arm

Kityo C, et al. CROI 2018. Abstract 500.

Slide credit: clinicaloptions.com

Étude GS1844: Switch Triumeq vers BIC/F/TAF

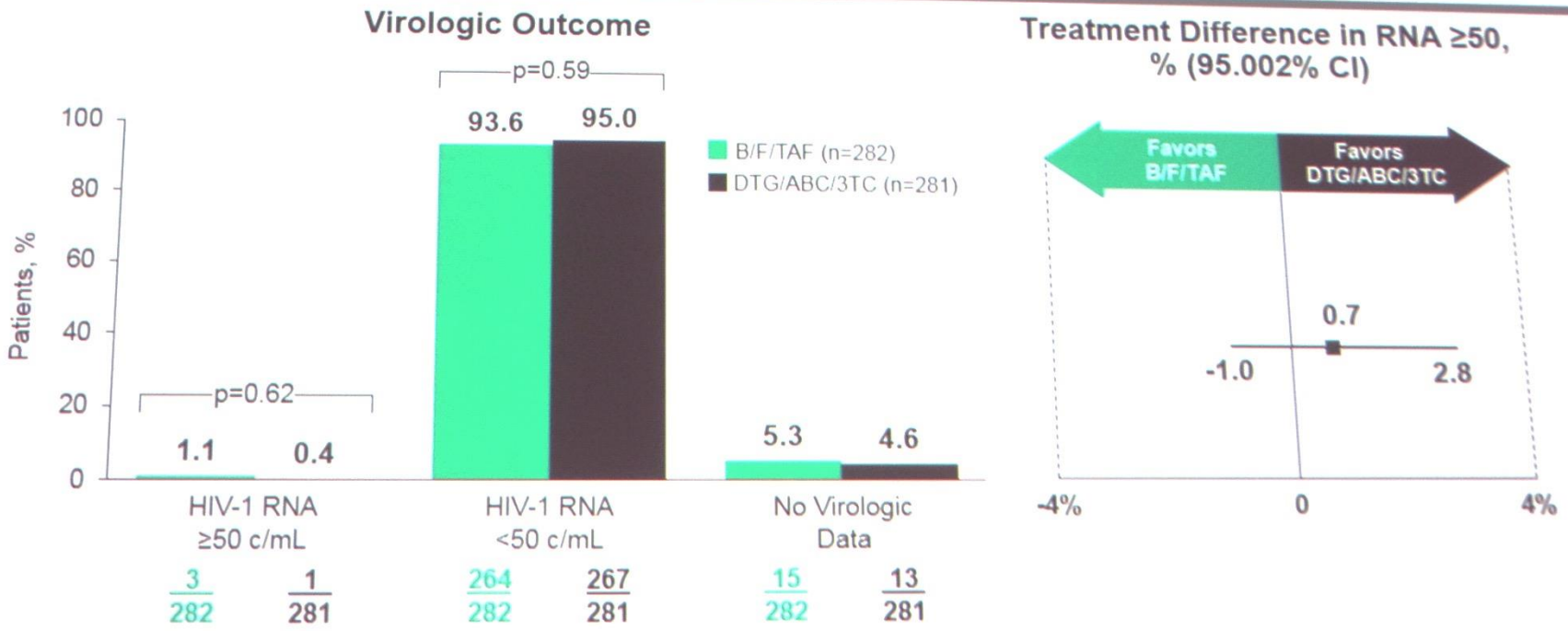


JM Molina , 22

Étude GS1844: Switch Triumeq vers BIC/F/TAF

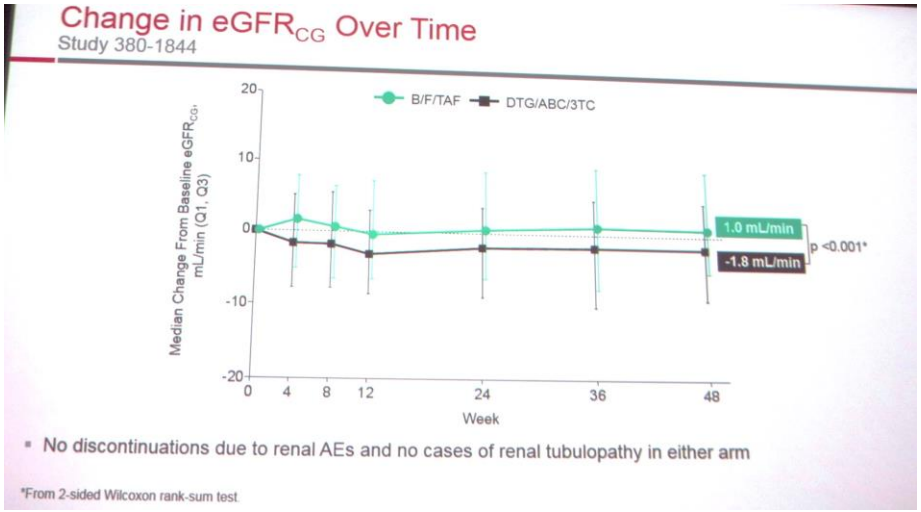
Virologic Outcome at Week 48

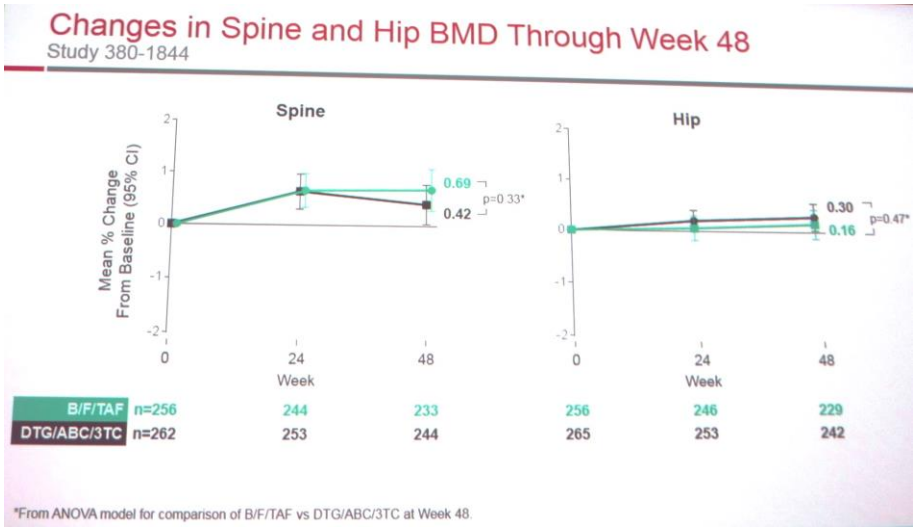
Study 380-1844

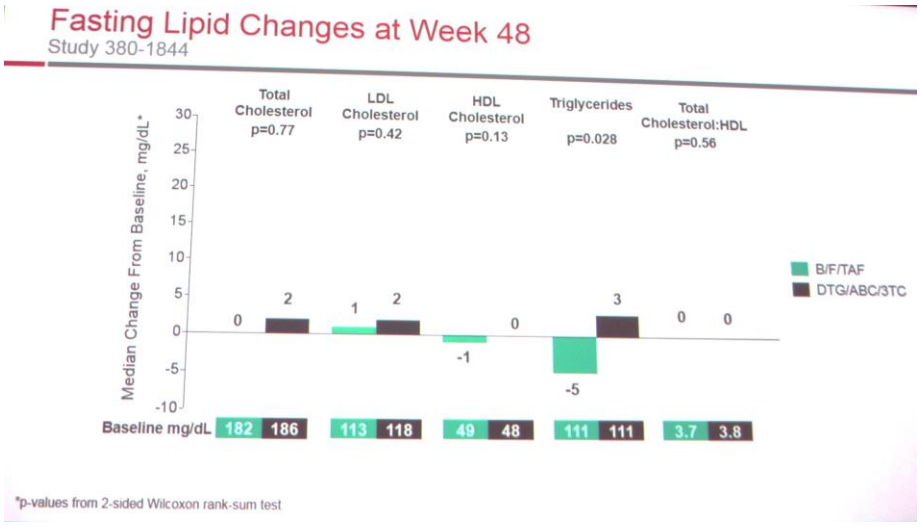


- Switching to B/F/TAF was noninferior to remaining on DTG/ABC/3TC

Étude GS1844: Switch Triumeq vers BIC/F/TAF







JM Molina , 22

Impact of previous M184V on virological outcome of switch to 3TC-based dual therapies

Poster 498

Gagliardini R[1,2], Ciccullo A[1], Borghetti A[1], Maggiolo F[3], Bartolozzi D[4], Borghi V[5], Pecorari M[6], Di Biagio A[7], Callegaro A[8], Bruzzone B[9], Saladini F[10], Paolucci S[11], Bellazzi L[12], Di Giambenedetto S[1], De Luca A[2]

[1]Institute of Infectious Diseases, Catholic University of Sacred Heart, Rome, Italy; [2]Infectious Diseases Unit, Siena University Hospital, Siena, Italy; [3]Division of Infectious Diseases, ASST Papa Giovanni XXIII, Bergamo, Italy; [4]Clinic of Infectious and Tropical Diseases, Azienda Ospedaliera Universitaria Careggi, Firenze, Italy; [5]Clinica Malattie Infettive e Tropicali, Azienda Ospedaliero Universitaria di Modena, Modena, Italy; [6]Microbiology and Virology Unit, Azienda Ospedaliero Universitaria di Modena, Modena, Italy; [7]Infectious Diseases, IRCCS AOU San Martino-IST, Genova, Italy; [8]Microbiology and Virology Unit, ASST Papa Giovanni XXIII, Bergamo, Italy; [9]Hygiene Unit, IRCCS AOU San Martino-IST, Genova, Italy; [10]Department of Medical Biotechnologies, University of Siena, Siena, Italy; [11]Virologia Molecolare, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [12]Infectious Diseases Clinic, S. Matteo Hospital, Pavia, Italy.

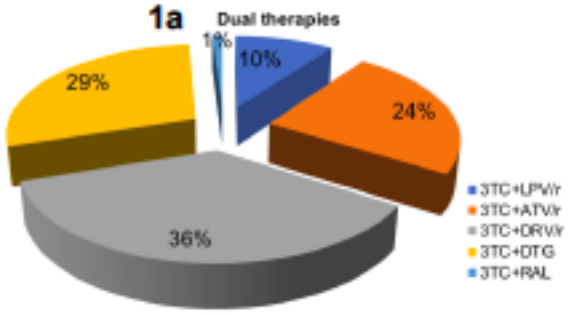
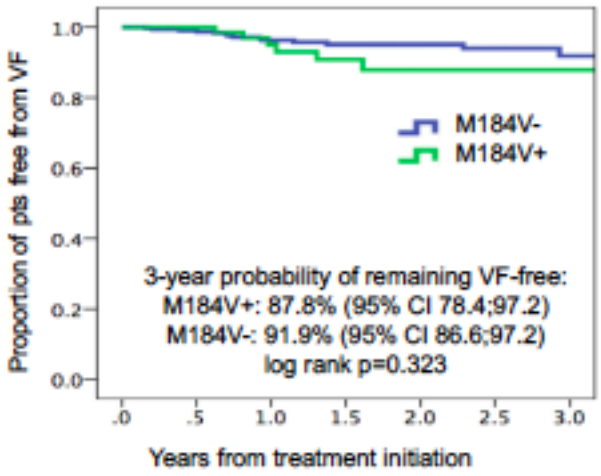


Table 1: patients baseline characteristics

	M184V- (n=349)	M184V+ (n=87)	p
Age, years*	46 (39; 53)	52 (48; 57)	<0.001
Male sex	257 (72%)	53 (61%)	0.019
Caucasians	308 (88%)	84 (97%)	0.077
Risk factor Sexual IDU Other/unknown	 225 (64%) 40 (11%) 84 (24%)	 56 (64%) 21 (24%) 10 (11%)	0.001
HCV infection	62 (18%)	24 (28%)	<0.001
HBsAg+	12 (3%)	2 (2%)	0.001
Previous AIDS events	40 (12%)	16 (18%)	0.084
HIV-RNA at zenith, cps/mL*	104,750 (35,807;329,250)	107,910 (27,000;252,900)	0.416
Years from HIV diagnosis*	7.8(3.8;13.7)	19.2 (16.1;23.0)	<0.001
Years from first ART initiation *	5.6 (2.8;10.0)	16.6 (12.8;18.9)	<0.001
Duration of viral suppression, years*	3.8 (2.2;6.4)	6.6 (3.7;8.9)	<0.001
Nadir CD4+, cells/µL*	224 (81;313)	147 (57;199)	<0.001
Current CD4+, cells/µL*	620 (453;780)	632 (409; 922)	0.131
Type of DT: lamivudine+bPI lamivudine+INI	 242 (69%) 107 (31%)	 64 (74%) 23 (26%)	0.441
Calendar year*	2014 (2013; 2015)	2014 (2012; 2015)	0.121
GSS of the 2nd drug **	0.99 (0.07)	0.91 (0.20)	<0.001

Data are shown as n (%); * median (IQR), ** mean (SD).
Notes: IDU, injecting drug users; HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen; ART, antiretroviral therapy; BL, baseline; DT, dual therapy; lamivudine; bPI, boosted protease inhibitors; INI, integrase inhibitor; GSS, genotypic sensitivity score.

Figure 2: estimated probability of remaining free from VF according to previous M184V detection



gure 3: estimated probability of remaining free from VF dual therapy for different time of viral suppression

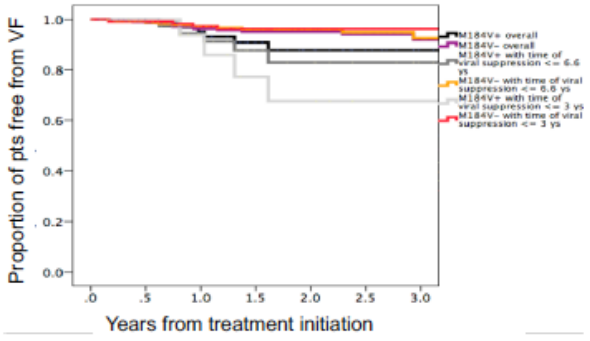
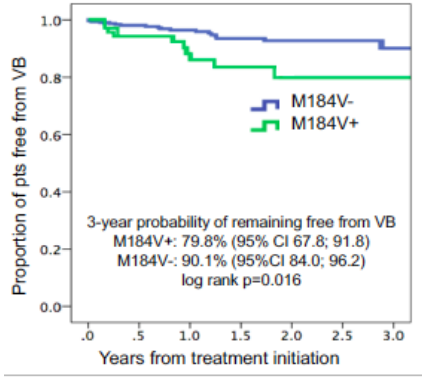


Figure 4: estimated probability of remaining free from viral blips



R Gagliardini, 498

POSTER #510

Virologic Response To 2-Drug ART Regimens Among Treatment-Experienced HIV+ Patients

Gerald Pierone[1], Cassidy Henegar[2], Jennifer Fusco[2], Vani Vannappagari[3], Michael Aboud[4], Leigh Ragone[1], Gregory Fusco[2]
[1]Infinite Family Health Center, Vero Beach, FL; [2]Epividian, Inc., Durham, NC; [3]ViiV Healthcare, Research Triangle Park, NC; [4]ViiV Healthcare, London, UK

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RESULTS

- 10,190 ART-experienced patients were identified (Figure 1) who switched during the study period to a 2-DR (n=1,337, 13%) or 3-DR (n=8,853, 87%)

Figure 1. Treatment Experienced Patients by Regimen Type and Stratification

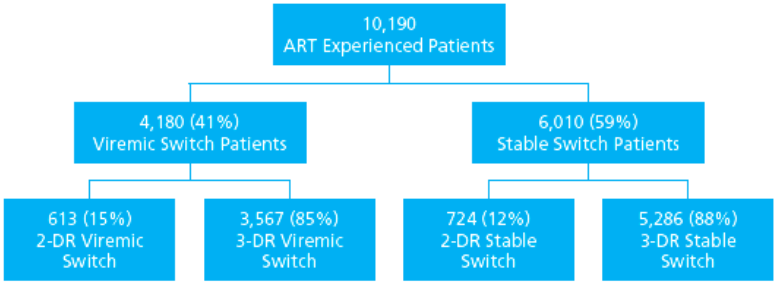

Table 2. Top 10 2-DRs and 3-DRs in Treatment Experienced Patients

	2-DR		3-DR	
	Regimen	N (%)	Regimen	N (%)
1.	darunavir/raltegravir	371 (27.7%)	efavirenz/emtricitabine/tenofovir	1,285 (14.5%)
2.	darunavir/dolutegravir	217 (16.2%)	darunavir/emtricitabine/tenofovir	1,022 (11.5%)
3.	etravirine/raltegravir	90 (6.7%)	abacavir/dolutegravir/lamivudine	877 (9.9%)
4.	darunavir/etravirine	89 (6.7%)	atazanavir/emtricitabine/tenofovir	731 (8.3%)
5.	atazanavir/raltegravir	75 (5.6%)	elvitegravir/emtricitabine/tenofovir	652 (7.4%)
6.	darunavir/tenofovir	52 (3.9%)	emtricitabine/raltegravir/tenofovir	613 (6.9%)
7.	atazanavir/tenofovir	48 (3.6%)	emtricitabine/rilpivirine/tenofovir	568 (6.4%)
8.	dolutegravir/rilpivirine	36 (2.7%)	emtricitabine/nevirapine/tenofovir	330 (3.7%)
9.	lopinavir/raltegravir	34 (2.5%)	abacavir/atazanavir/lamivudine	303 (3.4%)
10.	atazanavir/dolutegravir	18 (1.3%)	abacavir/darunavir/lamivudine	253 (2.9%)

Table 3. Baseline Demographics of Treatment-Experienced Patients Initiating 2-DRs and 3-DRs

	2-DR N= 1,337	3-DR N= 8,853	2-DR vs. 3-DR p-value
Age, median (IQR)	50.0 (44.0, 56.8)	46.4 (39.1, 52.7)	<.0001
Female Sex	296 (22.1%)	1441 (16.3%)	<.0001
African American Race	509 (38.1%)	2544 (28.7%)	<.0001
Hispanic Ethnicity	268 (20.0%)	2326 (26.3%)	<.0001
Risk of Infection: MSM	542 (40.5%)	4742 (53.6%)	<.0001
Region: South	813 (60.8%)	4031 (45.5%)	<.0001
Medicaid	369 (27.6%)	2106 (23.8%)	0.0025
Medicare	342 (25.6%)	1336 (15.1%)	<.0001
ADAP/Ryan White	297 (22.2%)	2610 (29.5%)	<.0001

Figure 2. Most Common 2-DRs and 3-DRs

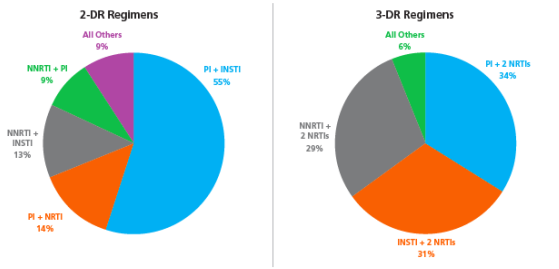

Table 4. Baseline Clinical Characteristics of Treatment-Experienced Patients Initiating 2-DRs and 3-DRs

	2-DR N= 1,337	3-DR N= 8,853	2-DR vs. 3-DR p-value
Experienced: 5+ prior lines of ART	558 (41.7%)	1773 (20.0%)	<.0001
Months since ART initiation, Median (IQR)	60.0 (20.1, 117.2)	45.8 (13.6, 98.1)	<.0001
Baseline Viral Load: Stable Switch <50 copies/mL	724 (54.2%)	5286 (59.7%)	<.0001
Baseline CD4 >500 cells/uL	528 (39.5%)	4367 (49.3%)	<.0001
AIDS defining event at or prior to regimen initiation	569 (42.6%)	2401 (27.1%)	<.0001
VACS Score†, Median (IQR)	27.0 (13.0, 43.0)	17.0 (6.0, 28.0)	<.0001
Cardiovascular Disease	282 (21.1%)	943 (10.7%)	<.0001
Invasive Cancers	175 (13.1%)	858 (9.7%)	0.0001
Endocrine Disorders	757 (56.6%)	4082 (46.1%)	<.0001
Liver Disease	353 (26.4%)	2034 (23.0%)	0.0058
Bone Disorders	71 (5.3%)	271 (3.1%)	<.0001
Peripheral Neuropathy	305 (22.8%)	1175 (13.3%)	<.0001
Renal Disease	437 (32.7%)	840 (9.5%)	<.0001
Hypertension	635 (47.5%)	2761 (31.2%)	<.0001

† VACS Mortality Index: Scored by summing pre-assigned points for age, CD4 count, HIV-1 RNA, hemoglobin, platelets, aspartate and alanine transaminase, creatinine, and viral hepatitis C infection. A higher score is associated with a higher risk of 5-year all-cause mortality.

G Pierone, 510

POSTER #510

Virologic Response To 2-Drug ART Regimens Among Treatment-Experienced HIV+ Patients

Gerald Pierone[1], Cassidy Henegar[2], Jennifer Fusco[2], Vani Vannappagari[3], Michael Aboud[4], Leigh Ragone[1], Gregory Fusco[2]

[1]Whole Family Health Center, Vero Beach, FL; [2]Epividian, Inc., Durham, NC; [3]ViiV Healthcare, Research Triangle Park, NC; [4]ViiV Healthcare, London, UK

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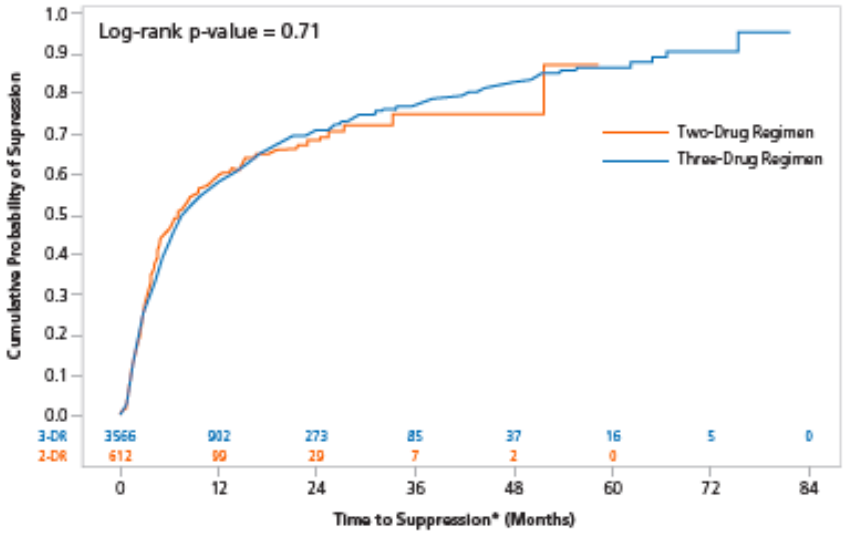
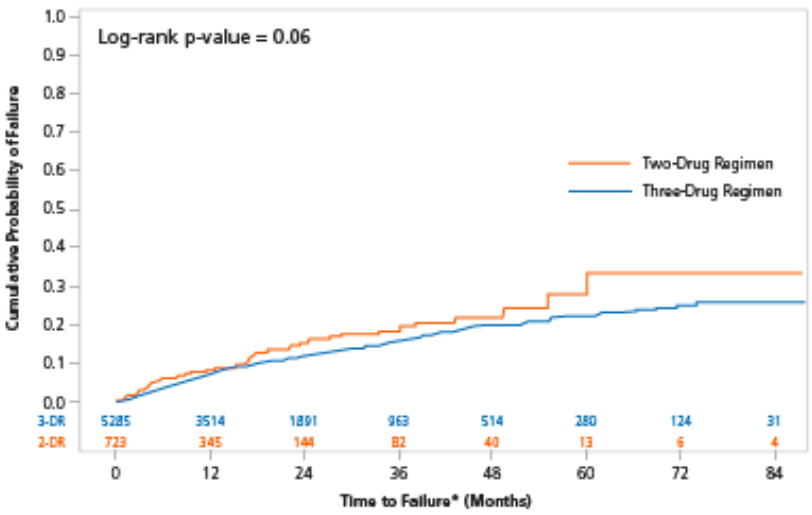
Figure 3. Kaplan Meier estimation of time to virologic suppression among treatment-experienced patients switching while viremic, stratified by regimen type



*Suppression: 1 VL <50 copies/mL

Figure 4. Kaplan Meier estimation of time to virologic failure among treatment-experienced patients switching while stable, stratified by regimen type



*Failure: 2 consecutive viral loads ≥200 copies/mL or one viral load ≥200 copies/mL followed by discontinuation

G Pierone, 510

507 - In Silico Clinical Trials for Evaluation of HIV Short-Cycle Strategies

Mélanie Prague[1,2,5], Chloé Pasin[1,2,5], Linda Wittkop[3], Pierre Duffau[4], Estibaliz Lazaro[4], Charles Cazanave[4], Marc Varell[3], Fabrice Bonnet[4], Rodolphe Thiébaut[1,2,4,5]
[1]Inria, Project Team SISTM, Bordeaux, France [2]Inserm U1219 (BPH), ISPED, Bordeaux University, France [3]Centre Hospitalier de Bayonne, France
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In silico Pipeline

An in silico clinical trial is a computer simulation used in the development of a medicinal product or intervention. It is based on a mathematical model with good predictions abilities. See [4] for an example.

Generate pseudo-patients:
Sample ($r = 1, \dots N$) parameters from the posterior distribution of θ
$\theta_r \sim N(\hat{\theta}, \widehat{H(\theta)})$

In silico data:
Simulate trajectories under various treatment and target population ($X, ARV^I(t)$)
$Y_r = ODE(\theta_r, ARV^I(t), X, t_{\mathcal{E}})$

Evaluate in silico outcomes:
Virological failure at 48 week $P\left(V_r > 50 \frac{copies}{mL}\right)$

Additional features: Basic reproduction number
$R_{\theta_r} = \frac{\lambda_r \pi_r \alpha_r \gamma_r}{\mu_{T_r} \mu_{V_r} (\rho_r \mu_{Q_r} + \alpha_r \mu_{T_r} + \mu_{Q_r} \mu_{T_r})}$, if <1, $V_r(\infty) \to 0$
$P(Y \leq x) = \int_{-\infty}^{x} f(t)dt$

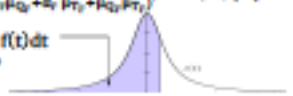


Fig. 2: Simulations algorithm

Review of Short-Cycle Therapies Trials

Short-cycle therapies (SCT) as opposed to continuous therapies (CT) is a type of regimen in which the patient takes combination of antiretroviral (ARV) therapies (c-ART) only x consecutive days in the week ($x<7$).

	Cohen et al. 2009	Reynolds et al. 2010	Butler et al. 2016	Rudy et al. 2009	Isibowitch et al. 2015	De Truchis et al. 2016	De Truchis et al. 2018
Names	FOTO	NCT00209456	BREATHER	ATN 065	ICARRE	ANRS-163	ANRS-QUATUOR
Type	5/7 randomized	5/7 randomized	5/7 randomized	4/7 Single arm	4/7 Single arm	4/7 Single arm	4/7 randomized
N	60 ($n_{SCT} = 30$)	146 ($n_{SCT} = 97$)	199 ($n_{SCT} = 99$)	$n_{SCT} = 35$	$n_{SCT} = 94$	$n_{SCT} = 100$	640 ($n_{SCT} = 320$)
Country	USA	Uganda	11 countries	USA	France	France	France
Pop.	Adult (85% men)	Adult (47% men)	8-24yr (51% men)	14-24yr (51% men)	Adult (83% men)	Adult (82% men)	Adult
c-ART	EFV/TDF/FTC	2NRTI+PI/EFV	2NRTI+EFV	2NRTI+PI	2NRTI+PI/NNRTI	2NRTI+PI/NNRTI	2NRTI+PI/ NNRTI/ II
Failure CT	14%	21.6%	7%	-	-	-	
Failure SCT	10%	11.5%	6%	37.5%	0%	4%	On going
Conclu.	Promising	Non-Inferiority	Non-Inferiority	Failure	Promising	Promising	

Tab. 1: List of funded SCT trials

Predicting 5/7

	Virological Failure: 1 cp/mL.	50 cp/mL.	R_0
EFV+TDF+3TC	0.9% [0%; 5%]	0.5% [0%; 4%]	0.77 [0.59; 0.92]
EFV+ABC+3TC	1.1% [0%; 14%]	0.6% [0%; 11%]	0.82 [0.64; 0.99]
EFV+AZT+3TC	2.4% [0%; 19%]	1.0% [0%; 16%]	0.84 [0.65; 1.03]
BREATHER trial	1.2% [0%; 15%]	1% [0%; 11.9%]	0.82 [0.63; 0.99]

Tab. 2: In silico trial for 5/7 SCT design

In BREATHER, the observed failure rate at 50 cp/mL is 6% [2%; 10%], the prediction confidence band overlaps the results of the trial.

Predicting 4/7

	Virological Failure: 1 cp/mL.	50 cp/mL.	R_0
EFV+TDF+3TC	5.3% [2.2%; 9.0%]	2.0% [0.0%; 4.0%]	0.91 [0.71; 1.11]
EFV+ABC+3TC	17.1% [11%; 23%]	11.9% [6%; 17%]	0.96 [0.74; 1.16]
EFV+AZT+3TC	21.4% [16%; 28%]	16.4% [10%; 23%]	0.97 [0.75; 1.18]
TDF+FTC+RIL	2.8% [0.2%; 6.6%]	1.2% [0%; 3%]	0.90 [0.70; 1.09]
TDF+FTC+DRV	1.4% [0%; 3.8%]	0.7% [0%; 3%]	0.88 [0.69; 1.08]
More potent (DOL-based?)	0.2% [0%; 1.2%]	0.1% [0%; 1%]	0.82 [0.63; 0.99]

Tab. 3: In silico trial for 4/7 SCT design

Projections for SCT are encouraging with high potency c-ART. However, for some c-ART it remains a risk of low-level viral replication. This low replication may however remain smaller than 1cp/mL.

R Thiebaut, 507

DTG Versus LPV/r in Second Line (DAWNING): Outcomes by WHO-Recommended NRTI Backbone

508

Michael Aboud,[1] Carlos Brites,[2] Hongzhou Lu,[3] Khuanchai Supparatpinyo,[4] Luis Hercilla,[5] Jörg Sievers,[1] Maria Claudia Nascimento,[1] Judy Hopking,[6] Mark Underwood,[7] Dannae Brown,[8] Martin Gartland,[7] Kimberly Smith[7]

[1]ViiV Healthcare, Brentford, UK; [2]Federal University of Bahia, Salvador, Brazil; [3]Fudan University, Shanghai, China; [4]Chiang Mai University, Chiang Mai, Thailand; [5]Hospital Nacional Alberto Sabogal Sologuren, Callao, Peru; [6]GlaxoSmithKline, Uxbridge, UK; [7]ViiV Healthcare, Research Triangle Park, NC, USA; [8]ViiV Healthcare, Abbotsford, Australia

Figure 1. DAWNING Study Design

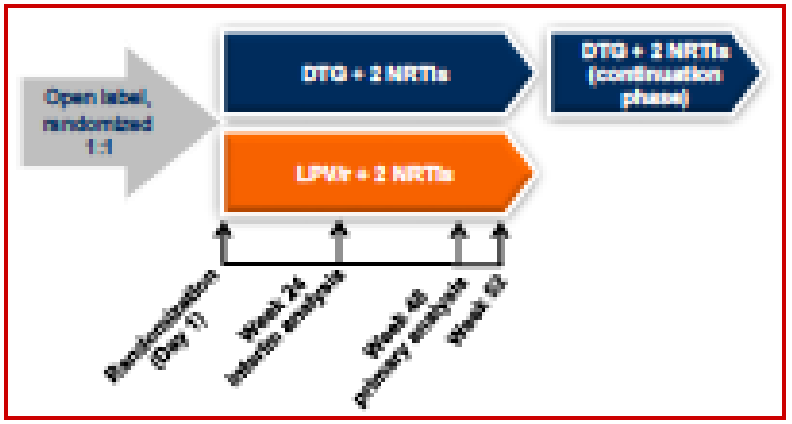
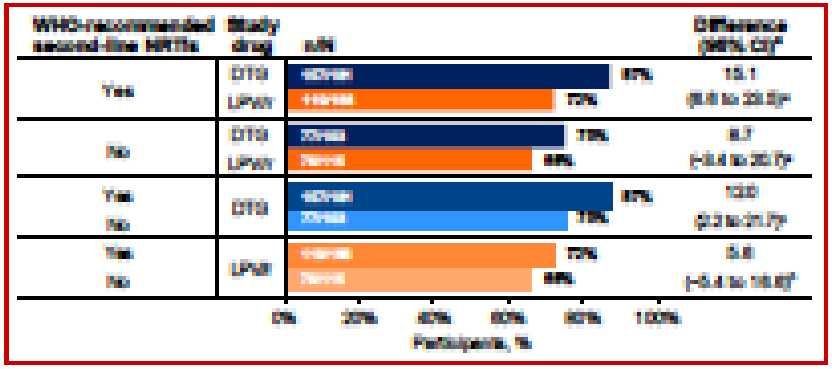


Table. Prior ART and Background NRTIs Received at Day 1

	DTG (n=312)	LPV/r (n=312)
First-line agent, n (%)		
Efavirenz	242 (78)	242 (78)
TDF	181 (58)	186 (60)
AZT	89 (29)	89 (29)
Second-line NRTI, n (%)		
AZT + 3TC	131 (42)	121 (39)
TDF + (FTC or 3TC)	128 (41)	134 (43)
TDF + AZT	38 (12)	40 (13)
ABC + 3TC	7 (2)	7 (2)
Other*	10 (3)	10 (3)

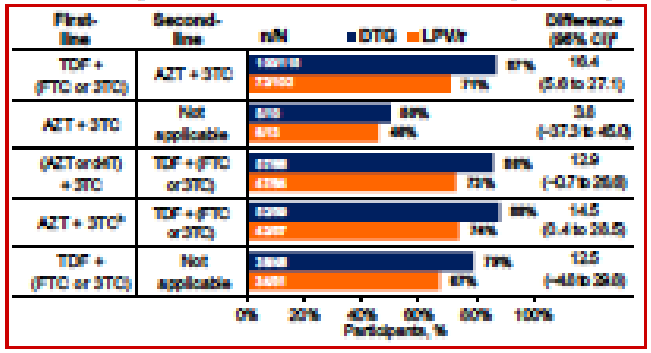
ABC, abacavir. *Includes AZT + ABC, AZT + TDF + 3TC, and TDF + ABC.

Figure 2. Proportion of Participants With Plasma HIV-1 RNA <50 c/mL at Week 24 by Second-Line Background Regimen: Snapshot Analysis



*Proportion on DTG – proportion on LPV/r.
†Proportion with WHO-recommended NRTIs – proportion without WHO-recommended NRTIs.

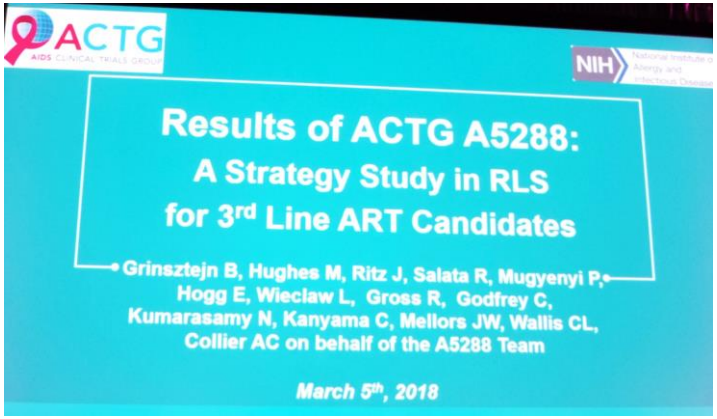
Figure 3. Proportion of Participants With Plasma HIV-1 RNA <50 c/mL at Week 24 by First- and Second-Line NRTI Choice: Snapshot Analysis

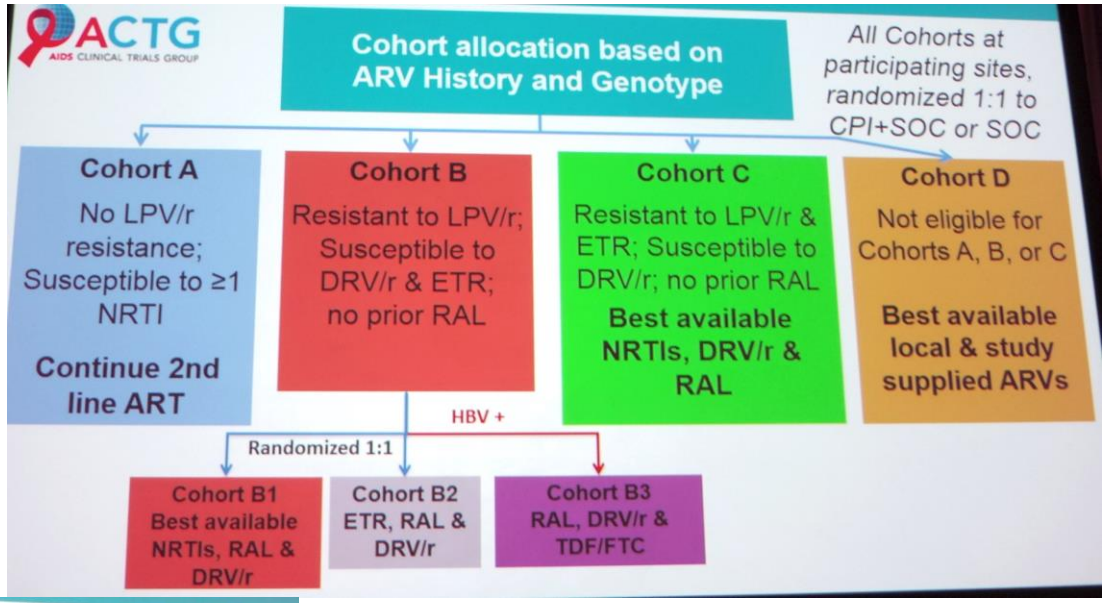


*Proportion on DTG – proportion on LPV/r (unadjusted).
†Excludes participants who received d4T + 3TC in their first-line regimen (7 per treatment arm).

M Aboud, 508

ACTG A5288: 3è ligne



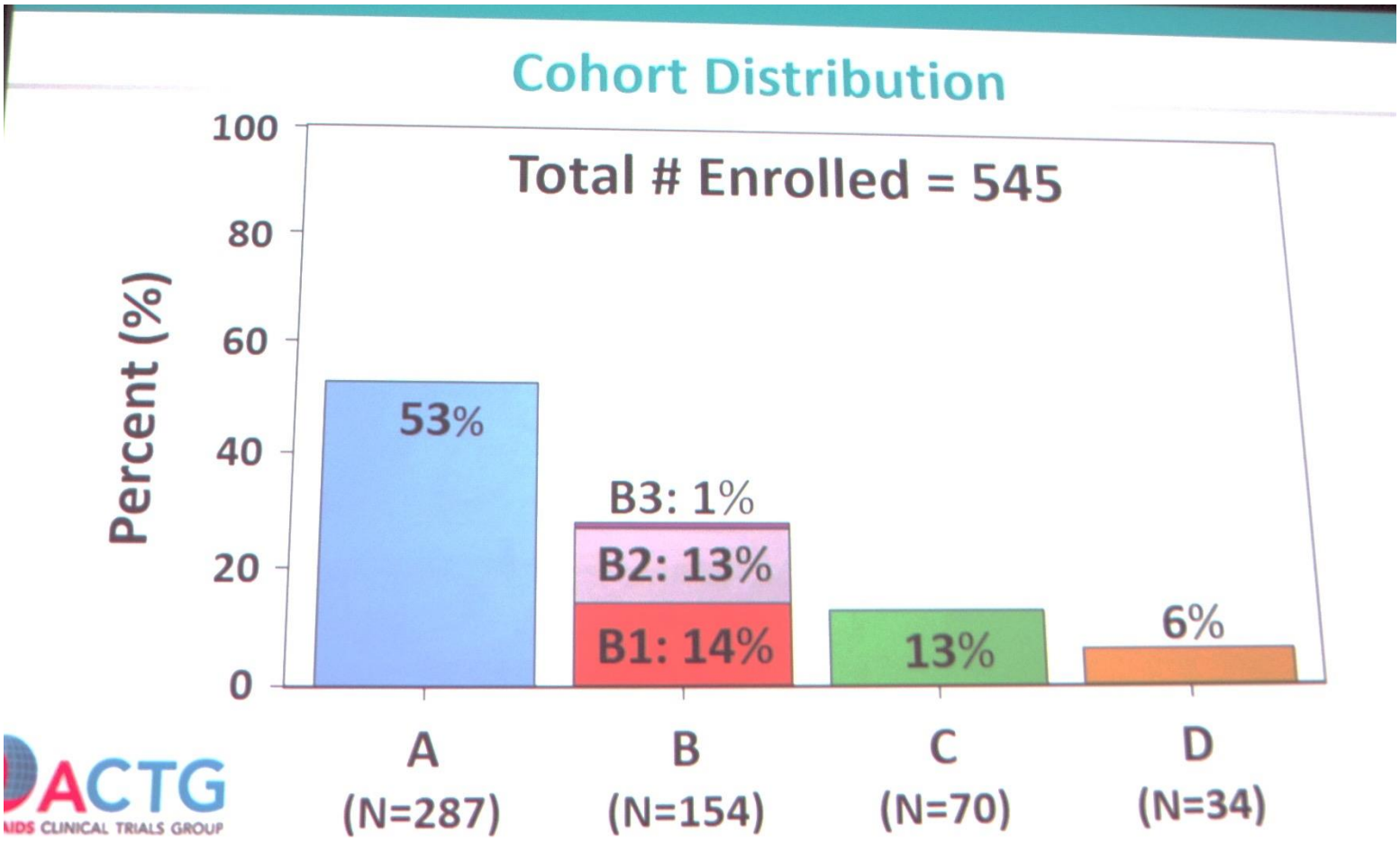


Baseline Characteristics

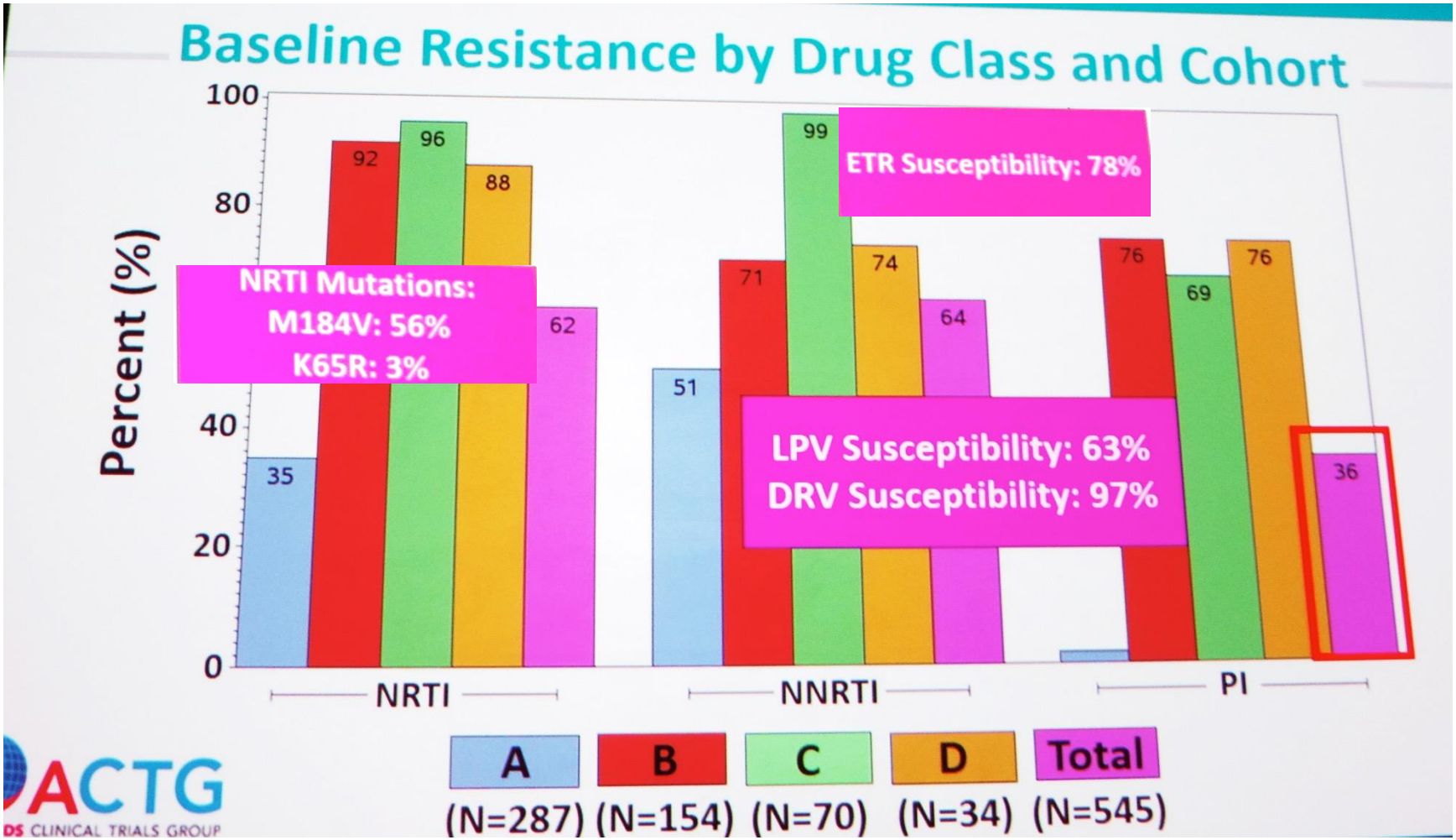
Characteristic	Cohort A (N = 287)	B (N = 154)	C (N = 70)	D (N = 34)	Total (N = 545)
Plasma HIV-1 RNA (log c/mL)					
Median (Q1, Q3)	4.3	3.9	4.6	4.2	**4.4 (3.5, 5.2)**
% ≥ 100,000 copies/mL	24%	25%	39%	35%	**31%**
CD4 Count (cells/mm³)					
Median (Q1, Q3)	171	250	161	189	**175 (71, 308)**
% < 50 cells/mm³	17%	13%	13%	21%	**17%**
Duration of ART use (years)					
Median (Q1, Q3)	7.9	8.0	8.1	7.8	**7.9 (5.9, 10.2)**

B Grinsztejn, 30LB

ACTG 5288

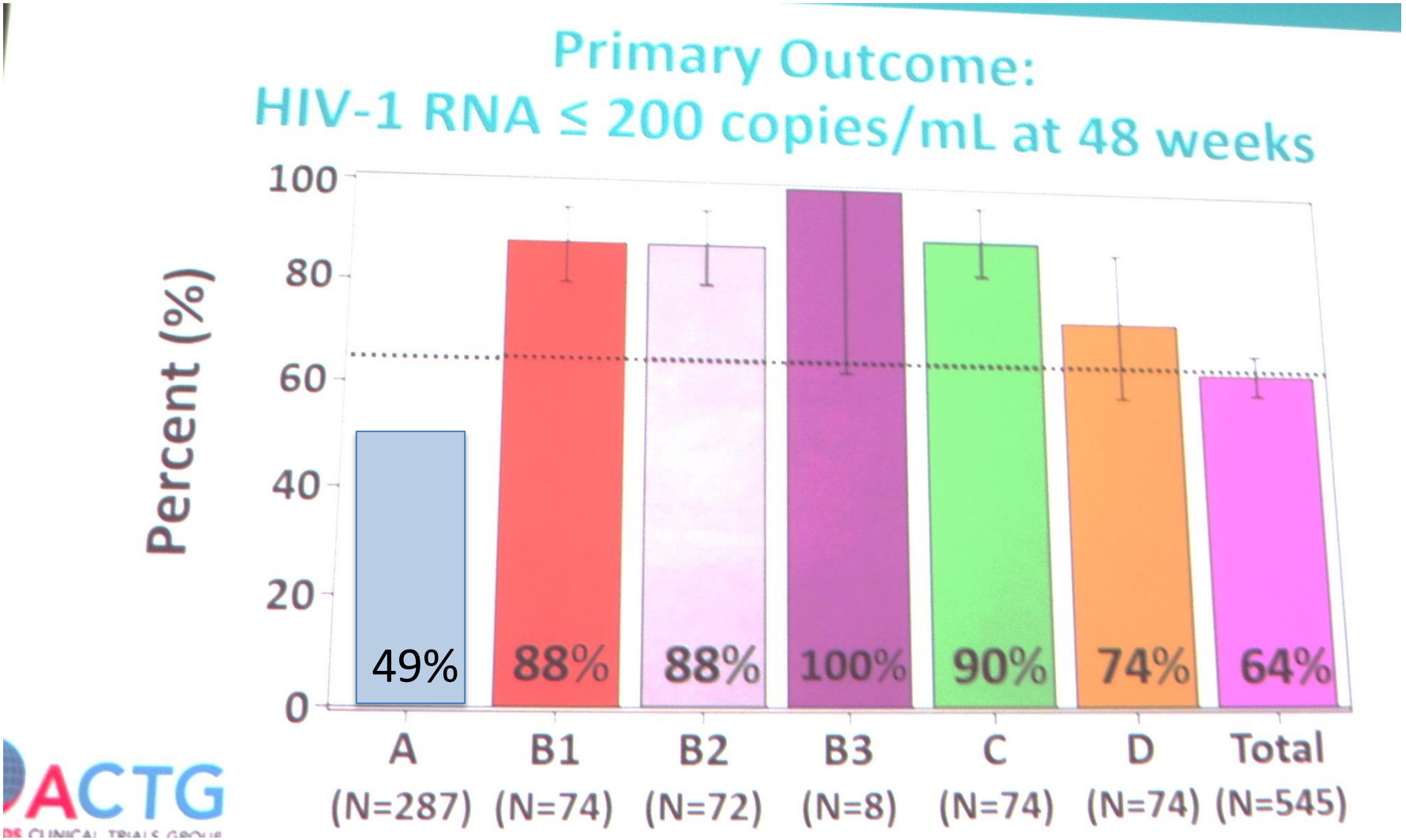


B Grinsztejn, 30LB



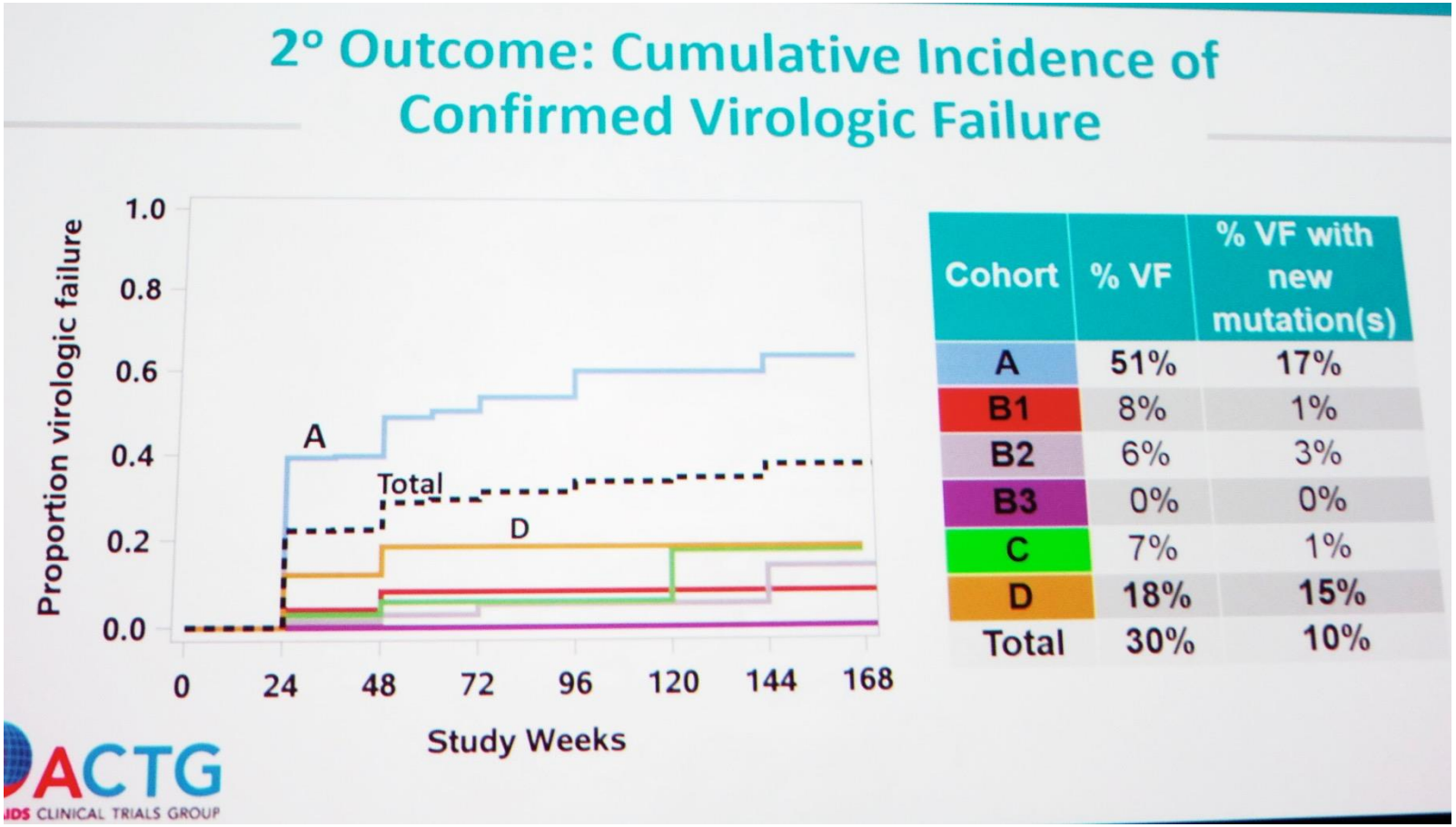
B Grinsztejn, 30LB

ACTG A5288



B Grinsztejn, 30LB

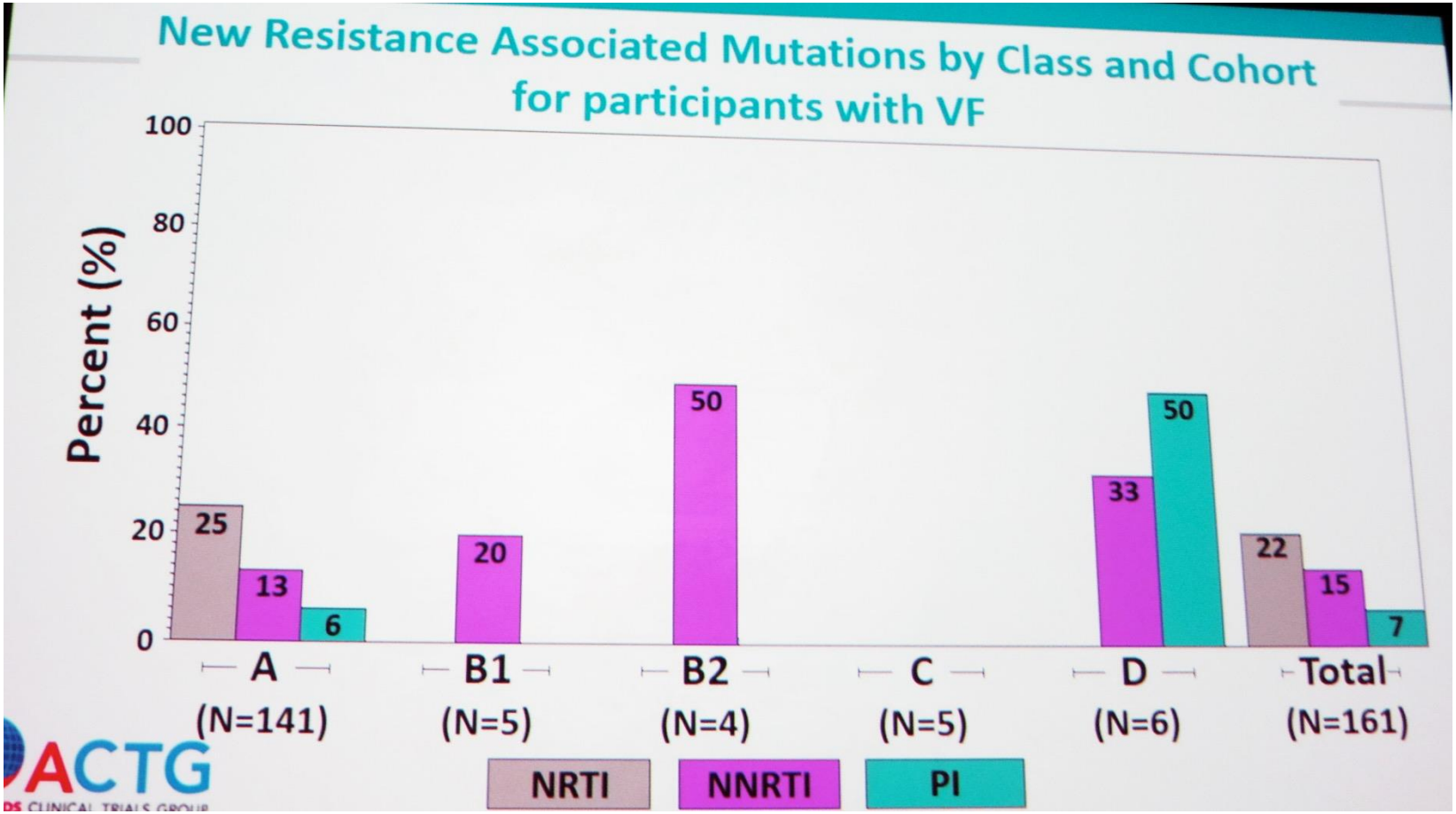
ACTG A5288



Cohort	% VF	% VF with new mutation(s)
A	51%	17%
B1	8%	1%
B2	6%	3%
B3	0%	0%
C	7%	1%
D	18%	15%
Total	30%	10%

B Grinsztejn, 30LB

ACTG A5288



B Grinsztejn, 30LB

InSTI Pharmacokinetics in lymphoid tissues

Results

- Pharmacologic evaluations have been completed in 34 persons.
  - INSTIs: DTG, n=11; EVG/cobi, n=17; and RAL, n= 6.
  - Concomitant NRTIs were: TDF/FTC, n=24; ABC/3TC, n=5; ABC/3TC/TDF, n=1; TDF/3TC, n=1; and TAF/FTC, n=5. ART regimen changes accounted for more regimens than participants.
- Samples quantified and analyzed:

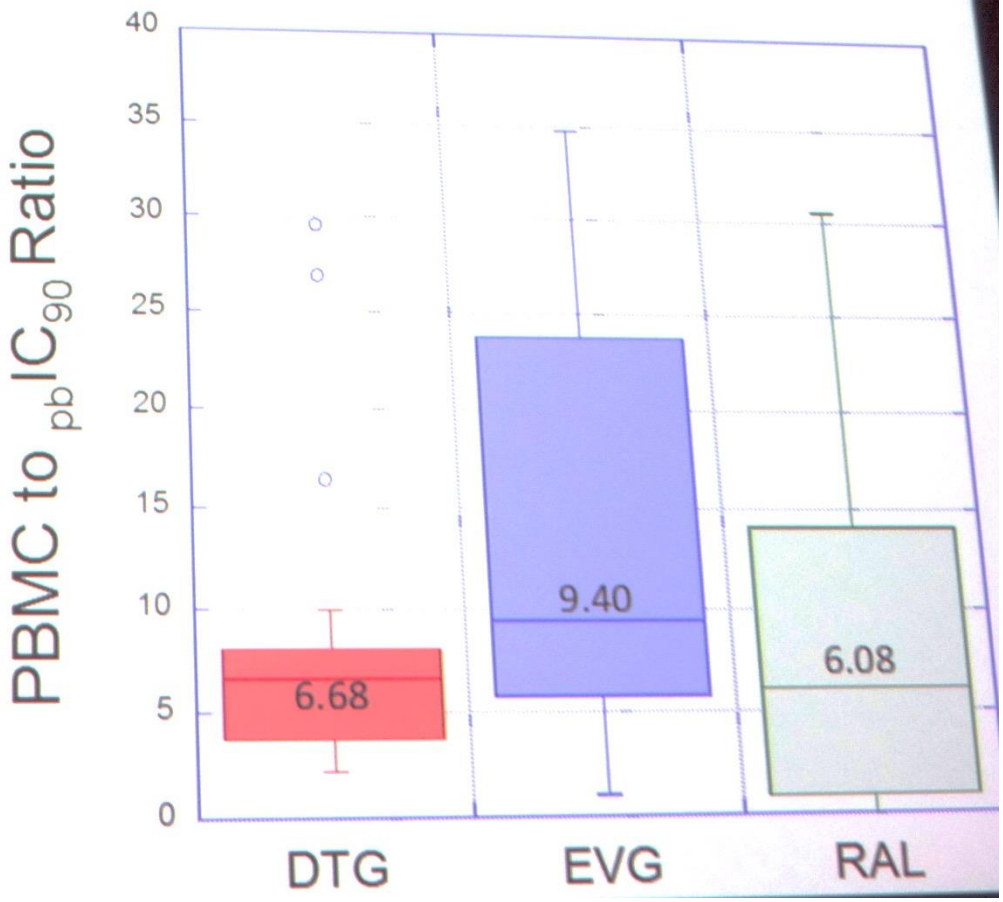
	DTG (n=11)	EVG (n=17)	RAL (n=6)
PBMCs	16/17	27/27	22/23
LN-MNCs	13/17	19/25	4/6
Ileal-MNCs	13/17	23/24	nd
Rectal-MNCs	13/17	27/27	6/6

C Fletcher, 27

InSTI Pharmacokinetics in lymphoid tissues

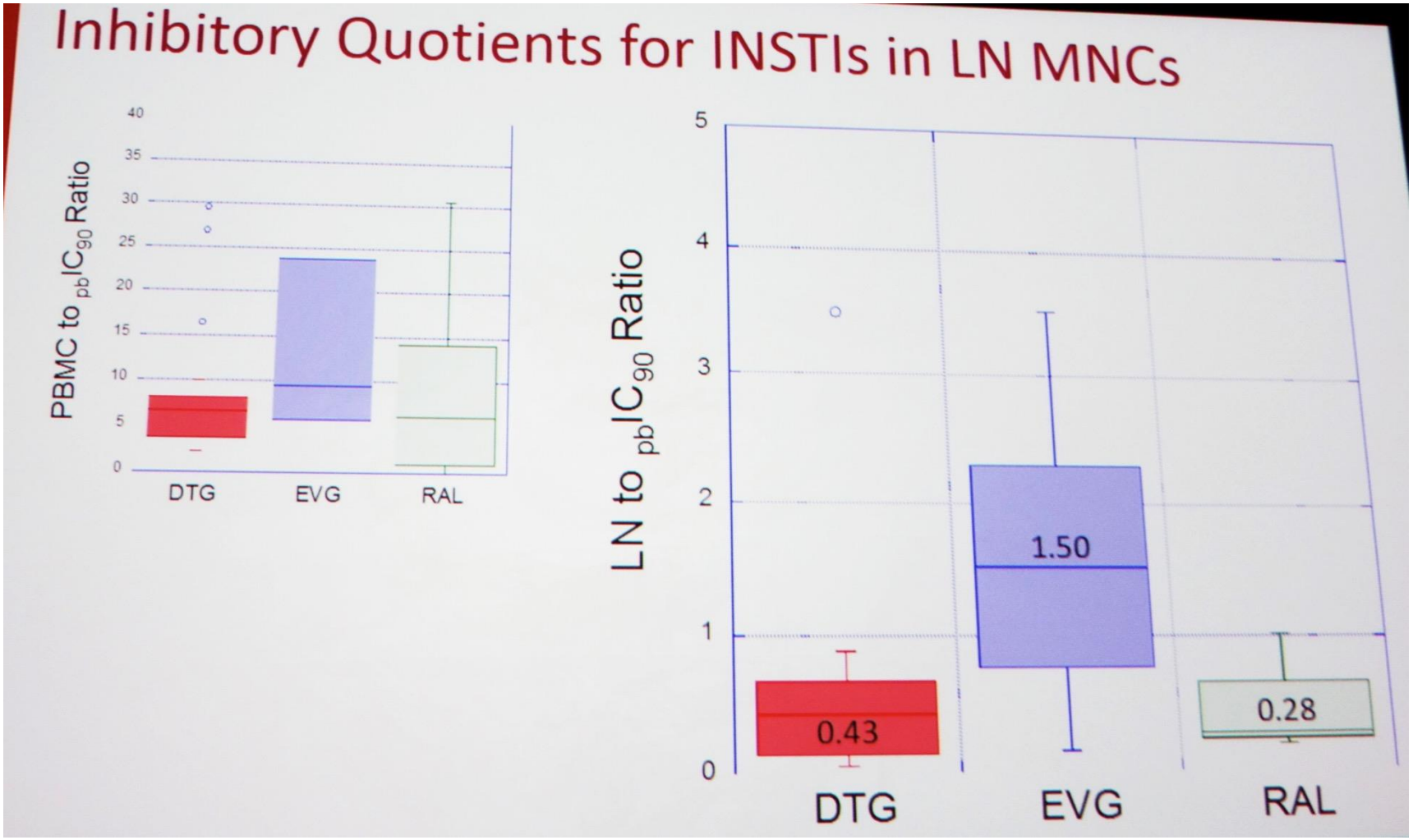
Inhibitory Quotients for INSTIs in PBMCs

	IC & IQ Values in Plasma		
	DTG	EVG	RAL
IC_{90}, ng/mL	64	NA	NA
IC_{95}, ng/mL	NA	44.9	14.7
C_{trough}, ng/mL	1100	450	124
IQ	17	10	8



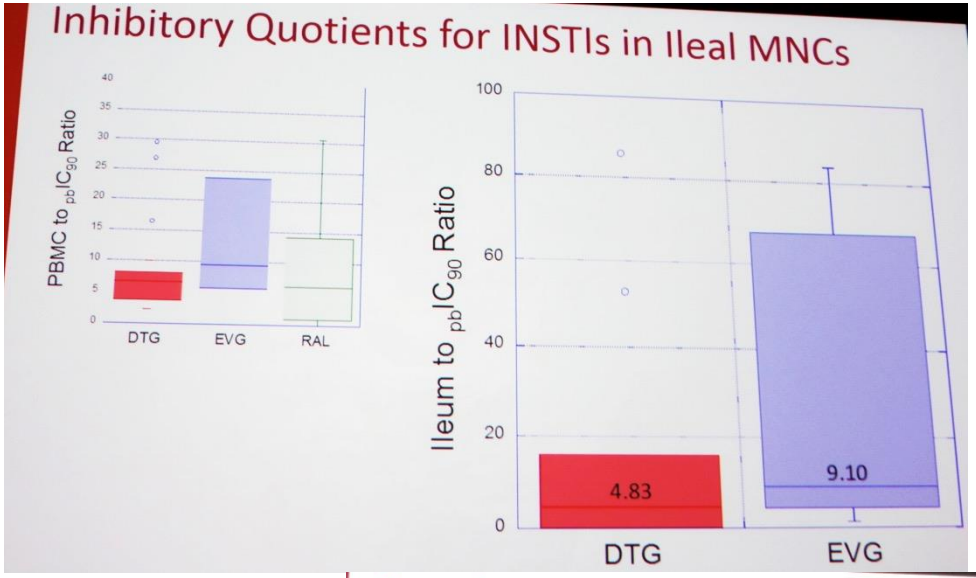
C Fletcher, 27

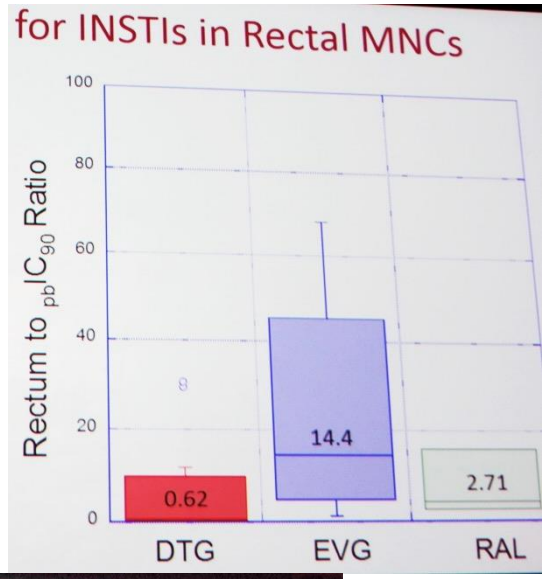
InSTI Pharmacokinetics in lymphoid tissues



C Fletcher, 27

InSTI Pharmacokinetics in lymphoid tissues





Results: Inhibitory Quotient Values

Matrix	Inhibitory Quotient (intracellular concentration/protein binding corrected IC_{90-95}) Median and Interquartile Range		
	DTG	EVG	RAL
PBMC	6.68 (4.06, 8.16)	9.40 (5.84, 22.84)	6.08 (0.94, 14.14)
LN	0.43 (0.13, 0.67)	1.50 (0.76, 2.29)	0.28 (0.26, 0.48)
Ileum	4.83 (0.38, 16.07)	9.10 (4.51, 65.37)	Not done
Rectum	0.62 (0.33, 9.68)	14.4 (4.65, 169.91)	2.71 (2.62, 5.91)

C Fletcher, 27

Anti-intégrases et risque IRIS

REALITY: Association Between RAL Intensification of First-line ART and IRIS

- Randomized, open-label phase III trial in Uganda, Kenya, Zimbabwe, and Malawi
  - Primary endpoint: 24-wk mortality
  - Endpoints assessed via "blinded" adjudication

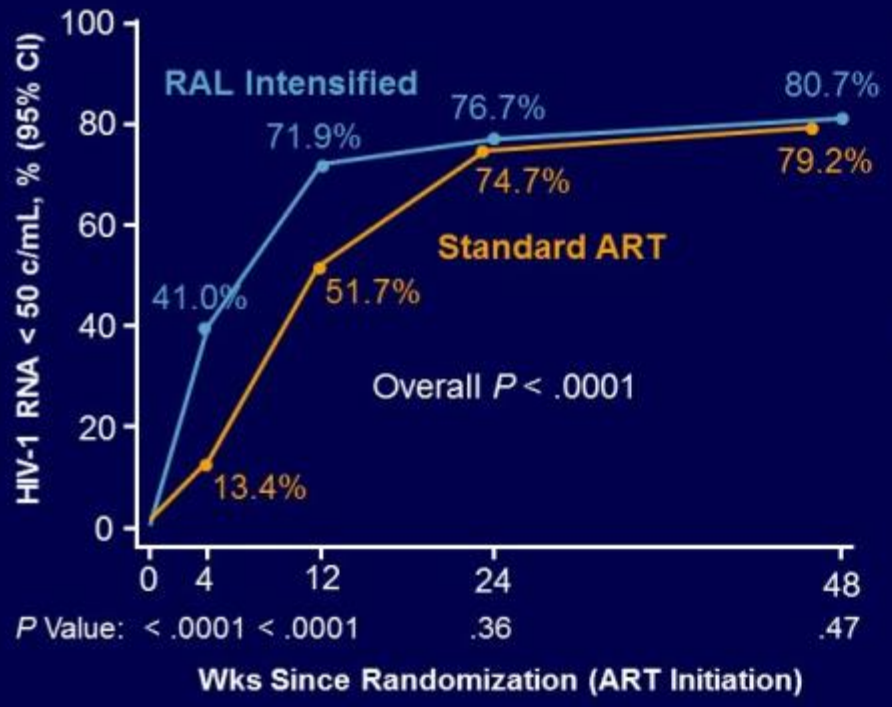
- Baseline characteristics well balanced between arms

Gibb DM, et al. CROI 2018. Abstract O23. ClinicalTrials.gov. NCT01825031.

Slide credit: clinicaloptions.com

Anti-intégrases et risque IRIS

RAL Intensification of First-line ART: Viral Load and All-Cause Mortality



- 24-wk mortality rate:
  - RAL intensified: 10.9%
  - Standard ART: 10.2%
  - **HR: 1.10 (95% CI: 0.82-1.46; *P* = .53)**
- 48-wk mortality rate:
  - RAL intensified: 12.4%
  - Standard ART: 13.0%
  - **HR: 0.98 (95% CI: 0.76-1.28; *P* = .91)**

Gibb DM, et al. CROI 2018. Abstract O23.

Slide credit: clinicaloptions.com

Anti-intégrases et risque IRIS

RAL Intensification of First-line ART: IRIS-Compatible Events and Prophylaxis Outcomes

IRIS-Compatible Events,* n (%)	RAL Intensified	Standard ART
All fatal events	36 (4.0)	31 (3.4)
▪ TB-IRIS	20 (2.2)	21 (2.3)
▪ Cryptococcal-IRIS	8 (0.9)	5 (0.6)
▪ Other of known etiology	5 (0.6)	4 (0.4)
▪ Unknown etiology	3 (0.3)	1 (0.1)
All fatal/nonfatal events	89 (9.9)	86 (9.5)
▪ TB-IRIS	53 (5.9)	54 (6.0)
▪ Cryptococcal-IRIS	15 (1.7)	16 (1.8)
▪ Other of known etiology	17 (1.9)	14 (1.6)
▪ Unknown etiology	4 (0.4)	2 (0.2)

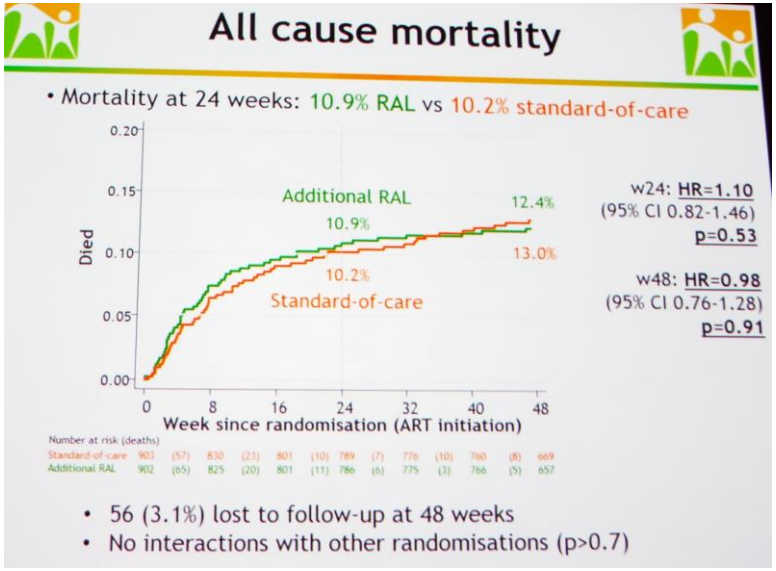
*P > .05 for all comparisons.

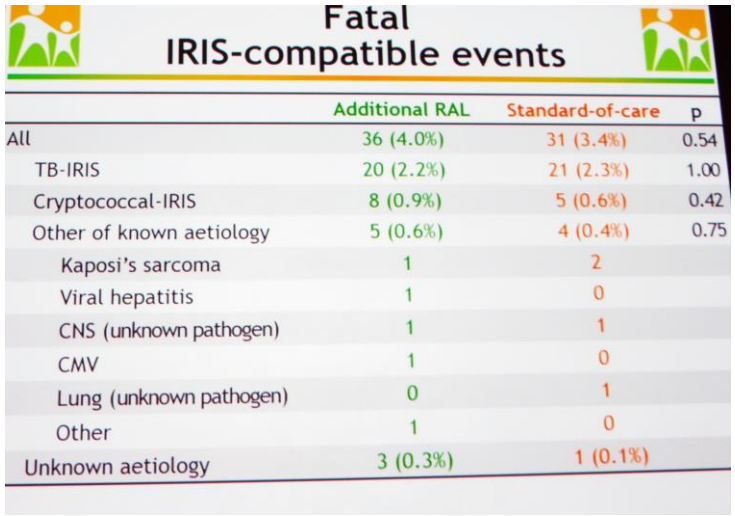
Independent Predictor of Fatal/Nonfatal IRIS Events	sHR (95% CI)	P Value
RAL intensified vs standard ART	1.08 (0.80-1.45)	.63
Enhanced vs standard prophylaxis	0.60 (0.44-0.82)	.001
CD4+ count (per 10 cells/mm^3 higher)	0.87 (0.82-0.93)	< .001
Age at last birthday (per yr older)		.03
▪ ≤ 29 yrs	1.07 (1.02-1.22)	.008
▪ ≥ 30 yrs	0.99 (0.97-1.01)	.44
Current TB disease at ART initiation	1.62 (1.11-2.37)	.01

Gibb DM, et al. CROI 2018. Abstract O23.

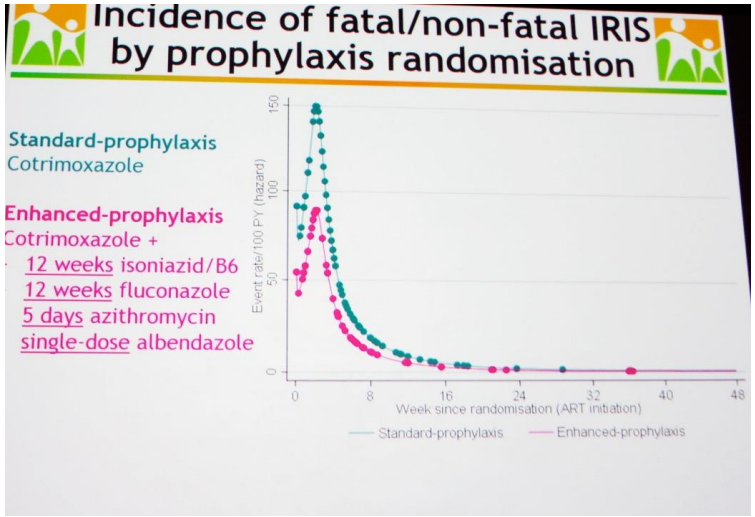
Slide credit: clinicaloptions.com

REALITY





	Additional RAL	Standard-of-care	p
All	36 (4.0%)	31 (3.4%)	0.54
TB-IRIS	20 (2.2%)	21 (2.3%)	1.00
Cryptococcal-IRIS	8 (0.9%)	5 (0.6%)	0.42
Other of known aetiology	5 (0.6%)	4 (0.4%)	0.75
Kaposi's sarcoma	1	2	
Viral hepatitis	1	0	
CNS (unknown pathogen)	1	1	
CMV	1	0	
Lung (unknown pathogen)	0	1	
Other	1	0	
Unknown aetiology	3 (0.3%)	1 (0.1%)	

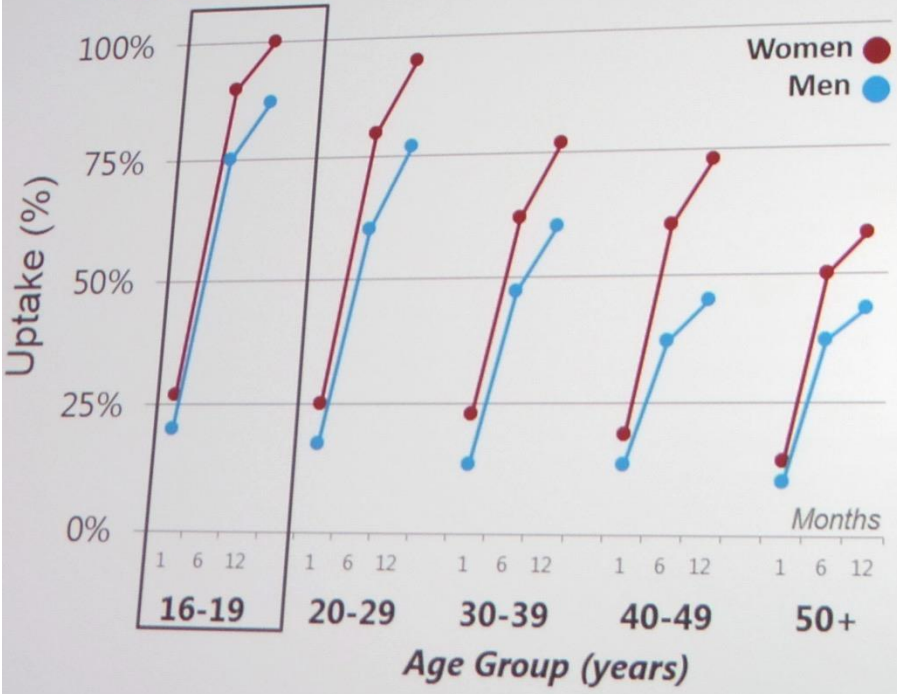


D. Gibb, 23

DEPISTAGE, PREVENTION

Population uptake since self-testing made available

- Trial of HIVST in 16,660 adults in 28 intervention clusters in Blantyre



High uptake

- Young people
- Male participation
- 44% first-time testers
- Early HIV & discordant couples

No major safety concerns

- 27,000 testing episodes
- Active surveillance for suicide
- In-depth social harms system

Mahesweran JIAS 2017
Witzel & Desmond JIAS 2016
Choko PLoS Med 2015 and PLoS Med 2011
MacPherson JAMA 2014

Increasing uptake of testing: What works?

LONDON SCHOOL of HYGIENE & TROPICAL MEDICINE

- *Provider-initiated*
- *Assisted partner notification*
- *Index-linked testing*
- *Antenatal clinic testing*
- *Testing in emergency depts*
- *STI clinics*
- *TB clinics*

Facility-based

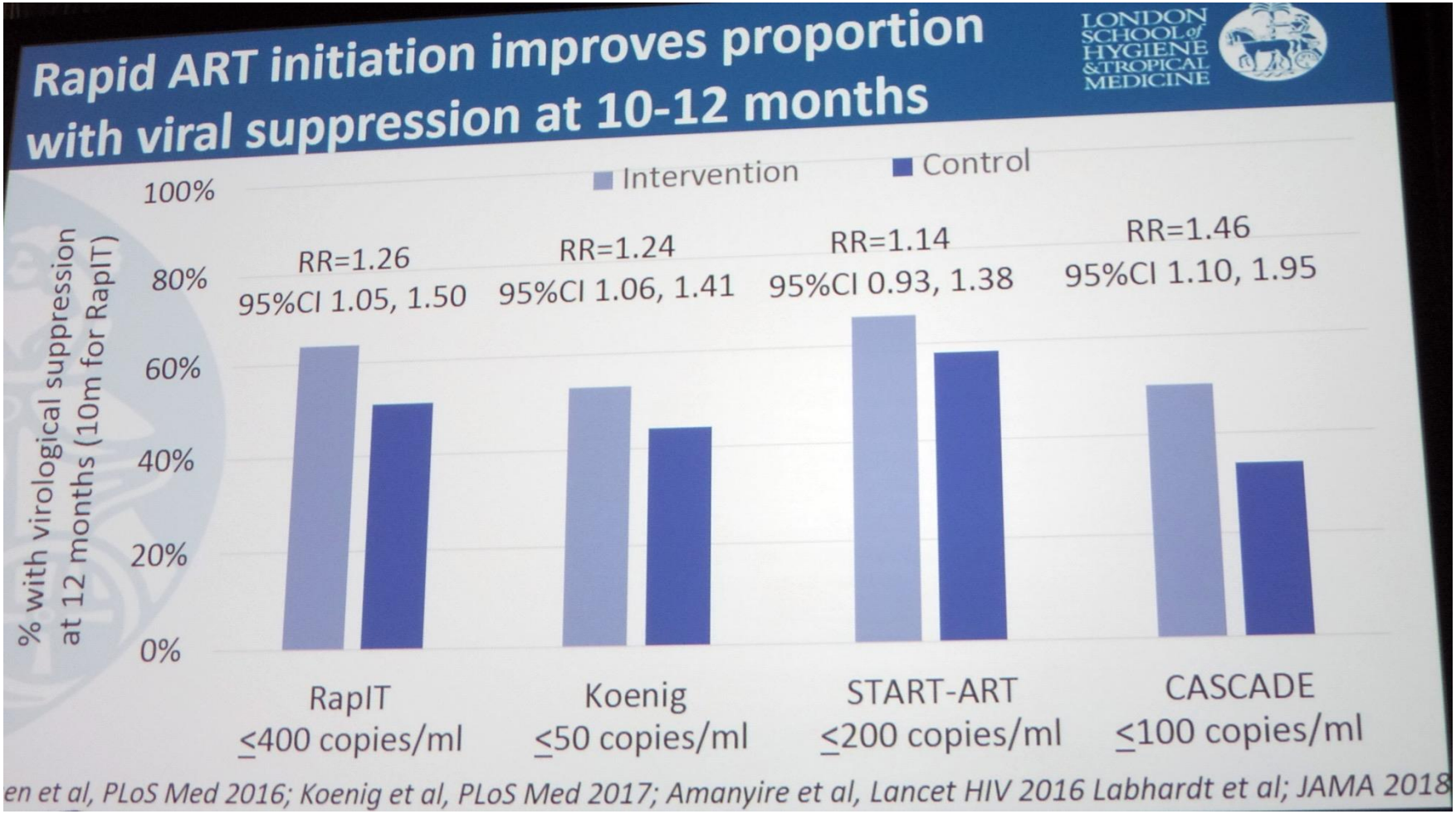
Community-based

- Home based
- Work based
- Mobile outreach
- Social network
- Campaigns

- ☑ **Males**
- ☑ **Youth**
- ☑ **Key populations**
- ☑ **First-time testers**

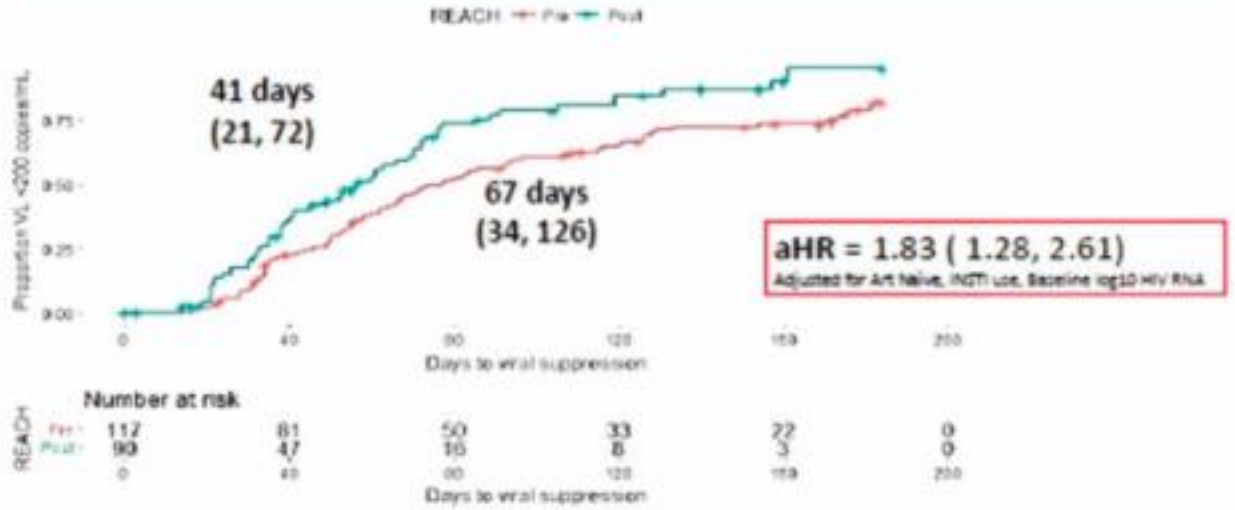
Adapted from Sharma et al, Nature 2015 528

Traitement rapide après dépistage



Same Day ART Start in Atlanta

Primary Outcome: Time to Viral Suppression



Secondary Outcomes

Outcomes	Pre-REACH (n=117)	Post-REACH (n=90)	p
Days to 1st scheduled provider visit	14 (12, 16)	4 (1, 6)	< 0.0001
Days to 1st attended provider visit	12 (6, 23)	2 (1, 4)	< 0.0001
Days to ART start	22 (13, 38)	4 (2, 8)	< 0.0001

Adjusted for age, race, sex and being ART Naive

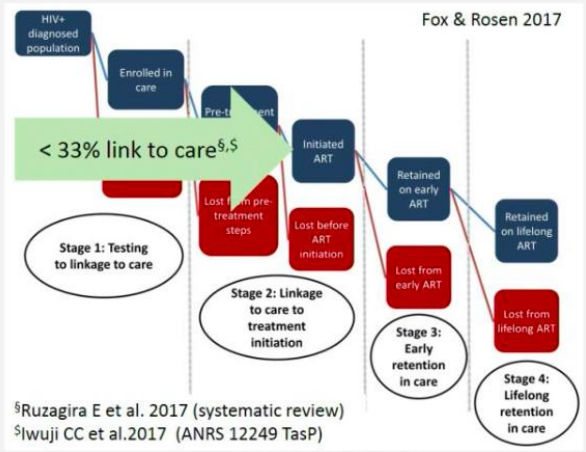
Outcomes	Pre-REACH (n=117)	Post-REACH (n=90)	aOR (95% CI)
Attended 1st scheduled appointment*	85 (73)	73 (81)	1.63 (0.82, 3.22)
Achieved viral suppression#	87 (74)	61 (68)	0.77 (0.39, 1.52)

*Adjusted for age, race, sex and being ART Naive
#Adjusted for age, race, baseline HIV RNA & INSTI use

Colasanti et al, CROI 2018, #1109

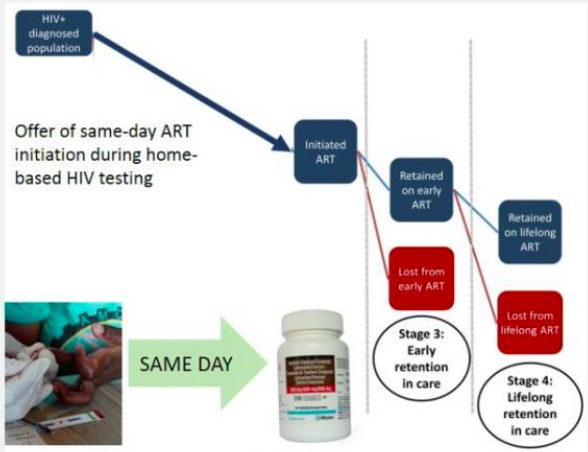
Cascade trial: Dépistage décentralisé et Traitement ARV immédiat

Background (2): Low linkage to care after home-based HIV testing



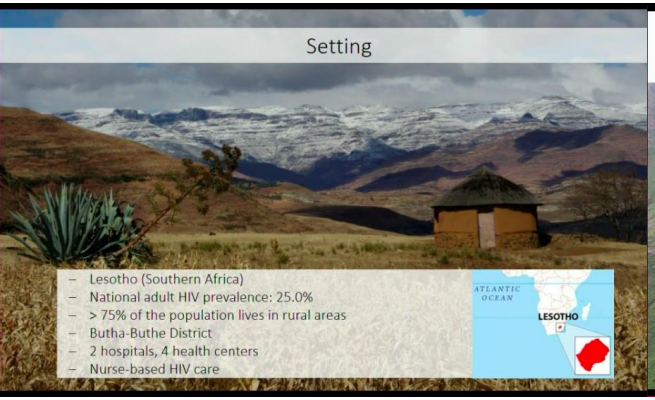
CROI 2018 - The CASCADE-trial ; ND Labhardt et al. 4

Rationale: Collapsing the cascade



CROI 2018 - The CASCADE-trial ; ND Labhardt et al. 5

ND Labhardt, 94



Design, Recruitment & Eligibility

Design:
- Multi-center two-group open-label randomized controlled trial
- Randomization: block-size of 4; 1:1 allocation (individuals from same-household → same group)

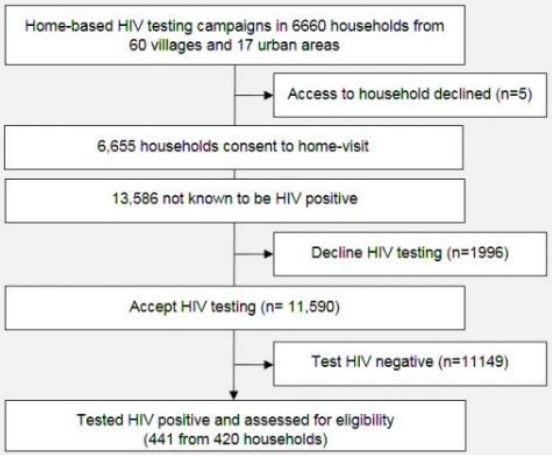
Recruitment:
- 3 study-teams (4 lay-counsellors, 1 team-leader, 1 nurse)
- Home-based HIV testing

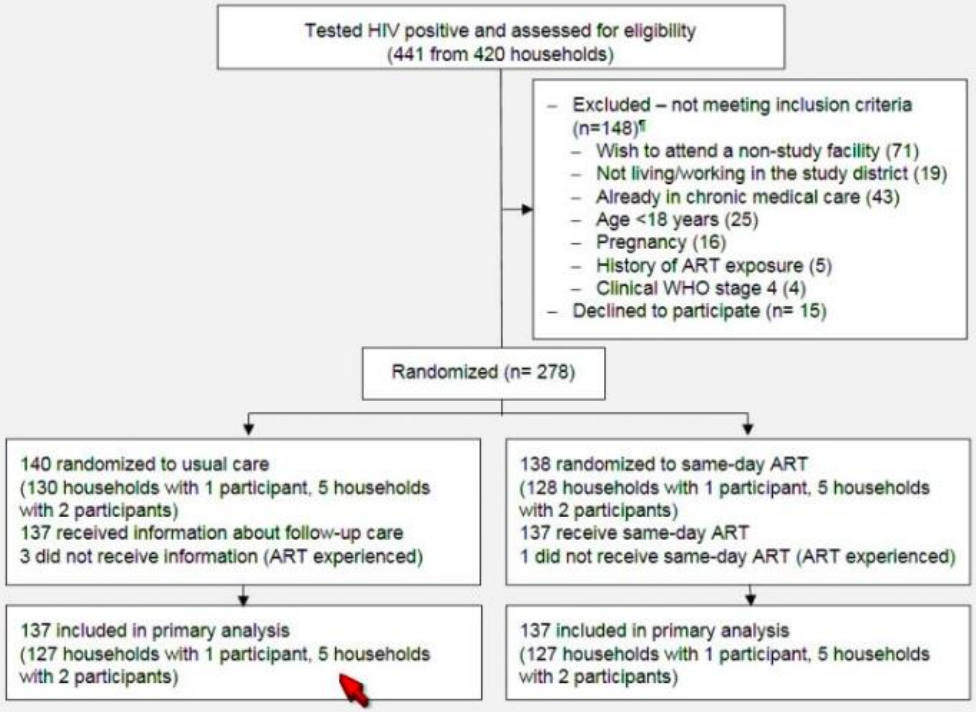
Eligibility:
- HIV+, cART-naïve; ≥ 18 years
- Resident or working in the study area
- Written informed consent

Exclusion:
- Already in chronic care for another medical condition (i.e. diabetes, tuberculosis)
- Wants to attend care in a non-study clinic
- Clinical WHO stage 4 or serum cryptococcal antigen positive
- Pregnancy, breastfeeding

CROI 2018 - The CASCADE-trial ; ND Labhardt et al. 7

CONSORT chart





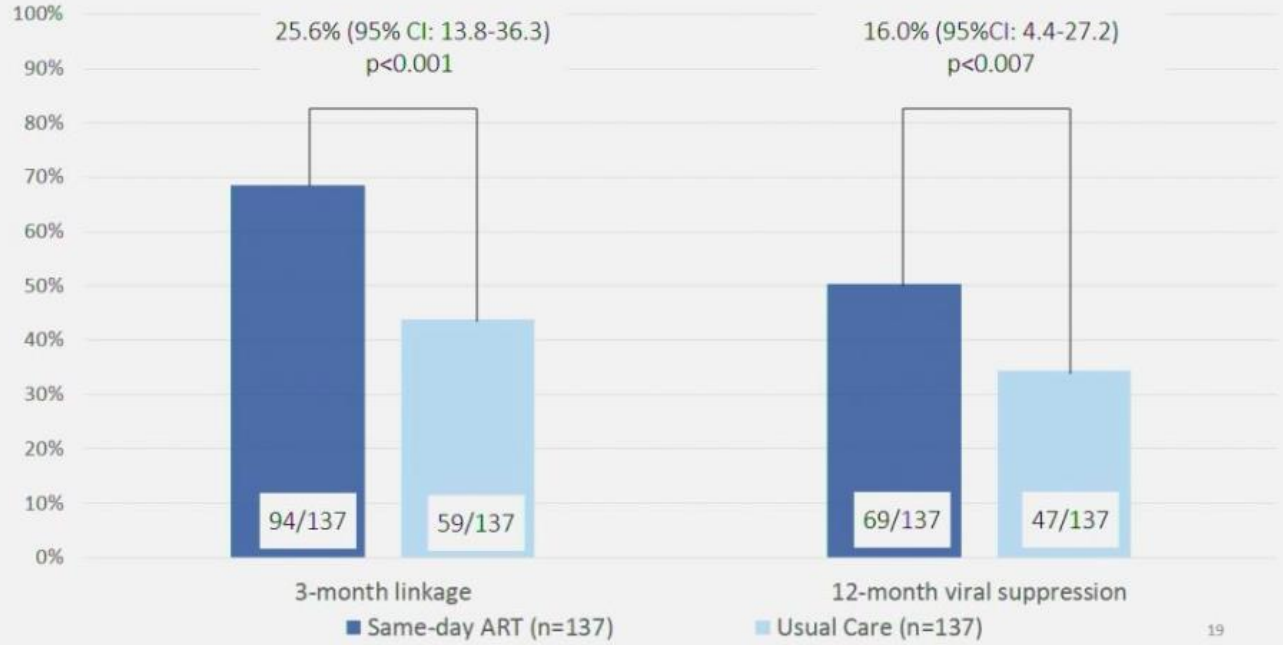
ND Labhardt, 94

Baseline characteristics (n=274)

Female	76%
Median age	39 years (IQR 28-52)
Completed primary education	48%
Regular employment	23%
Last contact with health facility > 1 year	46%
Walks to clinic	49%
Median travel-time to clinic (IQR)	1 hour (0.5-1.5)
WHO-stage 1	78%
Median CD4 count (IQR)	378 (246-530)
CD4-count<200	16%

ND Labhardt, 94

Primary Endpoints



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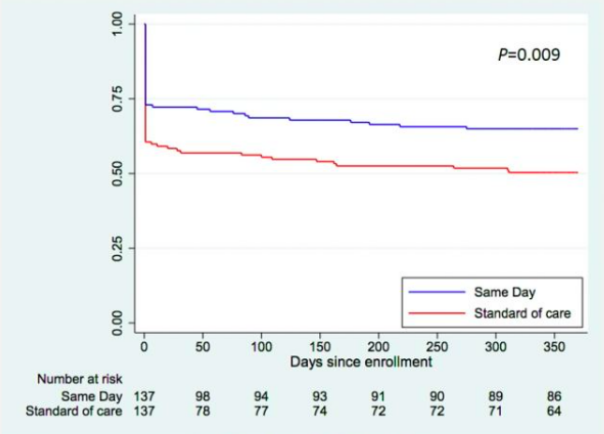
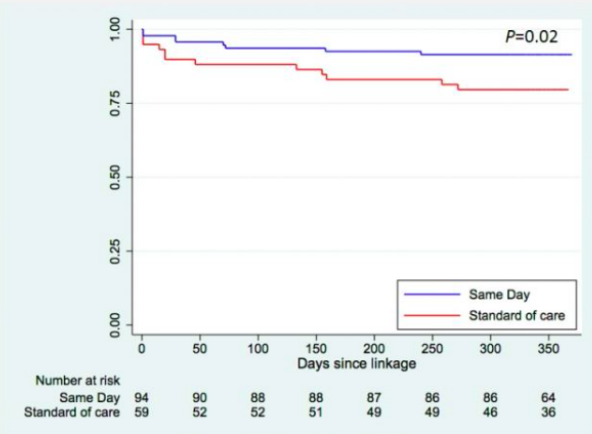
Retention in care after HIV test result



CROI 2018 - The CASCADE-trial ; ND Labhardt et al.

20

Retention in care after linkage to clinic

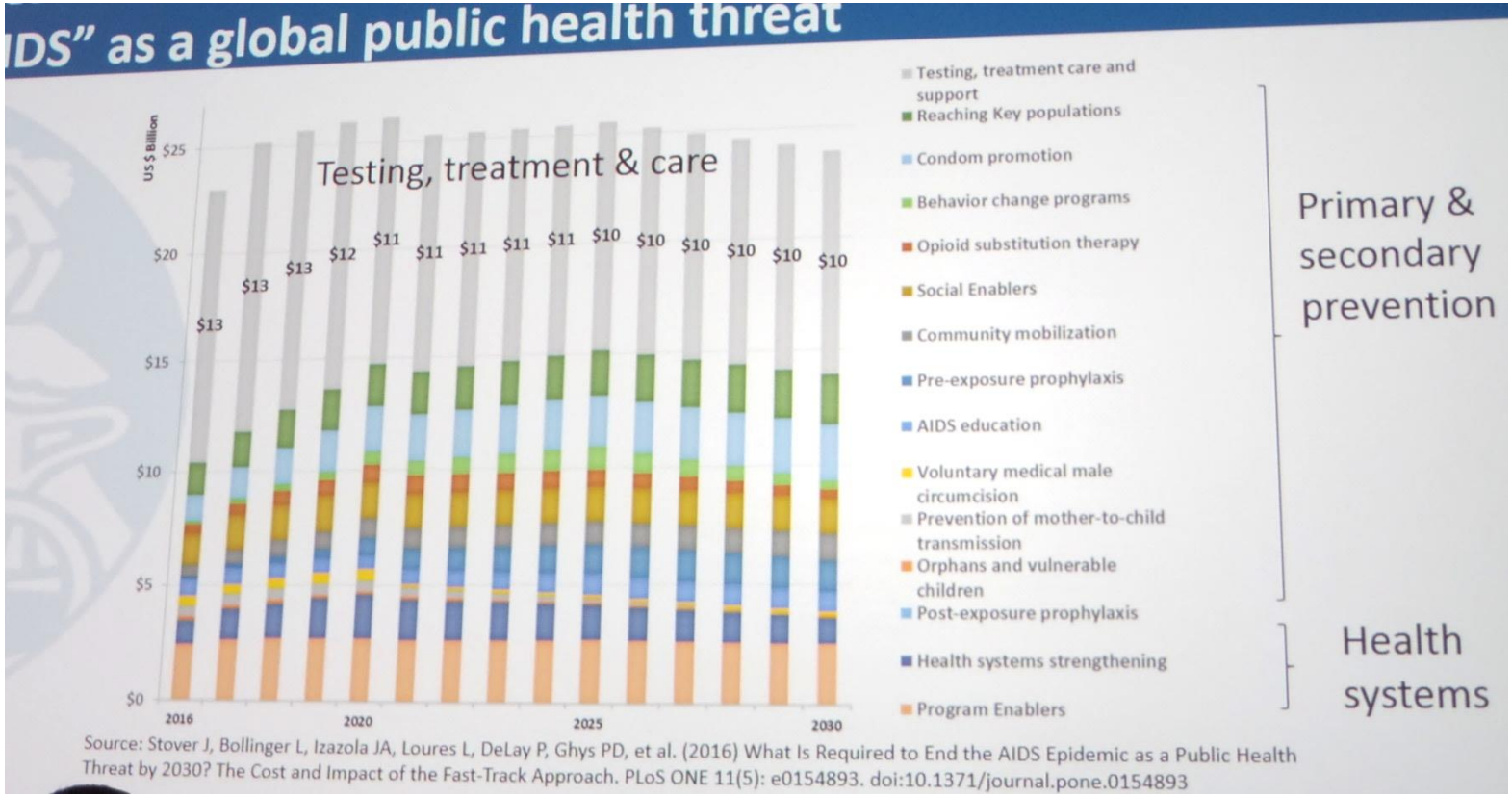


CROI 2018 - The CASCADE-trial ; ND Labhardt et al.

21

ND Labhardt, 94

Argent !



Proposed US budget cuts for bilateral HIV of $600m in 2018 could:

-increase the number of new HIV infections by 200,000 per year

-reduce the number of people on ART by 800,000 per year

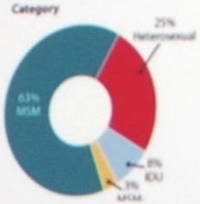
Kates et al, Kaiser Family Foundation analysis, June 2017

Bending the epidemic curve is possible if we:

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Intensify and focus prevention & treatment efforts

Leave no-one behind



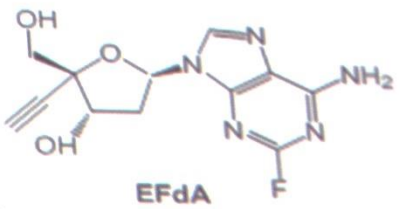
Know our epidemic, know our response

Ensure funding is expanded in the short-term

MK 8591 - EFdA

MK-8591: Highly Potent, Long-Acting Antiretroviral Agent

- Nucleoside reverse transcriptase translocation inhibitor (NRTTI) with novel mechanism of action
  - 4'-ethynyl-2-fluoro-2'-deoxyadenosine (EFdA)
  - Immediate chain termination via blockage of translocation
  - Delayed chain termination after incorporation and altered viral DNA structure
- Potent antiviral activity based on preclinical data
  - In vitro IC_{50} as low as 1.5 nM (equivalent to ~0.01 pmol/10^6 cells) MK-8591-triphosphate (MK-8591-TP)
  - Antiviral activity in macaque models ~0.2-0.4 pmol/10^6 cells
- Long half-life in preclinical and early clinical studies
  - MK-8591-TP half-life ~50 hr in macaque
  - MK-8591-TP half-life ~120 hr in healthy adults

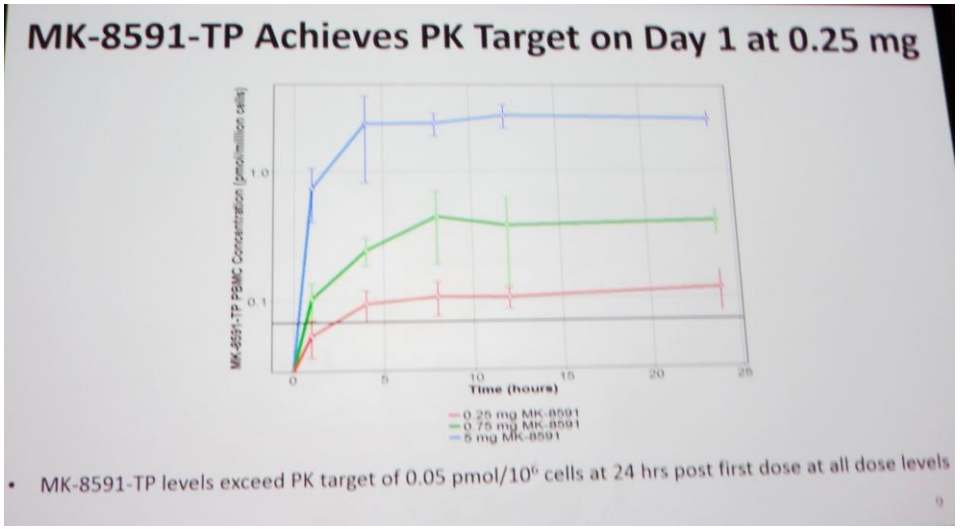


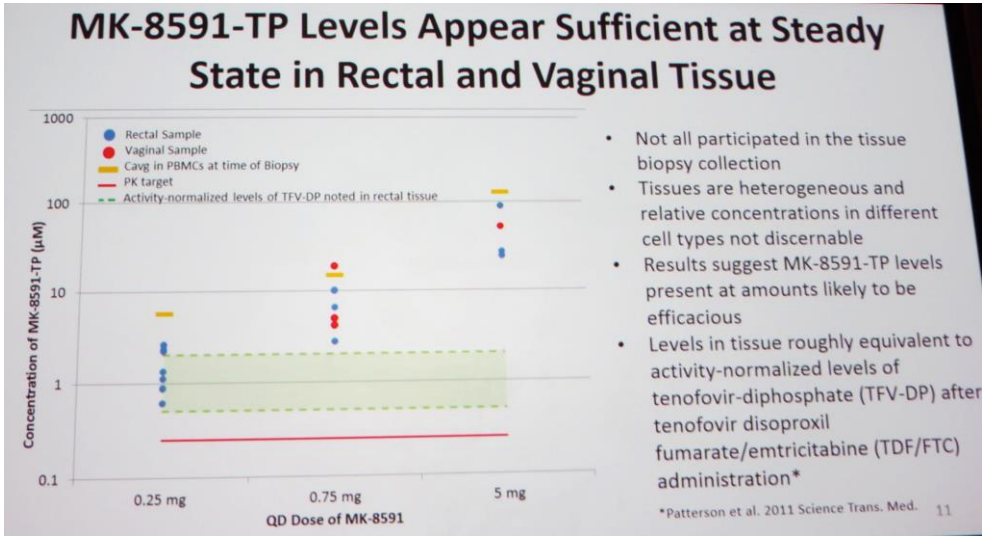
EFdA

Michailidis, E., et al. J. Biol. Chem., 2009, 284:35681-91
Michailidis, E., et al. J. Biol. Chem., 2014, 289:24533-48
Kirby, K. A., et al. Cell Mol. Biol., 2011, 57:40-6
Nakata, H., et al. Antimicrob. Agents Chemother., 2007: 51:270
Grobler et al., CROI 2016

R. Matthews, 26

MK 8591 – EFdA
Phase II





R. Matthews, 26

HIGH SEROCONVERSION RATES FOLLOWING PrEP DISCONTINUANCE IN A MONTREAL CLINIC

Poster # 1038

Zoë Greenwald, Marième Beauchemin, Khadija Benomar, Gabrielle Landry, Michel Boissonnault, Louise Charest, Danièle Longpré, Stéphane Lavoie, Réjean Thomas
Institution: Clinique médicale l'Actuel, Montréal, QC, Canada
zoe.greenwald@lactuel.ca

Presented at the CROI 2018 Conference
Boston, MA, March 7, 2018

FIGURE 1

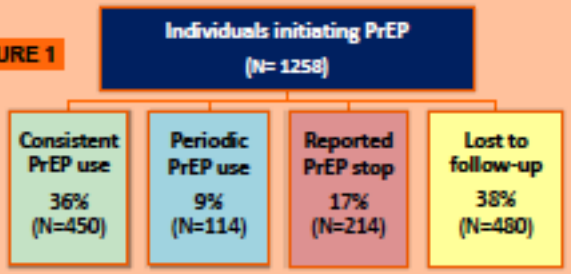


Table 1. Baseline Characteristics of Study Population

Variables	Consistent PrEP Use	Periodic PrEP use	Reported PrEP Stop	Lost to follow-up	TOTAL
Age, median (IQR)	37 (31-46)	37 (31-47)	34 (27-42)	35 (29-44)	36 (30-45)
PrEP regimen prescribed at baseline, N (% column)					
Daily	349 (77)	94 (82)	196 (91)	382 (80)	1021 (81)
Intermittent	88 (20)	16 (14)	19 (9)	83 (17)	206 (16)
Unknown	13 (3)	5 (4)	0	13 (3)	31 (3)
Year of consult, N (% row)					
2011-2013	4 (13)	1 (3)	10 (31)	17 (53)	32 (100)
2013-2015	67 (13)	67 (13)	97 (19)	268 (54)	499 (100)
2016-2017	379 (52)	47 (7)	108 (15)	193 (27)	727 (100)
Number of sexual partners in the last 12 months, N (% column)					
< 10	128 (28)	27 (24)	50 (23)	109 (23)	314 (25)
10-19	120 (27)	25 (22)	55 (26)	95 (20)	295 (23)
20-39	86 (19)	21 (18)	37 (17)	100 (21)	244 (19)
40 or more	64 (14)	25 (22)	43 (20)	96 (20)	228 (18)
Unknown	52 (12)	17 (15)	30 (14)	78 (16)	177 (14)
Education, N (% column)					
≤ Secondary	53 (12)	17 (15)	31 (14)	55 (12)	156 (12)
College	72 (16)	17 (15)	41 (19)	87 (18)	217 (17)
University	279 (62)	59 (51)	112 (52)	251 (52)	701 (56)
Unknown	46 (10)	22 (19)	31 (14)	85 (18)	184 (15)
Annual Revenue, N (% column)					
Under $20 000	62 (14)	17 (15)	40 (19)	81 (17)	200 (16)
$20 001 - 35 000	44 (10)	11 (10)	28 (13)	39 (8)	122 (10)
$35 001 - 55 000	88 (20)	18 (16)	45 (21)	97 (20)	248 (20)
Over $55 000	223 (50)	50 (44)	72 (34)	173 (36)	518 (41)
Unknown	33 (7)	19 (17)	30 (14)	88 (18)	170 (14)
TOTAL	450 (36)	114 (9)	214 (17)	480 (38)	1258

Figure 2. HIV Incidence following PrEP discontinuation

HIV incidence details:

- 203 individuals who stopped PrEP subsequently returned for routine HIV testing
- Time from PrEP stop to most recent HIV test on record totals 75.4 person-years at risk
- 3 individuals seroconverted during this time at 56 days, 107 days and 117 days subsequent to PrEP stops (Table 2)
- Measured HIV incidence is 3.9 cases per 100 person-years at risk following PrEP stop

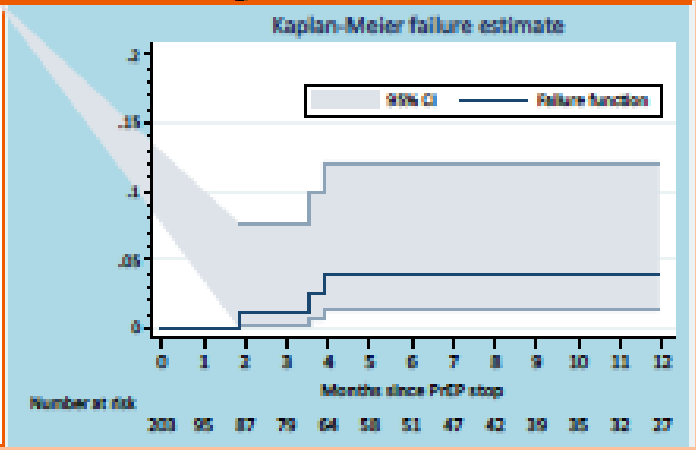


Table 3. Reported Stop Reasons

Stop reason	N	(%)
Side effects	30	13.5
Entry into stable relationship with HIV negative partner	28	12.6
Sexual abstinence	23	10.4
Cost	16	7.2
Individual preference	12	5.4
Entry into stable relationship with HIV undetectable partner	11	5
Break-up with HIV positive partner	9	4.1
Prefers uniquely using condoms for protection during sex	7	3.2
Health insurance issue	4	1.8

Table 2. Participants with HIV infection

Case	Duration on PrEP	Stop reason	Days from PrEP stop to HIV detection	Age at diagnosis	Viral load at diagnosis	CD4 count at diagnosis
1	10 months	Temporary stop due to expiration of health card	56	27 years	247 000 copies/ml	699 cells/ml
2	2 months	Side effects including diarrhea	107	25 years	103 000 copies/ml	430 cells/ml
3	12 months	Personal decision	117	26 years	65 885 copies/ml	440 cells/ml

Z Greenwald, 1038

Drogues dans les cheveux dans l'étude Ipergay

Table 1. Baseline characteristics of the study participants. Median (IQR) or n (%).

		Drug Sub-study population (N=69)	Ipergay Not in drug substudy population (N=360)	P-value
Age (years), median, IQR		34.7 [28,0- 40,9]	35,2 [29,9- 42,8]	0,21
Sexual orientation	Homosexual	67 (97%)	347 (96%)	1
	Bisexual	2 (3%)	13 (4%)	
Education level – no. (%), Postsecondary		45 (65%)	261 (74%)	0,28
Unemployed – no. (%),		15 (22%)	44 (12%)	0,06

Table 2. Molecules detected.

DRUGS	N Pts	%
COCAINE	47	68,1
MDMA	31	44,9
KETAMINE	26	37,7
SILDENAFIL	23	33,3
EPHEDRINE	18	26,1
TRAMADOL	15	21,7
MEPHEDRONE*	14	20,3
4 MEC*	12	17,4
CODEINE	9	13,0
NEXPAM	7	10,1
TADALAFIL	7	10,1
METHAMPHETAMINE	6	8,7
ETHYLPHENIDATE	5	7,2
AMPHETAMINE	4	5,8
METHYLONE*	4	5,8
DEXTROMETORPHANE	4	5,8

DRUGS	N Pts	%
METHOXETAMINE	4	5,8
PHOLCODINE	4	5,8
METHOPROPAMINE	3	4,3
PMMA	3	4,3
MDPV*	3	4,3
METAMFEPRAMONE*	2	2,9
VARDENAFIL	1	1,4
SF-PB22	1	1,4
METHYLPHENIDATE	1	1,4
NALMEFENE	1	1,4
DIPHENIDINE	1	1,4
PHENDIMETRAZINE	1	1,4
PHENTERMINE	1	1,4
a-METHYL-2AI	1	1,4
DIMETHYLONE*	1	1,4
BUTORPHANOL	1	1,4

NPS (*cathinones) Therapeutics drugs Conventional drugs

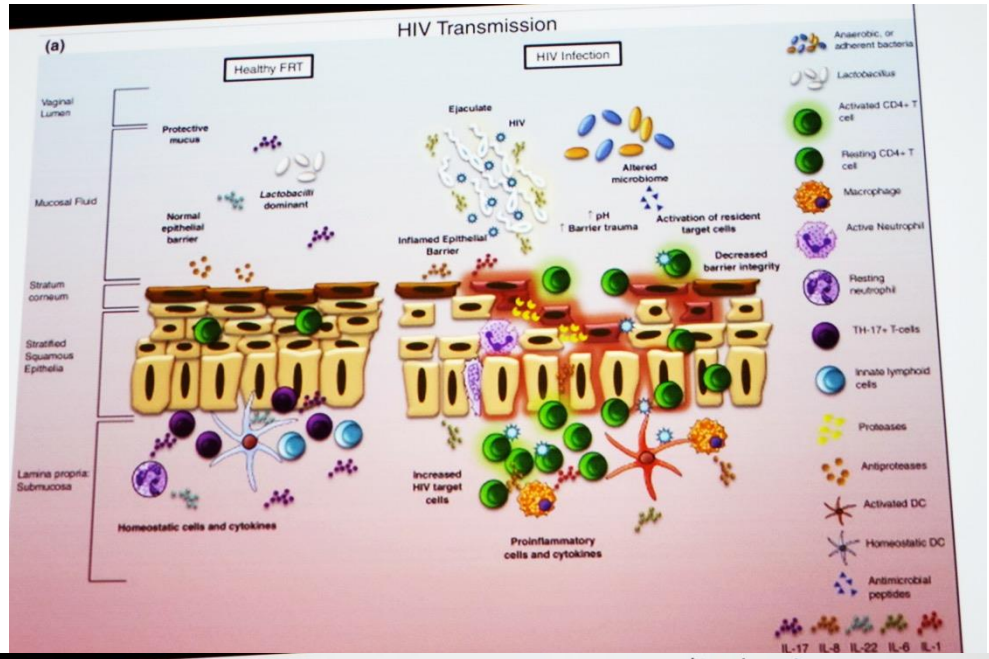
Table 3. Correlation between hair samples and self-reported questionnaires.

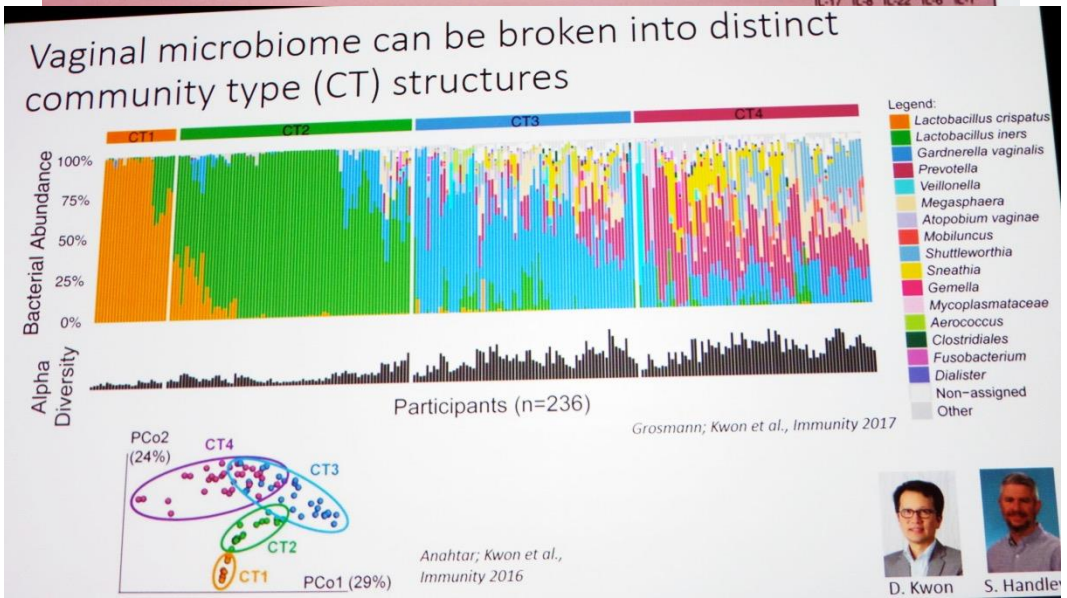
	Hair samples with drugs detected N = 53	Hair samples without drugs detected N = 16
Questionnaires with drugs consumption self-reported	32/69 (46%)	2/69 (4%)
Questionnaires without drugs consumption self-reported	21/69 (30%)	14/69 (20%)

MSM pts consuming drugs have more differents partners in past 2 months (p<0,0001) (Table 4)

JC Alvarez, 1029

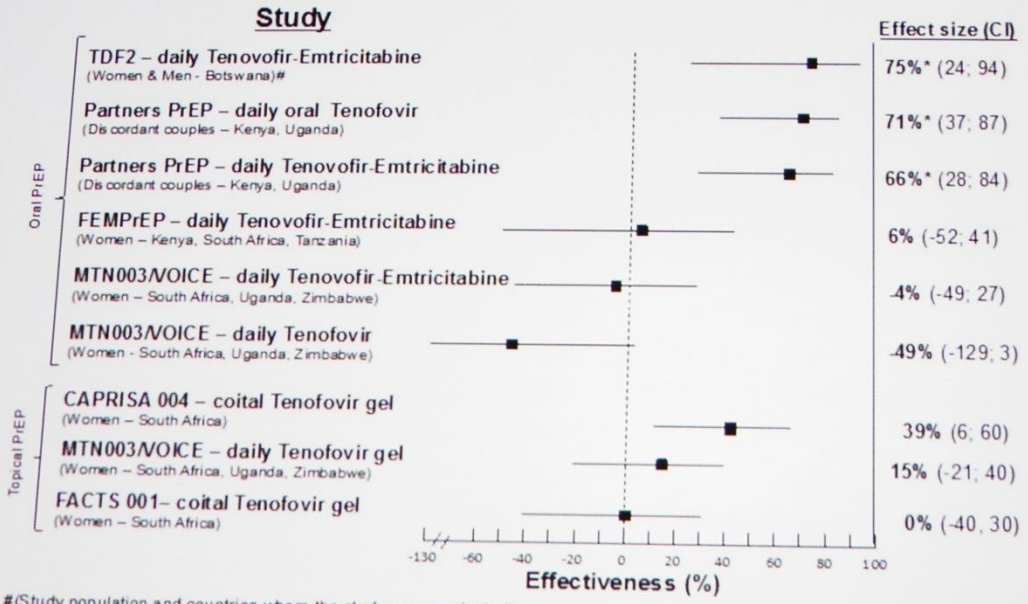
Microbiome vaginal et transmission du VIH





N. Klatt

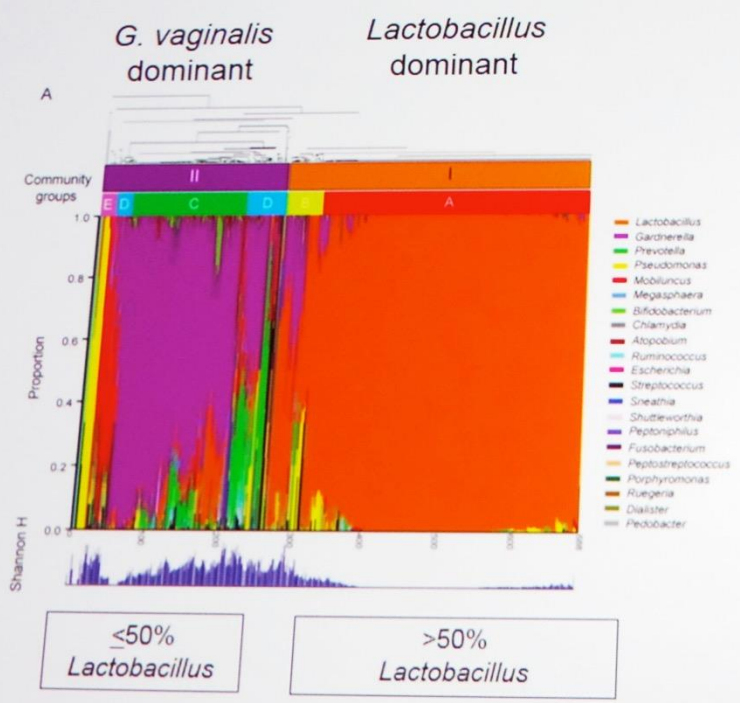
Effectiveness of pre-exposure prophylaxis (PrEP) is highly variable in women

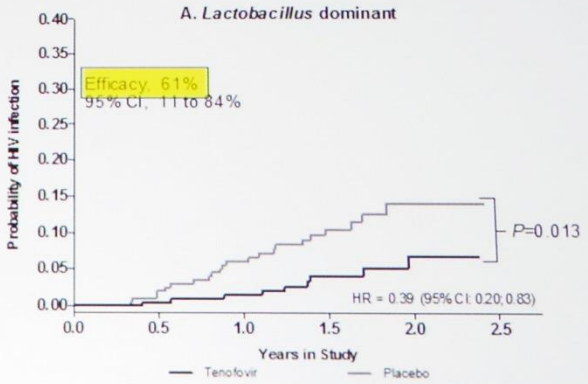


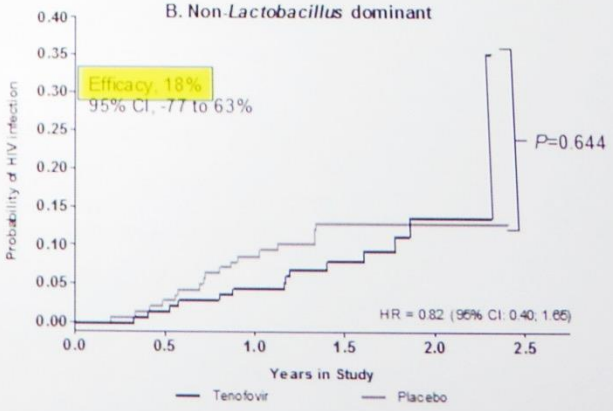
#(Study population and countries where the study was conducted)
*Effect size calculated from the incidence rate ratio for women only

Varying outcomes from PrEP trials - attributed to adherence
What biological factors affect PrEP?

Vaginal microbial groups in CAPRISA 004 alter efficacy

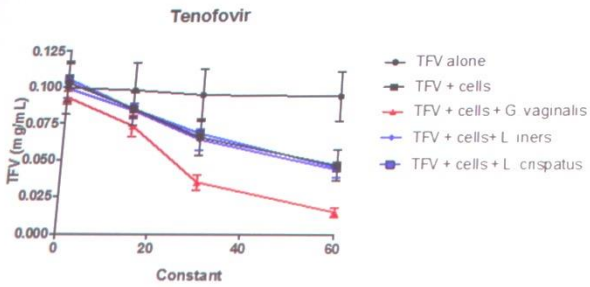




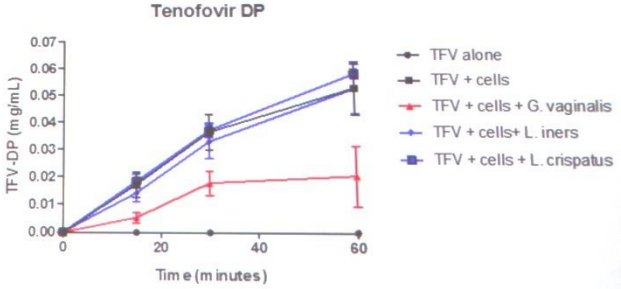


Klatt et al., Science 2017

Decreased metabolically active TFV-DP in presence of dysbiotic bacteria



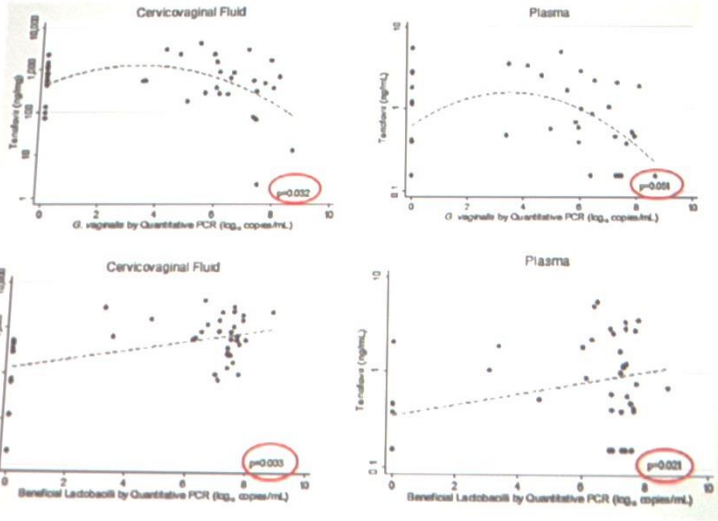
60 minutes:
G. vag vs TFV + cells: *P*=0.0001
G. vag vs. L. iners: *P*=0.0022
G. vag vs. L. crispatus: *P*=0.0238
Lactobacillus vs TFV/cells: *P*=ns



60 minutes:
G. vag vs TFV + cells: *P*=0.0002
G. vag vs. L. iners: *P*=0.0022
G. vag vs. L. crispatus: *P*=0.0238
Lactobacillus vs TFV/cells: *P*=ns

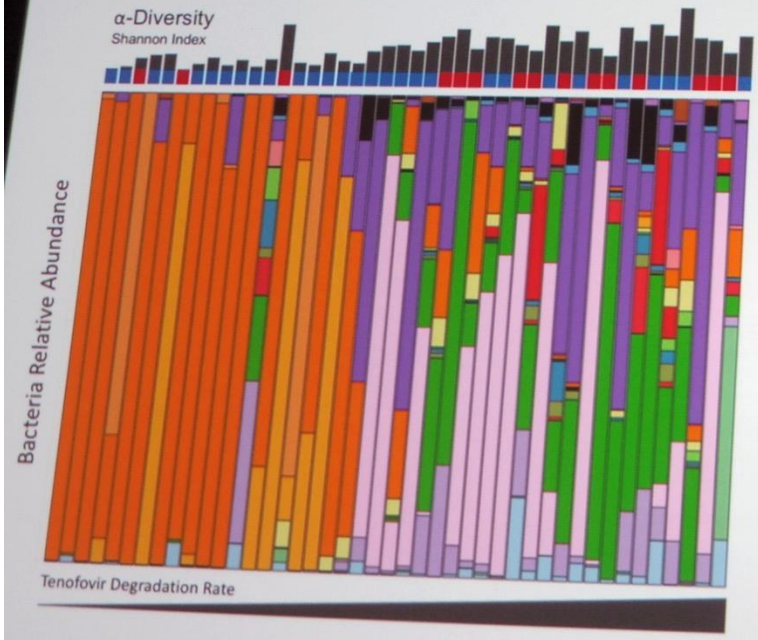
Klatt et al., Science 2017

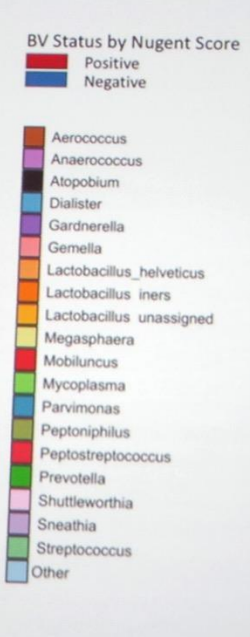
Dysbiotic bacteria decrease CVL and plasma TFV concentrations *in vivo*

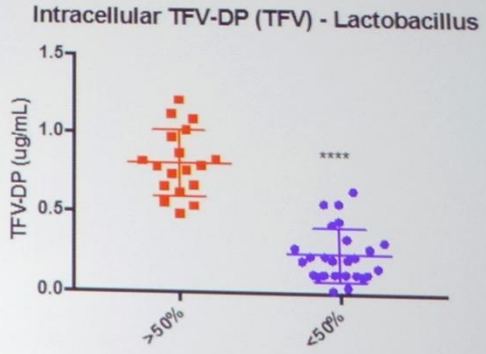


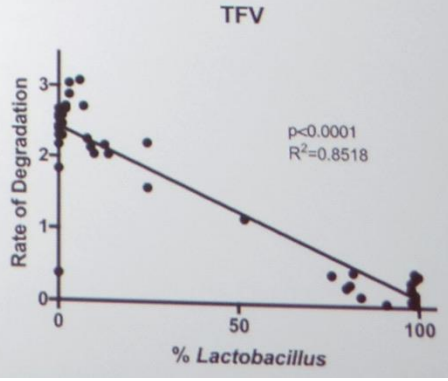
Hillier, CROI 2017

Dysbiotic bacteria metabolize **Tenofovir (TFV)**

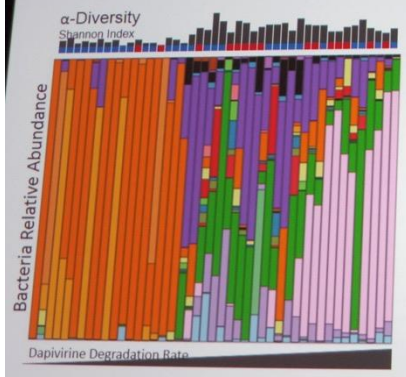


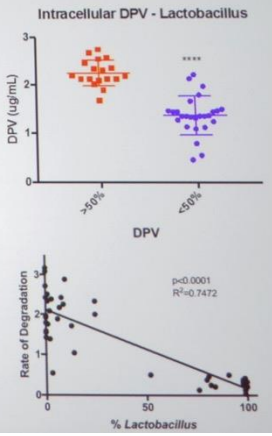




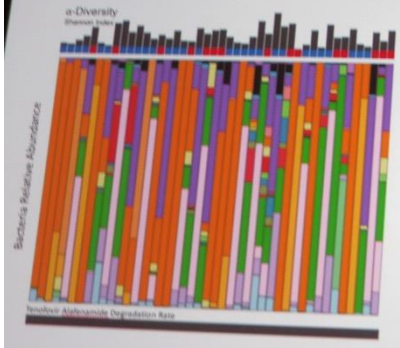


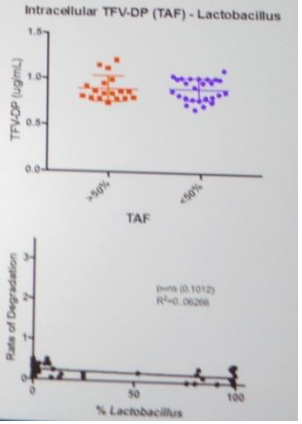
Dysbiotic bacteria metabolize **Dapivirine (DPV)**





Bacteria do not metabolize **Tenofovir Alafenamide (TAF)**

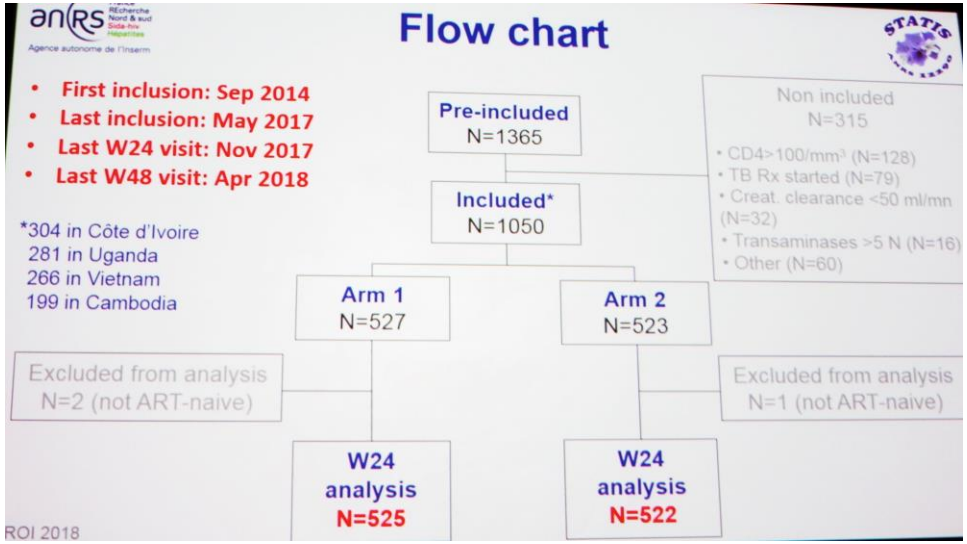


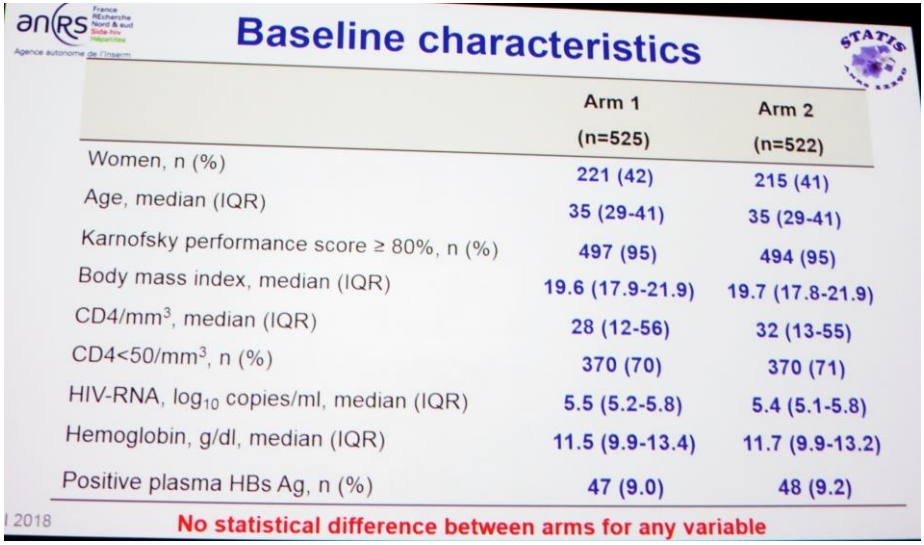


TUBERCULOSE

Essai ANRS Statis

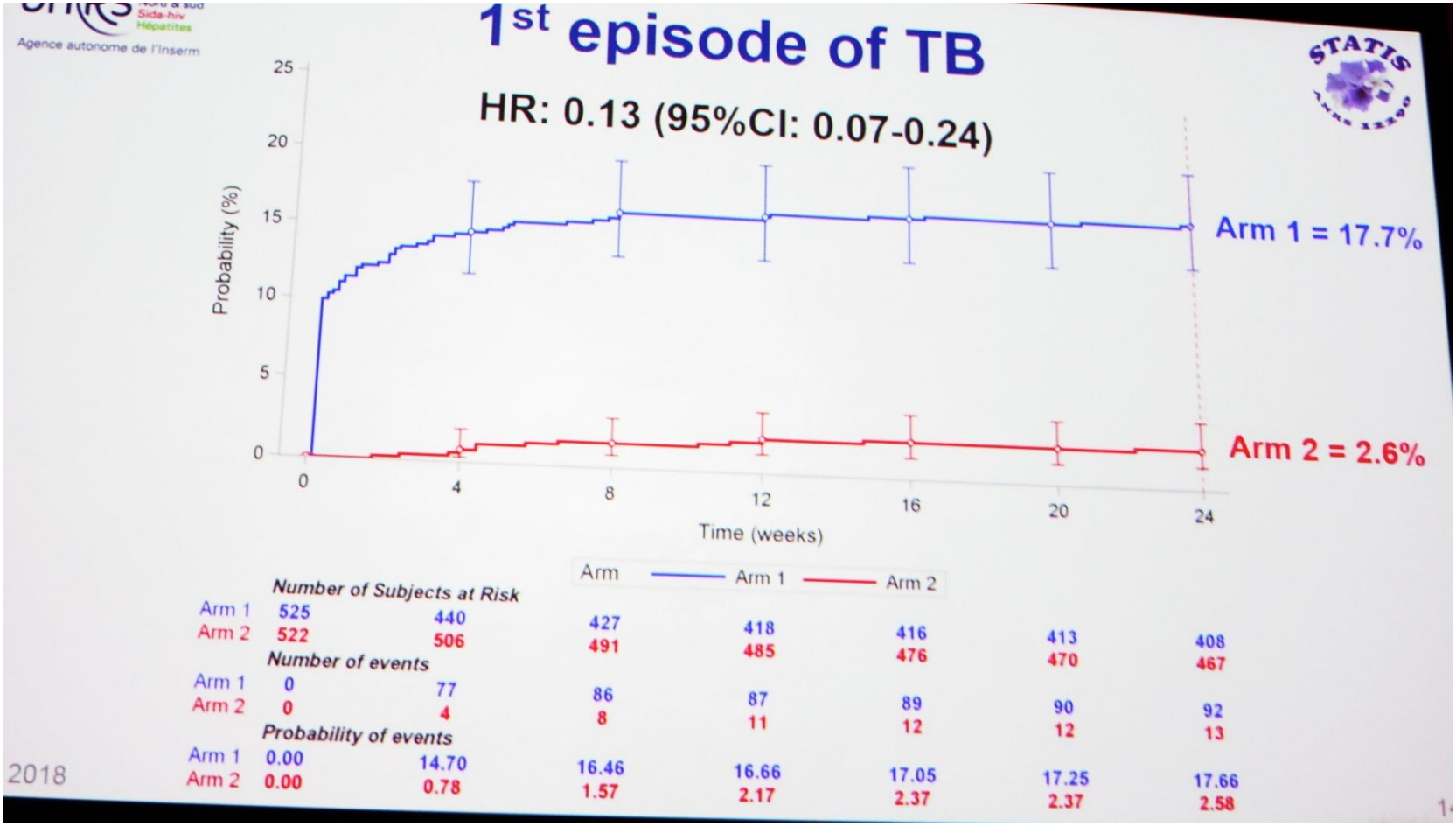
Traitement systématique TB (1) vs Traitement ciblé (2) guidé par (clinique + Rx+XPertTB-RIF + U-LAM) dans des pays à forte prévalence chez PVVIH dépistés tardivement.





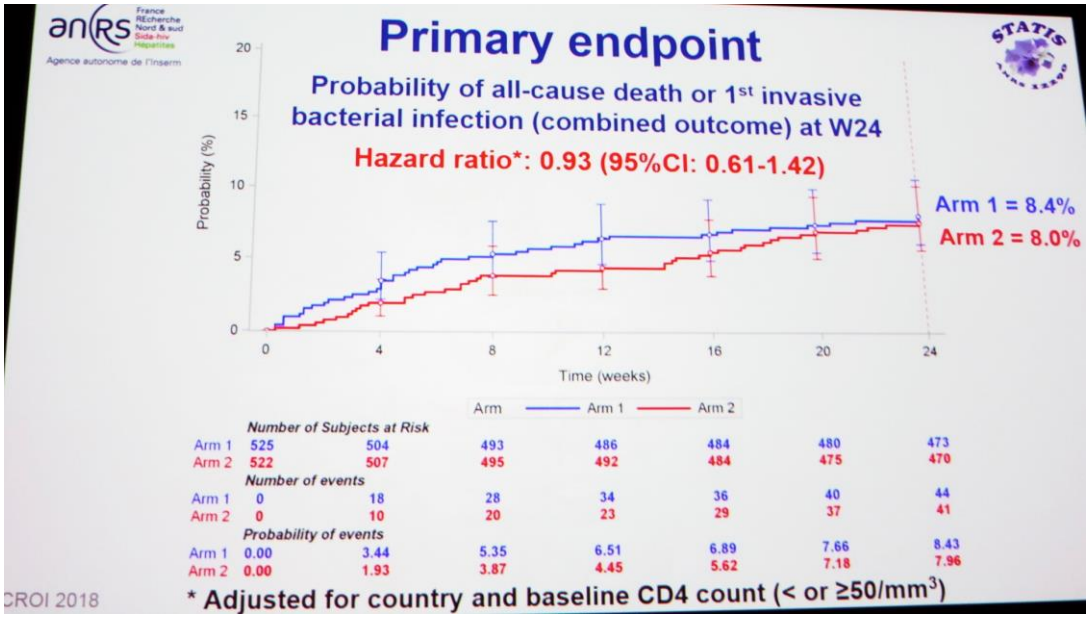
FX Blanc, 29LB

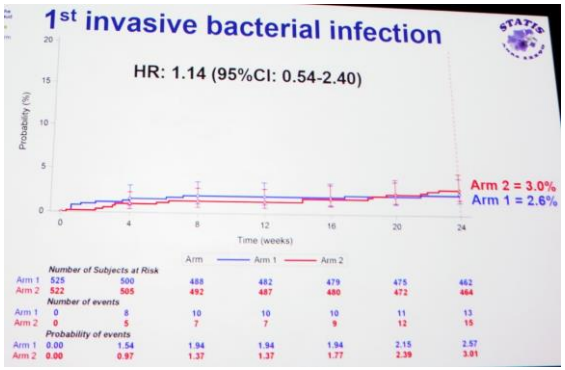
STATIS

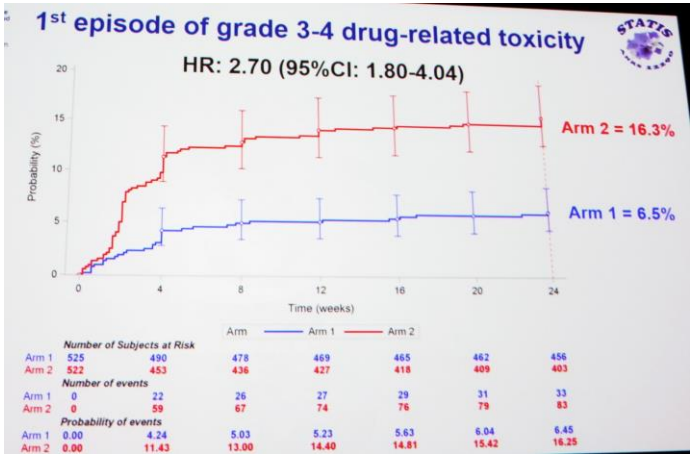


FX Blanc, 29LB

STATIS

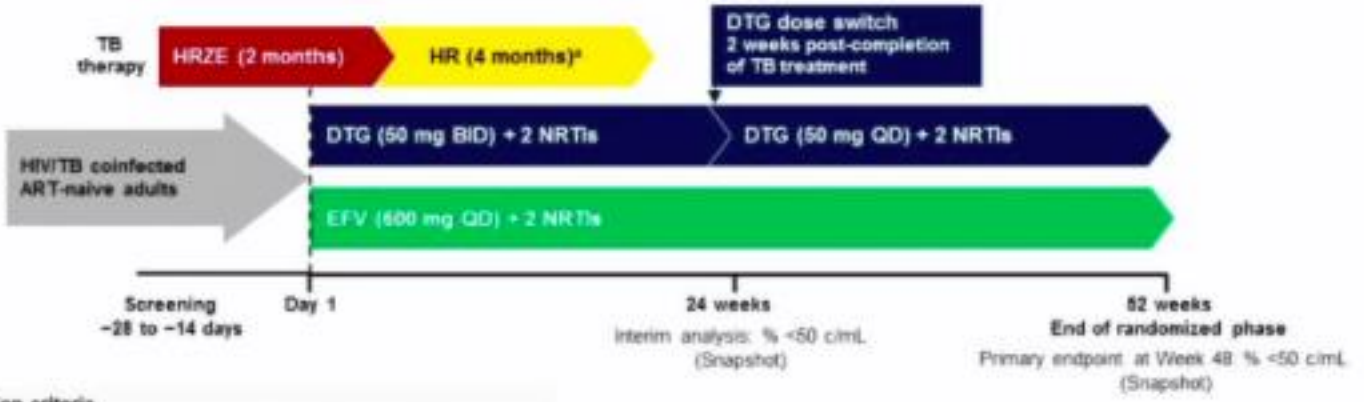






FX Blanc, 29LB

INSPIRING Study: Safety and Efficacy of Dolutegravir-Based ART in TB/HIV Co-infected Adults at Week 24



Inclusion criteria

- HIV-1 RNA ≥1000 copies/mL and CD4+ ≥50 cells/mm³
- Pulmonary, pleural, or lymph node tuberculosis confirmed by culture or GeneXpert
- RIF-containing TB treatment started up to a maximum of 8 weeks before randomization and no later than the screening date

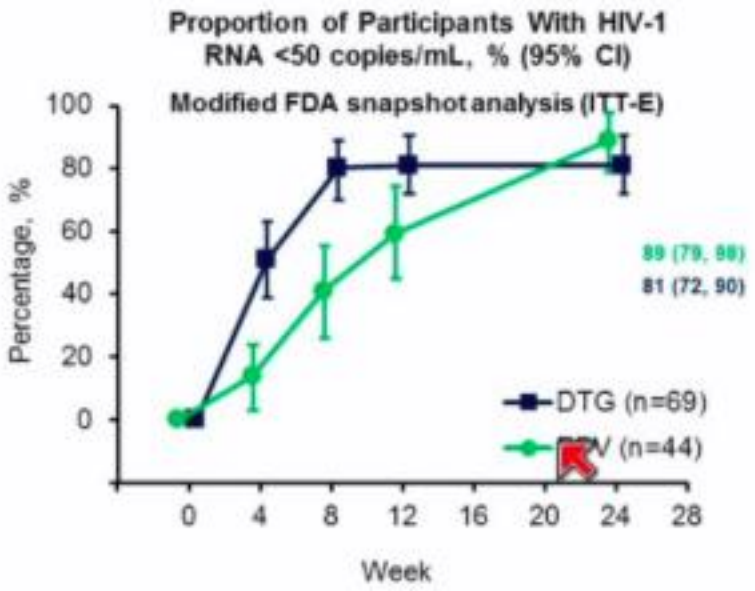
DTG:EFV 3:2 randomization stratified by

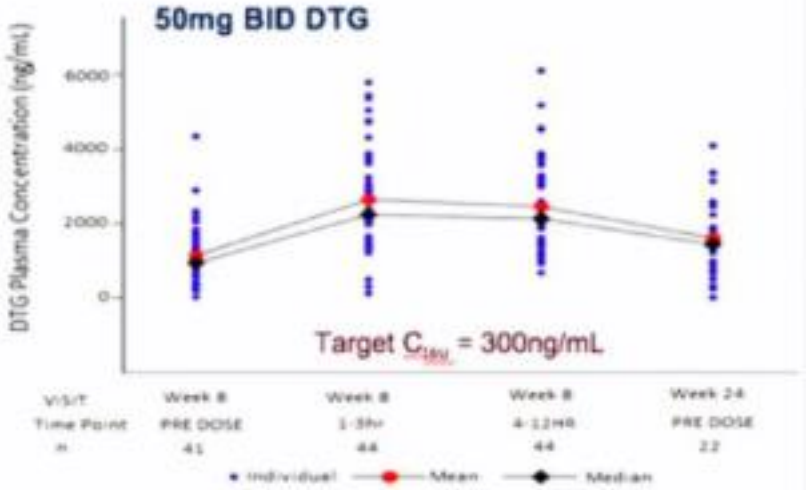
- Screening plasma HIV-1 RNA ≤100,000 or >100,000 copies/mL
- Screening CD4+ ≤100 cells/mm³ or >100 cells/mm³

Countries: Argentina, Brazil, Mexico, Peru, Russia, South Africa, Thailand

Dooley KE et al. CROI 2018 #33.

INSPIRING Study: Results





n (%)	DTG (n=69)	EFV (n=44)
Participants with events sent to adjudication committee for TB-associated IRIS	9 (13)	12 (27)
Met criteria for TB-associated IRIS	4[a] (6)	4[b] (9)
Possibly met criteria for TB-associated IRIS	0	0
Suspected TB-associated IRIS, but not possible to adjudicate	0	0
Participants with events sent to adjudication committee for other/general IRIS	2 (3)	3 (7)
Met criteria for general IRIS	1[c] (1)	0
Possibly met criteria for general IRIS	1[d] (1)	0
Suspected general IRIS, but not possible to adjudicate	0	0

Dooley KE et al. CROI 2018 #33.

One Month of Rifapentine/Isoniazid: Results/Conclusions

- Rates of TB were higher in those with +TST/IGRA or CD4 ≤250
- Rates of endpoints were higher in 1HP recipients with CD4 ≤250 vs 9H
- Safety was good and similar in both arms, with more hematologic toxicity with 1 HP and more liver and neuro-toxicity with 9H
- Completion of treatment was excellent in both arms but better 1HP (97% vs 90%)

Primary Endpoints

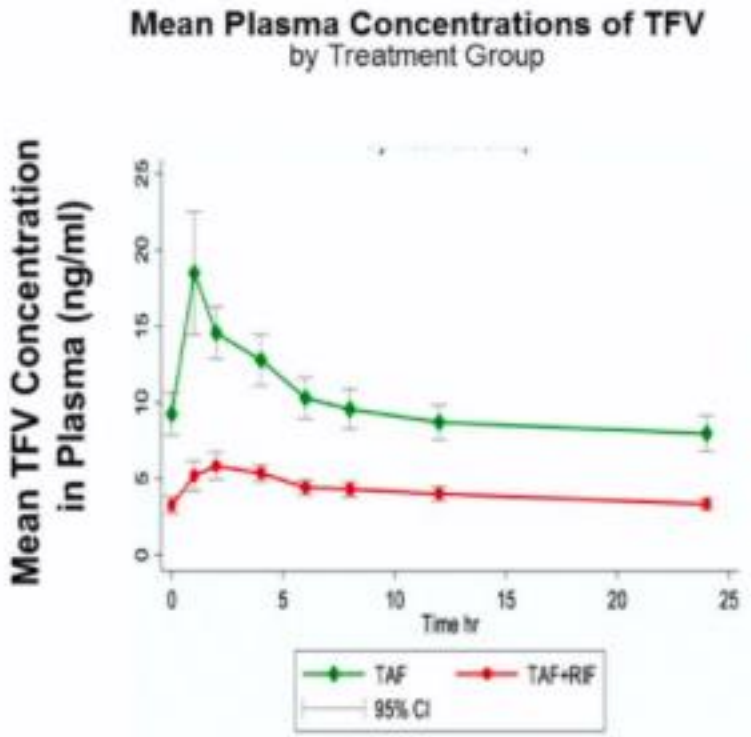
	Randomized Treatment		
First Outcome	**9H**	**1HP**	**Total**
All Outcomes	33	32	65
Active TB, Confirmed	14 (42%)	18 (56%)	32 (49%)
Active TB, Probable	10 (30%)	11 (34%)	21 (32%)
Death Related to TB	2 (6%)	0 (0%)	2 (3%)
Death from Unknown Cause	7 (21%)	3 (9%)	10 (15%)

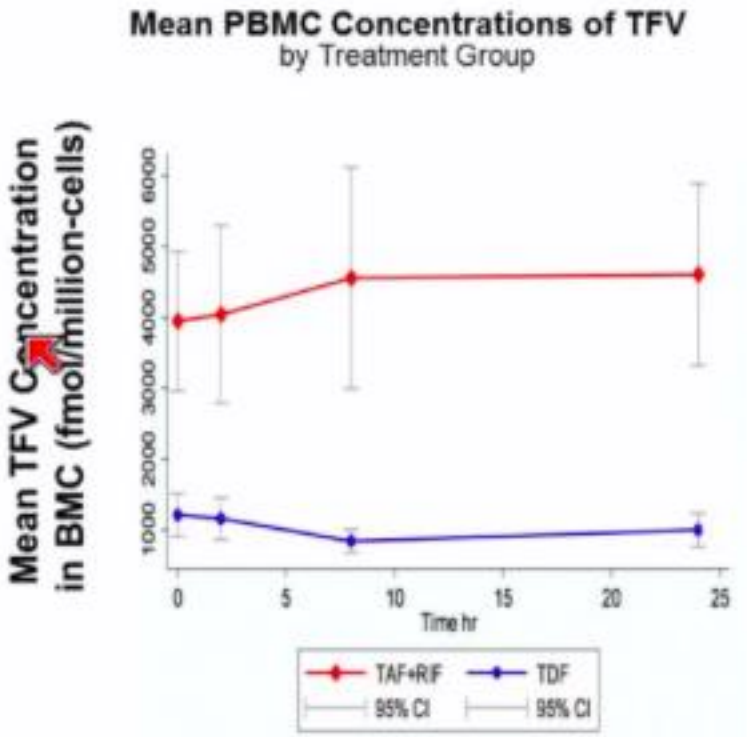
	9H	1HP	IRR Difference
Events/PY of follow up **Incidence per 100 PY**	33/4896 0.67	32/4926 0.65	0.023 (95% CI -0.30-.35)

Non-inferiority margin = 1.25 per 100 PY

Swindells S. et al. 25th CROI. Boston, MA. March 4-7, 2018. Abst. 37LB

TAF +Rifampicin:
Lower Plasma TFV but TFV-DP more than TDF alone





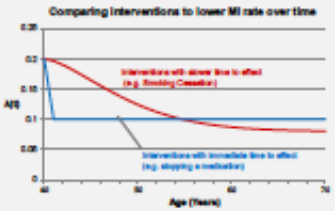
COMORBIDITÉS

Comparing Strategies for Reducing Myocardial Infarction Rates in HIV Patients

Priscilla Hsue, Grace A. McComsey, Calvin Cohen, Alejandro Sola, Anne C. Beaubrun
University of California San Francisco, San Francisco, CA, USA, University Hospitals Health System and Case Western Reserve University, Cleveland, OH, USA, Gilead Sciences, Inc, Foster City, CA, USA

Methods

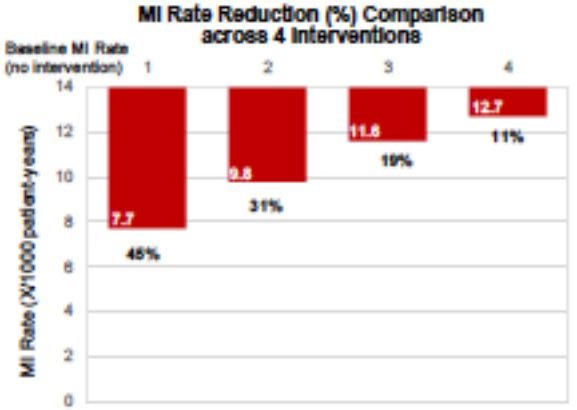
- Common strategies for reducing MI rates in HIV patients were compared using a decision tree model which was simulated over 10 years. These interventions included:
  - smoking cessation counseling,
  - substitution of abacavir with an alternative agent,
  - anti-hypertensive medication use
  - lipid-lowering medication use
- Assumptions about the effectiveness of interventions were based on publications from the HIV or general population, all adjusted for sex, age, and presence of the four risk factors
- **The base case was a 50 year old HIV positive male on an abacavir containing regimen who is also a smoker, with hypertension and hyperlipidemia**
- This model highlights the potential impact of addressing each intervention on it's own
- The interventions were compared based on published data on the probability of success of changing the risk factor and the impact of changing it when successful:
  - For counseling to smoking cessation, the impact was based on published quit rates following counseling, 36.5% after one year and 10% annual relapse rate
  - For the substitution of ABC, treating hypertension and hyperlipidemia, we applied a 100% success rate which assumes patient's adherence and compliance with the dosing and prescription
- The expected number of MI is calculated by numerically integrating MI incidence rates over a 10-year time period



Results

- Compared to no MI intervention, abacavir substitution prevented more MIs than counseling about smoking
  - In the base case of 50-year old HIV positive male smokers with hypertension and hyperlipidemia , who only replaced abacavir, there was a 45% reduction in the MI rate compared to those who continued abacavir
  - Men who are counseled and treated for smoking cessation which resulted in an 11% MI rate reduction versus those who did not attempt smoking cessation in10 years
- Treating hypertension and hyperlipidemia resulted in 19% and 31% reductions in MI risk, respectively (see Table)

Intervention Type	
HIV+ Patient Base Case Profile: 50 years old, Male, On Abacavir, Smoker, w/ Hypertension, w/ Hyperlipidemia	
1	Abacavir substitution with an alternative antiviral without association to higher MI rate [1][2][3]
2	Prescribing anti-hyperlipidemia medication [4][6]
3	Prescribing anti-hypertensive medication [4][7][8]
4	Counseling including standard treatment for smoking cessation such as nicotine patch and varenicline [4][5][6]



P Hsue, 692

Poster number 703

The Mediterranean Portfolio diet in HIV dyslipidaemia: a pilot randomised controlled trial

Clare Stradling[1], G N. Thomas[2], Karla Hemming[2], Shahrad Taheri[3], Stephen Taylor[1], Jonathan Ross[4], Satyajit Das[5]

[1]Heart of England NHS Foundation Trust, Birmingham, UK, [2]University of Birmingham, Birmingham, UK, [3]Weill Cornell Medicine College in Qatar, Doha, Qatar, [4]University Hospitals Birmingham, Birmingham, UK, [5]Coventry & Warwickshire Partnership NHS Trust, Coventry, UK

Methods

DESIGN & SETTING:
- pilot, parallel, randomized controlled trial (ISRCTN32090191)
- 3 HIV centres in UK with ethnically diverse population

PARTICIPANTS:
- adults with stable HIV infection on ART >6 months
- LDL-cholesterol (LDL-C) >3mmol/l, not on lipid lowering agents

RANDOMIZATION:
- 1 to 1 ratio, independently computer generated allocation sequence with random block sizes, stratified by gender and smoking, concealed in envelopes
- Participants were unaware of the content of the other group's diet

INTERVENTION
- Diet1: dietary advice to reduce saturated fat to <10% of energy intake
- Diet2: advice on adopting Mediterranean Diet with supplies of cholesterol-lowering foods (daily: 2g plant stanols, 15g soya protein, 57g nuts, 15g soluble fibre - oats, pearl barley, flaxseed, beans and pulses).

Figure 1 CONSORT Flow Diagram summarising trial allocation and follow-up

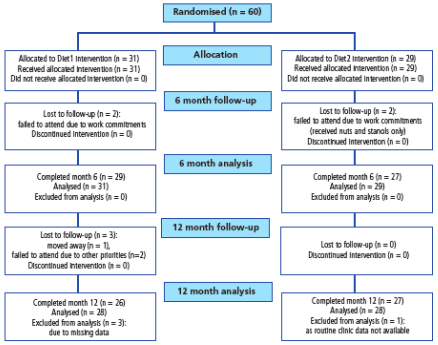


Figure 2: LDL-cholesterol (mmol/l) during 1-year follow-up, by intervention group (mean value represented by red dotted line)

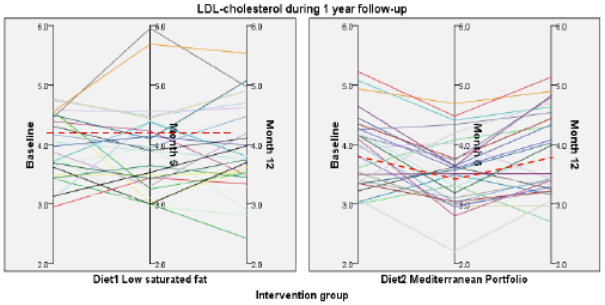
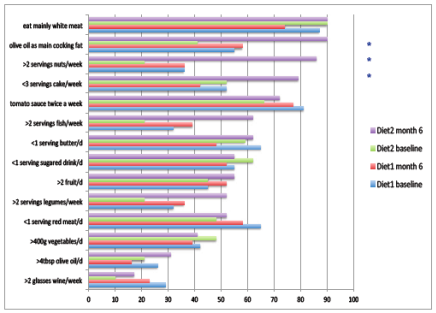


Table 1: Baseline characteristics of trial participants according to study group (n = 60), expressed as mean (SD) or count (%)

Characteristic	Diet1 Reduced saturated fat (n = 31)	Diet2 Mediterranean Portfolio (n = 29)	Total (n = 60)
Age, years	42.8 (7.1)	42.0 (6.5)	42.4 (6.8)
Women (%)	17 (55)	14 (48)	31 (52)
Ethnicity (%)			
– White European	13 (42)	11 (38)	24 (40)
– Black African	14 (45)	16 (55)	30 (50)
– Black Caribbean	2 (6.5)	0 (0)	2 (3)
– Asian	2 (6.5)	2 (7)	4 (7)
Disease duration, years	6.6 (3.2)	8.9 (4.5)	7.7 (4.0)
Current CD4, cells/mm³	546 (204)	616 (210)	580 (209)
Duration of treatment, years	8.2 (3.9)	7.3 (4.2)	7.8 (4.0)
Antiretroviral class (%)			
– NNRTI	20 (65)	18 (62)	38 (63)
– Boosted Protease Inhibitor	11 (35)	7 (24)	18 (30)
– Integrase inhibitor	0 (0)	4 (14)	4 (7)
Socio-economic class (%)			
I Managerial & professional	9 (29)	15 (52)	24 (40)
II Intermediate	5 (16)	2 (7)	7 (12)
III Working	17 (55)	12 (41)	29 (48)
Recruitment centre (%)			
– Heartlands	20 (65)	20 (69)	40 (66)
– Queen Elizabeth	4 (13)	3 (10)	7 (12)
– Coventry	7 (22)	6 (21)	13 (22)
QRISK, % 10 year risk of CVD	3.1 (2.9)	2.8 (2.6)	2.9 (2.7)
– Non smoker	19 (61)	20 (69)	39 (65)
Systolic blood pressure, mm Hg	123 (15)	125 (14)	124 (14)
Diastolic blood pressure, mm Hg	78 (12)	78 (9)	78 (10)
Lipid profile, mmol/l			
– HDL-cholesterol	1.5 (0.5)	1.5 (0.6)	1.5 (0.5)
– LDL-cholesterol	3.9 (0.5)	3.9 (0.6)	3.9 (0.6)
– Triglycerides	1.2 (0.5)	1.2 (0.5)	1.2 (0.5)
Body mass index, kg/m²	27.9 (5.9)	28.1 (5.7)	28.0 (5.7)

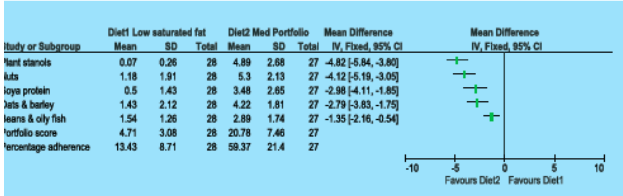
Table 2: Mean difference between low saturated fat (Diet1) and Mediterranean Portfolio (Diet2) groups at month 6

Endpoint	Time	Diet1 low saturated fat group Mean ±SD (n = 29)	Diet2 Med Portfolio group mean ±SD (n = 31)	Mean difference (MD), adjusted for baseline value (95% CI)	P value	MD, adjusted for baseline value, smoking, gender, socioeconomic status, baseline MDS (95% CI)	P value
olesterol f)	Baseline	3.9±0.5	3.9±0.6				
	Month 6	3.9±0.7	3.5±0.6	-0.4 (-0.7 to -0.1)	0.01	-0.5 (-0.8 to -0.2)	0.002
HDL-erol ratio	Baseline	4.3±0.9	4.4±1.4				
	Month 6	4.3±1.0	4.1±1.2	-0.3 (-0.6 to -0.1)	0.01	-0.4 (-0.6 to -0.1)	0.004
BP g)	Baseline	123±15	125±14				
	Month 6	127±17	121±10	-7 (-2 to -12)	0.008	-8 (-13 to -2)	0.005
ic BP g)	Baseline	78±12	78±9				
	Month 6	80±10	78±8	-2 (-6 to 2)	0.3	-2 (-6 to 2)	0.2
rranean Diet 14-item)	Baseline	6.8±2.4	6.0±2.3				
	Month 6	6.6±2.9	9.5±2.2	3.3 (2.0 to 4.7)	<0.001	3.1 (1.6 to 4.5)	<0.001
Saturated fat (g/day)	Baseline	24.5±13.5	25.0±16.5				
	Month 6	23.6 ± 12.4	20.2±10.1	-3.5 (-10.4 to 3.5)	0.3	-2.7 (-11.1 to 5.6)	0.5
Waist circumference (cm)	Baseline	93.4 +/- 12.7	93.9 (11.4)				
	Month 6	92.7 (14.1)	92.6 (10.6)	-1.0 (-3.4 to 1.3)	0.4	-1.3 (-3.9 to 1.4)	0.3
Subcutaneous fat (%)	Baseline	30.8 (12.5)	30.4 (11.9)				
	Month 6	28.4 (14.1)	30.6 (11.2)	2.0 (-0.8 to 4.7)	0.2	1.4 (-1.5 to 4.3)	0.3



Key: * P<0.05 difference between groups at month 6 determined by Chi square test

Figure 4: Adherence to Portfolio food components at month 6 (35-item score)



C Stradling, 703

MARIJUANA SMOKING IMPACTS PULMONARY DISEASE IN HIV-INFECTED MEN

Abstract ID: 2106
Poster #: 747

David R. Lorenz[1] and Dana H. Gabuzda[1,2]
[1]Cancer Immunology & Virology, Dana-Farber Cancer Institute; Harvard Medical School, Boston MA

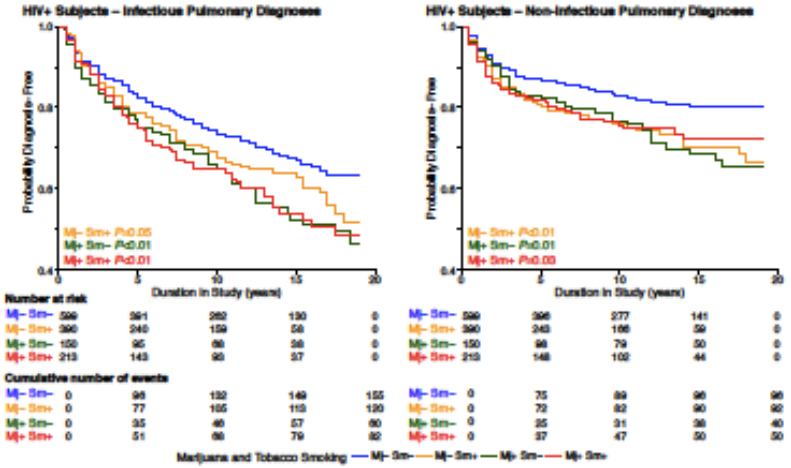


Figure 1. Kaplan-Meier curves of infectious (left panel) and non-infectious (right panel) pulmonary diagnoses in HIV+ subjects. Subjects were stratified by marijuana and tobacco smoking during follow-up as follows: Mj+, ≥1 years daily or weekly marijuana smoking; Mj-, <1

Table 3. Marijuana smoking is associated with increased risk of infectious pulmonary diagnoses in HIV-infected individuals.

	Univariate	Model 1	HIV+ Model 1 - Sensitivity Analysis	Model 2	Univariate	HIV- Model 1	Model 2
	HR (95% CI); p	HR (95% CI); p	HR (95% CI); p	HR (95% CI); p	HR (95% CI); p	HR (95% CI); p	HR (95% CI); p
Marijuana smoking - current							
Daily or weekly	1.37 (1.07, 1.76); p=0.014	1.33 (1.03, 1.71); p=0.031	1.43 (1.08, 1.89); p=0.012		0.91 (0.62, 1.34); p=0.633	0.82 (0.55, 1.21); p=0.308	
Monthly or less	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)		1.00 (Ref.)	1.00 (Ref.)	
Marijuana smoking - recent (per 10 days use/month increase)	1.09 (0.99, 1.21); p=0.077			1.07 (1.04, 1.10); p<0.001	1.01 (0.7, 1.47); p=0.953		0.94 (0.88, 1.02); p=0.224
Cigarette smoking - current							
≥ 0 packs/day	1.24 (1, 1.54); p=0.052	1.18 (0.92, 1.53); p=0.203	1.24 (0.97, 1.6); p=0.089		1.53 (1.19, 2.02); p=0.001	1.74 (1.33, 2.29); p<0.0001	
0 packs/day	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)		1.00 (Ref.)	1.00 (Ref.)	
Cigarette smoking - recent (per packs/day increase)	1.05 (0.83, 1.34); p=0.690			1.03 (0.89, 1.03); p=0.268	1.29 (0.96, 1.71); p=0.091		1.44 (1.26, 1.61); p<0.0001
Baseline calendar year							
2001-2014	0.67 (0.53, 0.83); p<0.001	0.69 (0.54, 0.89); p=0.004	0.68 (0.49, 0.93); p=0.032	0.7 (0.55, 0.92); p=0.009	0.92 (0.71, 1.19); p=0.510	0.97 (0.72, 1.3); p=0.831	0.99 (0.72, 1.3); p=0.914
1996-2000	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
CD4 count (cells/uL)							
<200	2.97 (2.29, 3.89); p<0.0001	2.64 (2.01, 3.47); p<0.0001	-	2.68 (2.02, 3.56); p<0.0001	-	-	-
200-349	1.25 (0.95, 1.66); p=0.116	1.18 (0.89, 1.58); p=0.256	-	1.18 (0.88, 1.58); p=0.262	-	-	-
350+	1.00 (Ref.)	1.00 (Ref.)	-	1.00 (Ref.)	-	-	-

Cox Proportional Hazard models of first incident infectious pulmonary diagnosis (influenza or viral pneumonia, bacterial pneumonia, other pneumonia, tuberculosis).
Model 1 compared current time-updated marijuana and cigarette smoking.
Model 1 - Sensitivity Analysis compared current time-updated marijuana and cigarette smoking for a subset of 17,836 person-visits with CD4 count ≥ 200 cells/µl (n=268 events).
Model 2 evaluated recent marijuana and cigarette smoking as continuous variables (mean days of use/month and packs/day, respectively, in the prior 2 years).
All models were adjusted by race, education, and current cART use; age was used as the time variable.

Table 4. Marijuana smoking is associated with increased risk of non-infectious pulmonary diagnoses in HIV-infected individuals.

	Univariate	Model 1	HIV+ Model 1 - Sensitivity Analysis	Model 2	Univariate	HIV- Model 1	Model 2
	HR (95% CI); p	HR (95% CI); p	HR (95% CI); p	HR (95% CI); p	HR (95% CI); p	HR (95% CI); p	HR (95% CI); p
Marijuana smoking - current							
Daily or weekly	1.34 (0.99, 1.82); p=0.061	1.49 (1.04, 2.01); p=0.029	1.44 (0.96, 2.13); p=0.079		0.94 (0.63, 1.42); p=0.778	0.79 (0.51, 1.19); p=0.261	
Monthly or less	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)		1.00 (Ref.)	1.00 (Ref.)	
Marijuana smoking - recent (per 10 days use/month increase)	1.06 (0.92, 1.41); p=0.103			1.09 (1.02, 1.13); p=0.003	1.00 (0.87, 1.49); p=0.998		0.93 (0.83, 0.99); p=0.133
Cigarette smoking - current							
≥ 0 packs/day	1.44 (1.11, 1.88); p=0.006	1.49 (1.11, 1.99); p=0.007	1.42 (1.02, 1.99); p=0.038		1.9 (1.43, 2.52); p<0.0001	2.14 (1.6, 2.86); p<0.0001	
0 packs/day	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)		1.00 (Ref.)	1.00 (Ref.)	
Cigarette smoking - recent (per packs/day increase)	1.80 (1.15, 1.97); p<0.0001			1.40 (1.35, 1.48); p<0.0001	2.43 (1.83, 3.23); p<0.0001		2.03 (1.84, 2.11); p<0.0001
Baseline calendar year							
2001-2014	0.68 (0.49, 0.93); p=0.022	0.82 (0.58, 1.16); p=0.263	0.76 (0.51, 1.13); p=0.173	0.81 (0.57, 1.14); p=0.221	0.69 (0.51, 0.93); p=0.016	0.7 (0.51, 0.95); p=0.023	0.7 (0.51, 0.95); p=0.022
1996-2000	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
CD4 count (cells/uL)							
<200	2.21 (1.56, 3.14); p<0.0001	2.14 (1.5, 3.06); p<0.0001	-	2.12 (1.49, 3.03); p<0.0001	-	-	-
200-349	1.39 (1, 1.92); p=0.047	1.39 (0.99, 1.95); p=0.057	-	1.34 (0.96, 1.85); p=0.092	-	-	-
350+	1.00 (Ref.)	1.00 (Ref.)	-	1.00 (Ref.)	-	-	-

Cox Proportional Hazard models of first incident infectious pulmonary diagnosis (chronic bronchitis, COPD or emphysema, lung cancer, other non-infectious diagnoses, other lung disease (NOS)).
Model 1 compared current time-updated marijuana and cigarette smoking.
Model 1 - Sensitivity Analysis compared current time-updated marijuana and cigarette smoking for a subset of 18,098 person-visits with CD4 count ≥ 200 cells/µl (n=308 events).
Model 2 evaluated recent marijuana and cigarette smoking as continuous variables (mean days of use/month and packs/day, respectively, in the prior 2 years).
All models were adjusted by race, education, and current cART use; age was used as the time variable.

D Lorenz, 747

Abstract Nr: 529
Poster Nr: 763
March 4 - 7, 2018
Boston, MA

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Novel Biomarkers Predictive of Non-AIDS Events during ART-mediated Viral Suppression

Martin Hoenigl*[1,2], Carlee Moser[3], Nicholas Funderburg[4], Ronald Bosch[3], Amy Kantor[3], Yonglong Zhang[5], Jesper Eugen-Olsen[6], Malcolm Finkelman[5], Jochen Reiser[7], Alan Landay[7], Michael M. Lederman[8], Sara Gianella[1], for the ACTG NWCS 411 study team

[1]University of California, San Diego, La Jolla, CA, [2] Section of Infectious Diseases AND Division of Pulmonology, Medical University of Graz, Austria, [3]Harvard T.H. Chan School of Public Health, Boston, MA, USA, [4] The Ohio State University, Columbus, OH, USA, [5] Associates of Cape Cod, Inc, Falmouth, MA, USA, [6] Hvidovre Hospital, Hvidovre, Denmark, [7]Rush University Medical Center, Chicago, IL, USA, [8]Case Western Reserve University, Cleveland, OH, USA

- **Measures:** Markers of gut epithelial dysfunction (i.e. lipopolysaccharide binding protein [LBP], beta-D-glucan [BDG], intestinal fatty acid binding protein [I-FABP]), oxidized [ox]LDL, and markers of chronic inflammation/monocyte activation (soluble urokinase plasminogen activator receptor [suPAR], soluble CD163 [sCD163]) were measured at all timepoints.

Figure 1: Distributions of suPAR, BDG and LBP

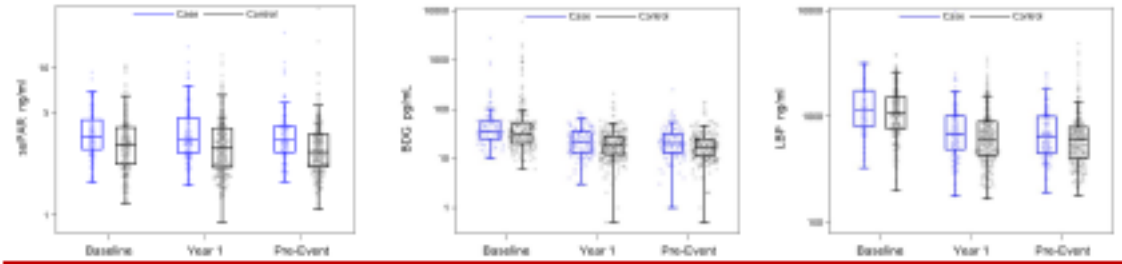


Figure 2: Heatmap of Correlations between Biomarkers

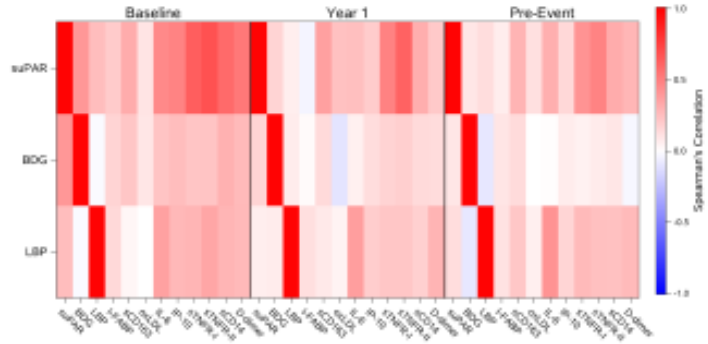


Table 1: Associations between Biomarkers and non-AIDS events

Biomarker	Baseline N=325 *		Year 1 N=418 *		Pre-Event N=377 *	
	Unadjusted OR (95% CI) per one IQR; p-value #	Range of Adjusted OR per one IQR §	Unadjusted OR (95% CI) per one IQR; p-value #	Range of Adjusted OR per one IQR §	Unadjusted OR (95% CI) per one IQR; p-value #	Range of Adjusted OR per one IQR §
suPAR	**1.7 (1.2-2.5) p=0.002**	1.6 – 1.9	**2.0 (1.4-2.7) p<0.001**	1.8 – 2.0	**2.1 (1.5-3.0) p<0.001**	1.7 – 2.3
BDG	1.0 (0.8-1.3) p=0.83	1.0 – 1.1	**1.5 (1.1-2.0) p=0.008**	1.4 – 1.6	**1.4 (1.1-1.7) p=0.016**	1.2 – 1.4
LBP	1.1 (0.9-1.4) p=0.2	1.1 – 1.2	**1.4 (1.1-1.8) p=0.01**	1.3 – 1.4	**1.7 (1.3-2.3) p<0.001**	1.6 – 1.8
I-FABP	0.9 (0.6-1.2) p=0.44	0.8 – 0.9	1.0 (0.7-1.3) p=0.98	0.9 – 1.0	0.9 (0.7-1.3) p=0.6	0.8 – 0.9
sCD163	1.2 (0.9-1.7) p=0.2	1.1 – 1.3	1.3 (1.0-1.6) p=0.08	1.2 – 1.3	1.2 (0.9-1.6) p=0.15	1.1 – 1.2
oxLDL	0.9 (0.7-1.2) p=0.46	0.8 – 0.9	0.8 (0.6 – 1.1) p=0.13	0.7 – 0.8	0.7 (0.5-1.0) p=0.05	0.7 – 0.8

* = Baseline: N=111 cases and N=214 controls; Year 1: N=134 cases and N=284 controls; Pre-Event: N=122 cases and N=255 controls.
# = significant (p<0.05) results are bold
§ = Adjustments: i.) HIV-disease measure (Baseline: log-10 HIV RNA level, Year 1 and Pre-event: CD4 cell count); ii.) Baseline injection drug use; Time-updated: iii.) Chronic Hepatitis B/C status, iv.) Smoking status, v.) Waist-to-hip ratio, vi.) Diabetes status, vii.) Hypertension status, viii.) Use of antihypertensive or lipid lowering medications, ix.) Family history of myocardial infarction.
Abbreviations: CI, confidence interval; IQR, interquartile range; OR, odds ratio.

Conclusions

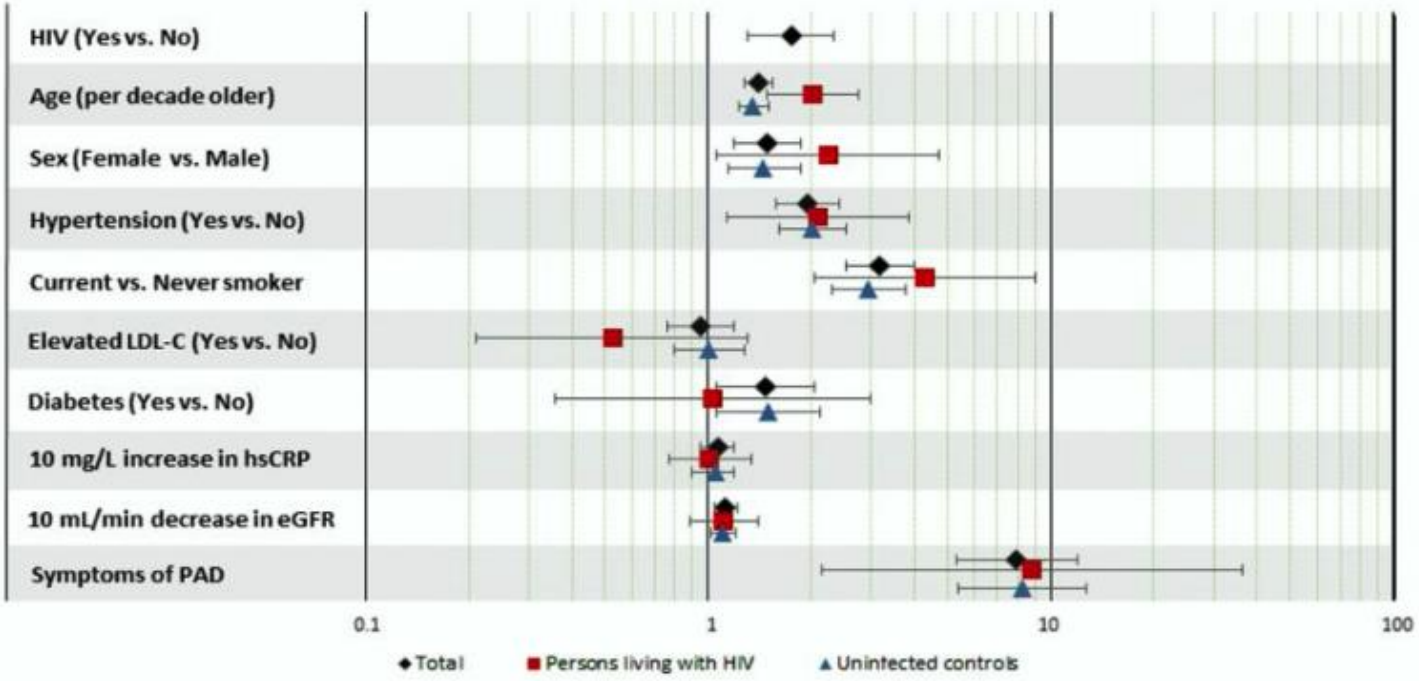
- Elevated levels of suPAR were most strongly and consistently predictive of non-AIDS events.
- suPAR showed strong correlation with other plasma inflammatory markers before ART; correlations became weaker while on ART.
- After 1 year of ART, elevated BDG and LBP were also predictive of non-AIDS events, similar to IL-6, D-dimer, and sTNFR-I and –II (Tenorio, JID 2014, PMID: 24795473).
- These biomarkers may be used for future larger cohort studies aimed at predicting specific (e.g. cardiovascular, cancer) morbidity/mortality in ART-treated HIV infection.

M Hoenigl, 763

INCREASED RISK OF PERIPHERAL ARTERY DISEASE IN PERSONS WITH HIV COMPARED TO CONTROLS

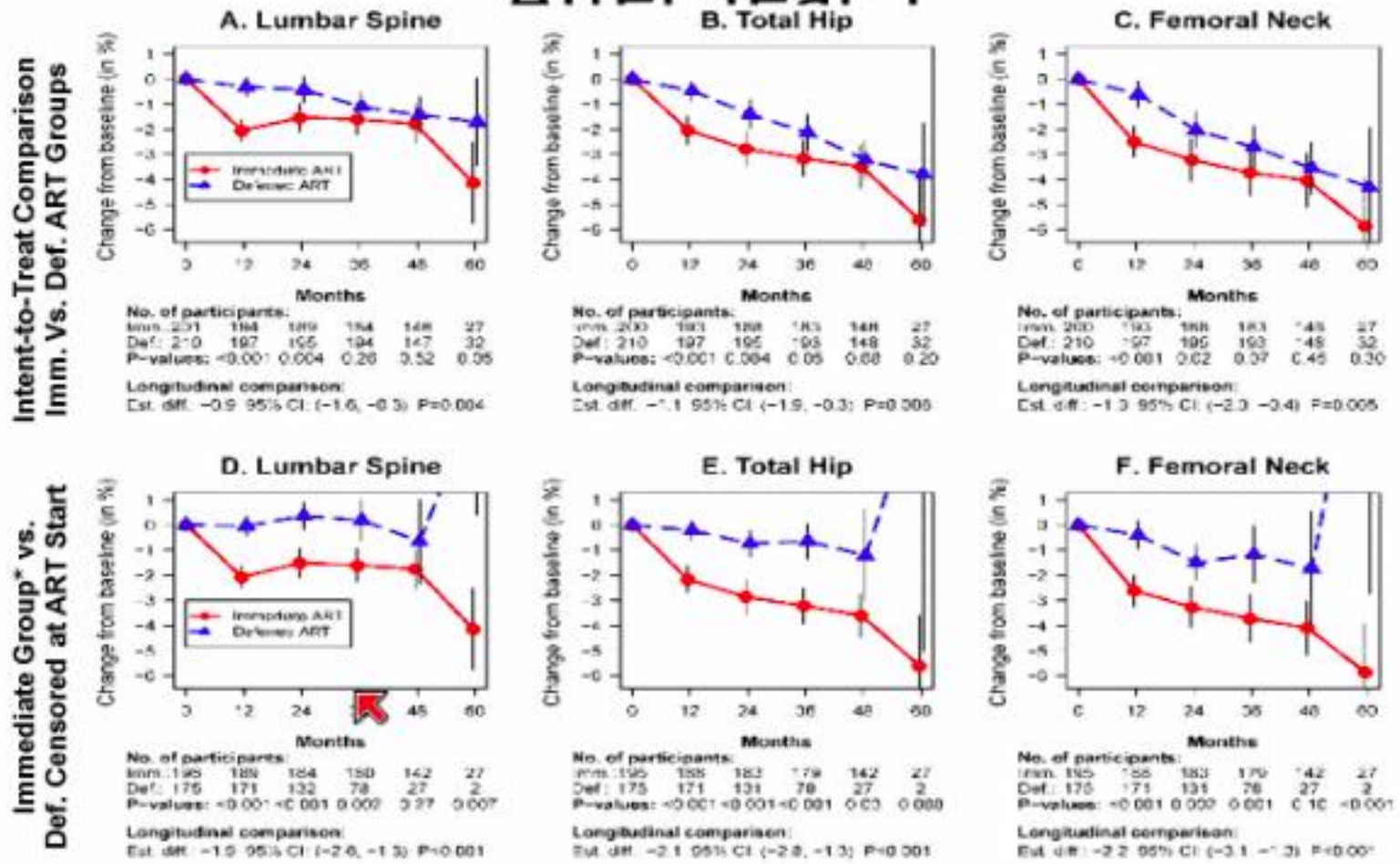
Andreas D. Knudsen, Jens D. Lundgren, Marco Gelpi, Ashley Roen, Amanda Mocroft, Shoaib Afzal, Børge Nordestgaard, Henrik Sillesen, Andreas Ronit, Anne-Mette Lebech, Lars Køber, Klaus F. Kofoed, Susanne D. Nielsen.

ODDS RATIO OF PERIPHERAL ARTERY DISEASE



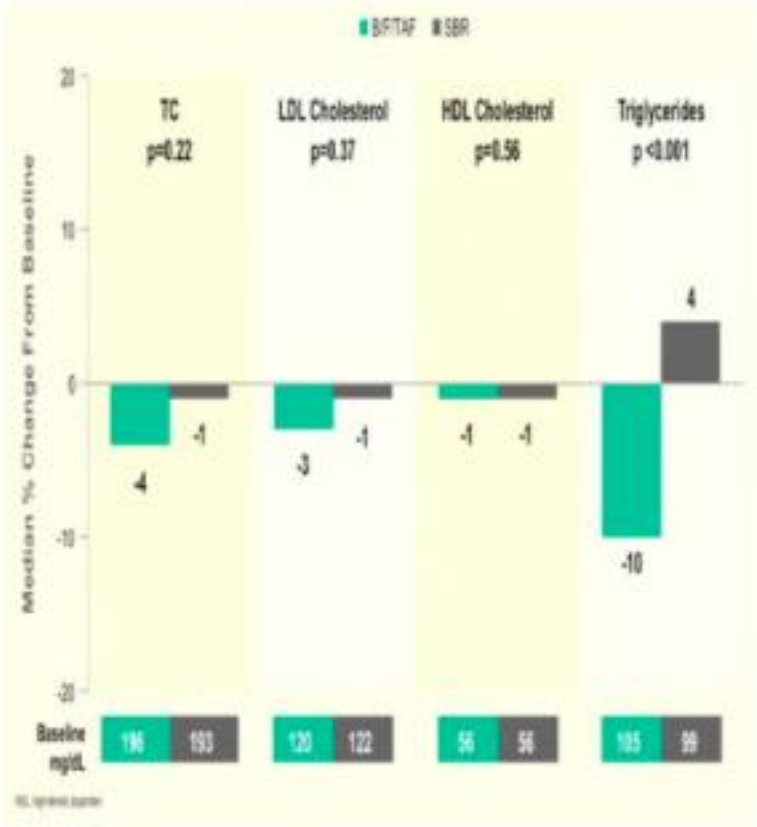
Adjusted for age, sex, smoking status, elevated LDL-C, diabetes, hypertension and hsCRP

START: Bone Loss After ART Slows After Year 1

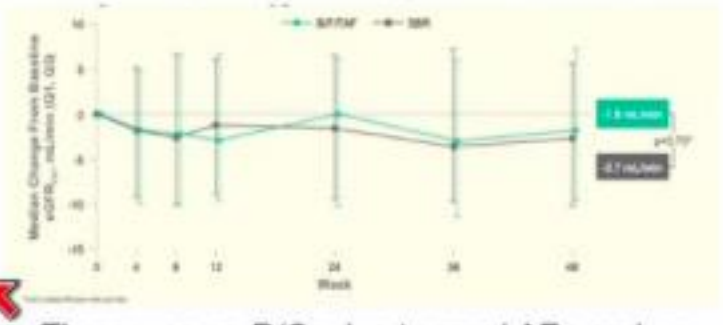


Switch to B/F/TAF from E/c/F/TDF or TAF, ATV/r+TDF/F in Women (n=472)

Changes From Baseline in Fasting Lipid Parameters

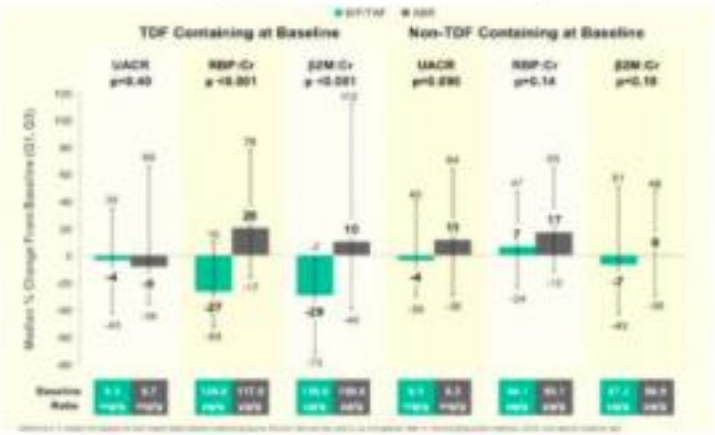


Changes in $EGFR_{CG}$ Over Time



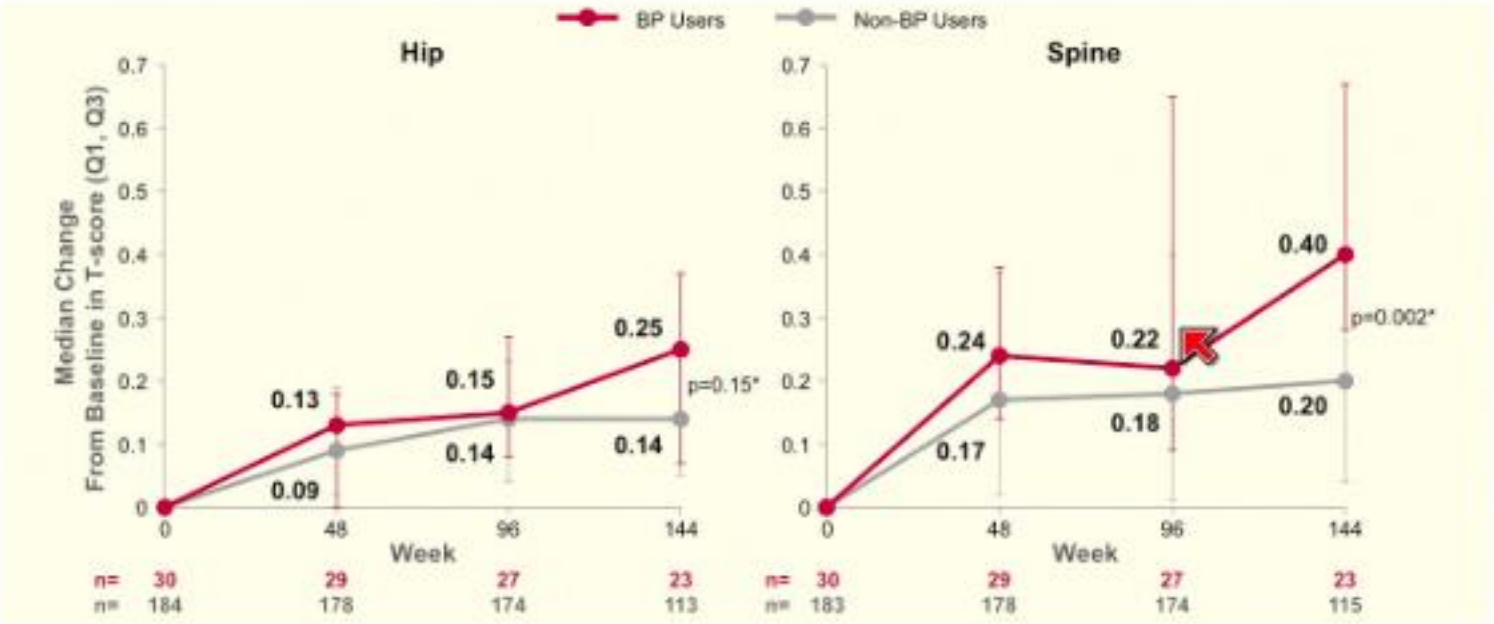
- There was no D/Cs due to renal AEs and no proximal tubulopathy in either arm

Changes in Quantitative Proteinuria at Week 48 by Prior Treatment Regimen*



TDF to TAF +/- Bisphosphontes (BP)

Median Changes in T-scores Through Week 144

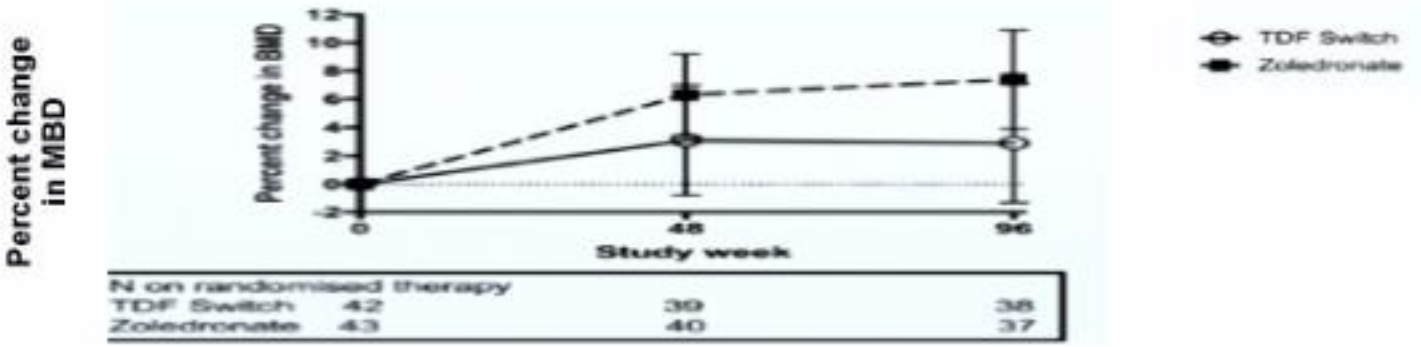


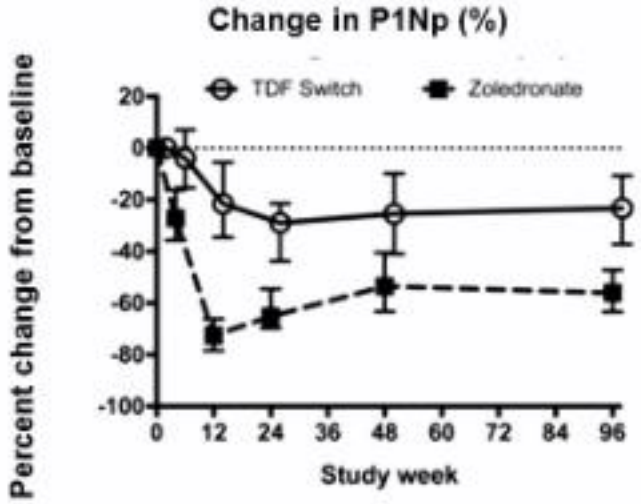
- Both BP and non-BP users had significant increases from baseline in hip and spine T-scores ($p<0.001$)
- BP users had a more significant increase in spine T-score than non-BP users ($p=0.002$)

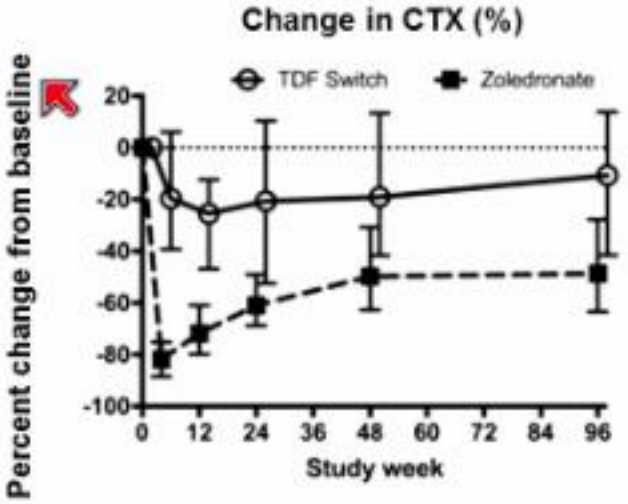
* Estimated from Wilcoxon rank-sum test

Brown T, et al. 20th CROI. Boston, MA. March 4-7, 2013. Abst 724

Zolendronic Acid more BMD and Slow Bone Turnover Than Switch To TAF







D:A:D: Serious Clinical Events in Patients With HIV and Chronic Kidney Disease (CKD)

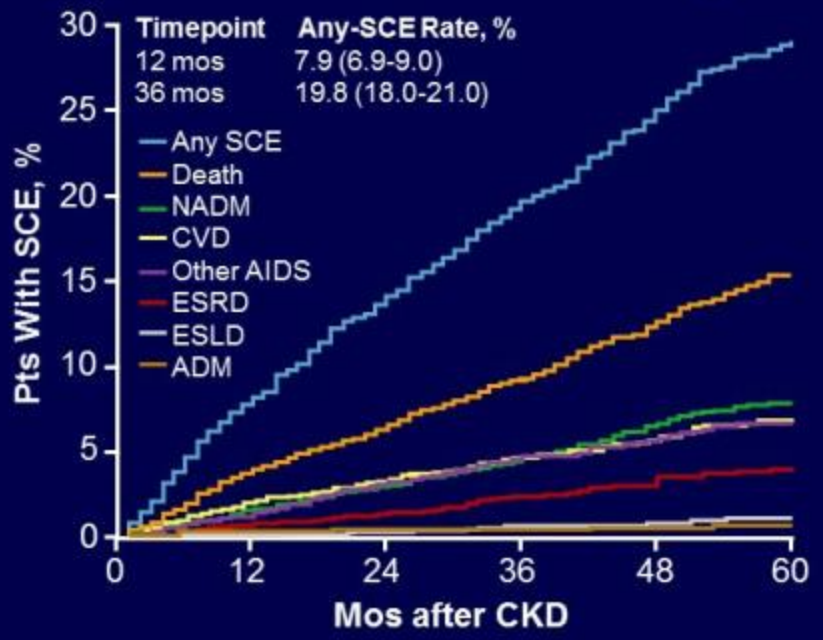
- D:A:D analysis of serious clinical events (SCE) following CKD diagnosis
  - Included pts with baseline creatinine assessment in 2004 with available eGFR data (N = 2467)
  - Incident CKD: eGFR ≤ 60 mL/min/1.73 m^2 (confirmed ≥ 3 mos apart) or 25% decrease in eGFR when BL eGFR ≤ 60 mL/min/1.73 m^2
  - Centrally validated SCE included CVD (MI, stroke, CV procedures), ESRD, ESLD, AIDS-defining malignancies (ADM), non–AIDS-defining malignancies (NADM), other AIDS events (excludes malignancies), death
    - Excluded recurrent SCE when same type
  - Pts followed to first occurrence of incident SCE, 6 mos after last visit, or February 1, 2016

Ryom L, et al. CROI 2018. Abstract O75.

Slide credit: clinicaloptions.com

Serious Clinical Events in Patients With HIV and CKD: Time to Event and Incidence

Kaplan-Meier Time to SCE Following CKD



- Descriptive analysis performed to determine crude SCE rates in pts followed from first eGFR to SCE

Parameter	Pts Without CKD* (n = 34,116)	Pts With CKD* (n = 2460)
PYFU	272,4242	7328
Median f/u, yrs (IQR)	8.8 (5.8-10.8)	2.1 (9.4-4.9)
Pts with any SCE, n (%)	6300 (18.5)	467 (18.9)
Incidence per 1000 PYFU	23.0 (22.4-23.6)	63.7 (57.9-69.5)

*Descriptive population had different inclusion and exclusion criteria than other analyses.

Ryom L, et al. CROI 2018. Abstract O75.

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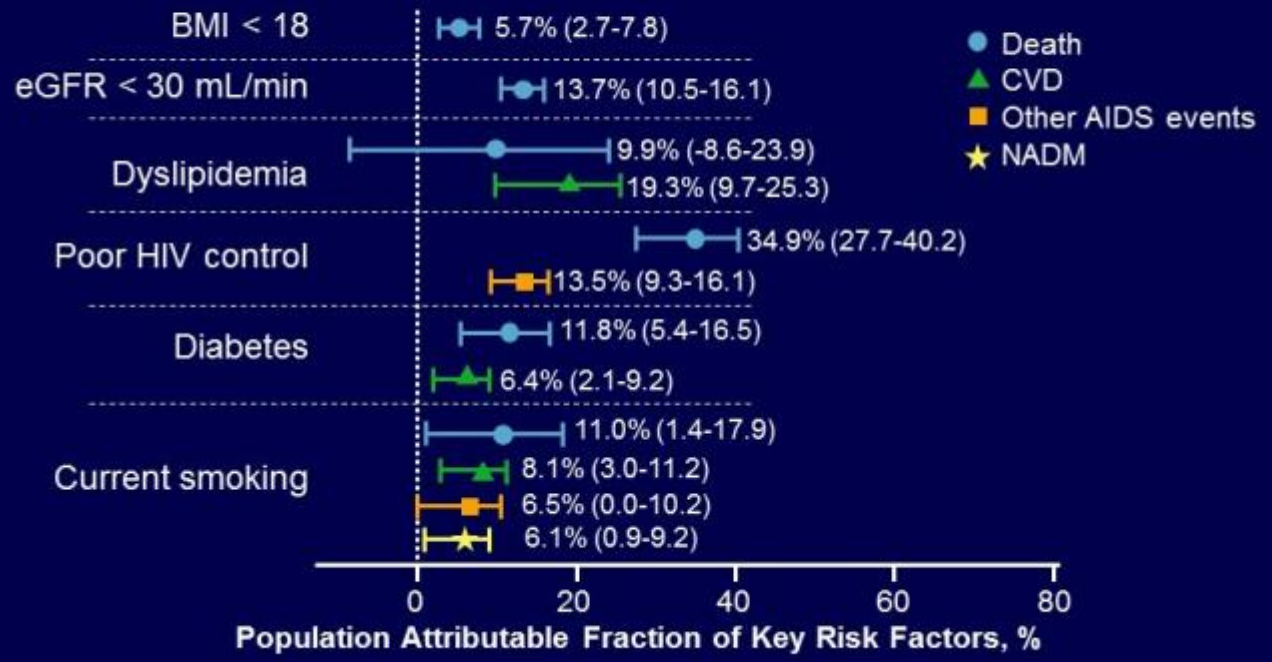
Serious Clinical Events in Patients With HIV and CKD: Risk Factors

Population Attributable Fraction > 5% of Key Risk Factors For SCE Following CKD



Ryom L, et al. CROI 2018. Abstract O75.

Slide credit: clinicaloptions.com

VACS cohort: Statines et Cancer

Statin Use and Cancer Risk: General Population

Cancer Type	N	Effect	Reference:
Liver	12 Studies;	RR=0.58 (0.51 – 0.67)	Shi. BMJ Open. 2014
Colorectal	40 Studies; 13 Cohort studies	RR=0.89 (0.74 – 1.07) RR=0.91 (0.83 – 1.00)	Lytras. World J Gastro. 2014
Kidney	12 Studies	RR=0.92 (0.71 – 1.19)	Zhang. Br J Clin Pharmacol. 2014
Lung	14 Studies 20 Studies	RR=0.91 (0.76 – 1.09) RR=0.89 (0.78 – 1.02)	Tan. PLoS One. 2013 Wang. PLoS One. 2013
Bladder	13 Studies	RR=1.07 (0.95 – 1.21)	Zang. Cancer Causes Control 2013

VACS cohort: Statines et Cancer

Statin Use and Cancer Risk in HIV

- Chao et al.[1] (Kaiser Permanente)
  - Nested case control: 259 NHL cases and 1295 controls
  - HR for statin ever-users: 0.55 (0.31 – 0.95)
- Overton et al.[2] (ALLRT Cohort)
  - 484 of 3,601 non-users at entry initiated statins during f/u (15 135 PY)
  - Non-AIDS Malignancies: aHR: 0.43 (0.19 – 0.94)
- Galli et al.[3] (Italy)
  - 52 663 person-years, 740 (14%) patients had a history of statin use
  - AIDS and non-AIDS Malignancies: aHR= 0.45 (0.17 – 0.71)

1. AIDS 2011;25(14):1771-7; 2. CID 2013; 56(10):1471-9; 3. AIDS 2014;28(16):2407-15

Statin Use and Mortality in HIV

- Moore et al.; Johns Hopkins University
  - 1538 HIV+ on HAART; 238 (16%) received a statin
  - HR: 0.33 (95% CI: 0.14, 0.76) in adjusted analysis
  - Prominent causes of death:
    - Malignancy, non-AIDS infection & liver failure
- Rasmussen et al.; Danish National Health Registry
  - 1738 HIV+
  - Non significant: aMRR 0.75 (0.33–1.68)

Moore et al. PLoS One. 2011;6(7):e21843
Rasmussen et al. PLoS One. 2013;8(3):e52828

Analyses

- Propensity score (PS) model for statin use:
  - Age, calendar year, smoking
  - Chronic diseases (DM, HTN, HIV, HCV co-infection, alcohol)
  - Laboratory values (LDL, albumin, FIB-4 index)
  - Statin user matched to non-user
- Cox proportional hazards models
- Virus-related (e.g. anal, liver, NHL) and non-virus-related
- Interaction b/w HIV status and statin use examined:
  - P≤0.1 considered significant

Patient Population

	Study Sample	Propensity Matched Sample
n	72,211	24,082
Statin User	25,081	12,041
Statin Nonuser	47,130	12,041
HIV+	18,002	5,015

Cancer Incidence

- Incident cancer diagnoses: 1,799
  - HIV+: 449 (9%)
  - Uninfected: 1,350 (7%)
- PS-matched Cohort F/U until cancer diagnosis:
  - 5.0 years in statin users and 3.8 years in statin non-users
  - 3.6 years in HIV+ and 4.5 years in uninfected

VACS cohort: Statines et Cancer

Statin Exposure and Risk of Cancer: By HIV Status and Cancer Type

Cancer type	All Participants HR (95% CI)	Uninfected HR (95% CI)	HIV + HR (95% CI)	P for interaction
Any Cancer				
n=1799	0.61 (0.56 – 0.67)	0.65 (0.59 – 0.72)	0.51 (0.40 - 0.64)	0.051
AIDS-Defining Cancers				
n=64	0.31 (0.18 – 0.53)	0.39 (0.16 – 0.95)	0.28 (0.06 – 1.29)	0.8
Non-AIDS Defining Cancers				
n=1712	0.63 (0.58 – 0.69)	0.67 (0.60 – 0.74)	0.53 (0.41 – 0.67)	0.1

R. Bedimo, 132

Statin Exposure and Risk of Cancer: Virus-Related Cancers

Cancer type	All HR (95% CI)	Uninfected HR (95% CI)	HIV + HR (95% CI)	P for interaction
All	**0.64 (0.50 – 0.82)**	**0.59 (0.41 – 0.84)**	**0.57 (0.27 - 1.19)**	**0.9**
Anal	0.62 (0.45 – 0.86)	0.82 (0.55 - 1.24)	0.28 (0.10 - 0.82)	0.1
Oropharynx	0.35 (0.18 – 0.67)	0.24 (0.08 - 0.72)	0.49 (0.08 - 3.06)	0.6
Liver	0.62 (0.45 – 0.86)	0.82 (0.55 - 1.24)	0.28 (0.10 - 0.82)	0.1
Hodgkin's Lymphoma	0.43 (0.15 – 1.25)	N/A	1.00 (0.14 – 7.10)	.
NHL	0.29 (0.16 – 0.54)	0.36 (0.14 - 0.91)	0.30 (0.05 - 1.63)	0.9

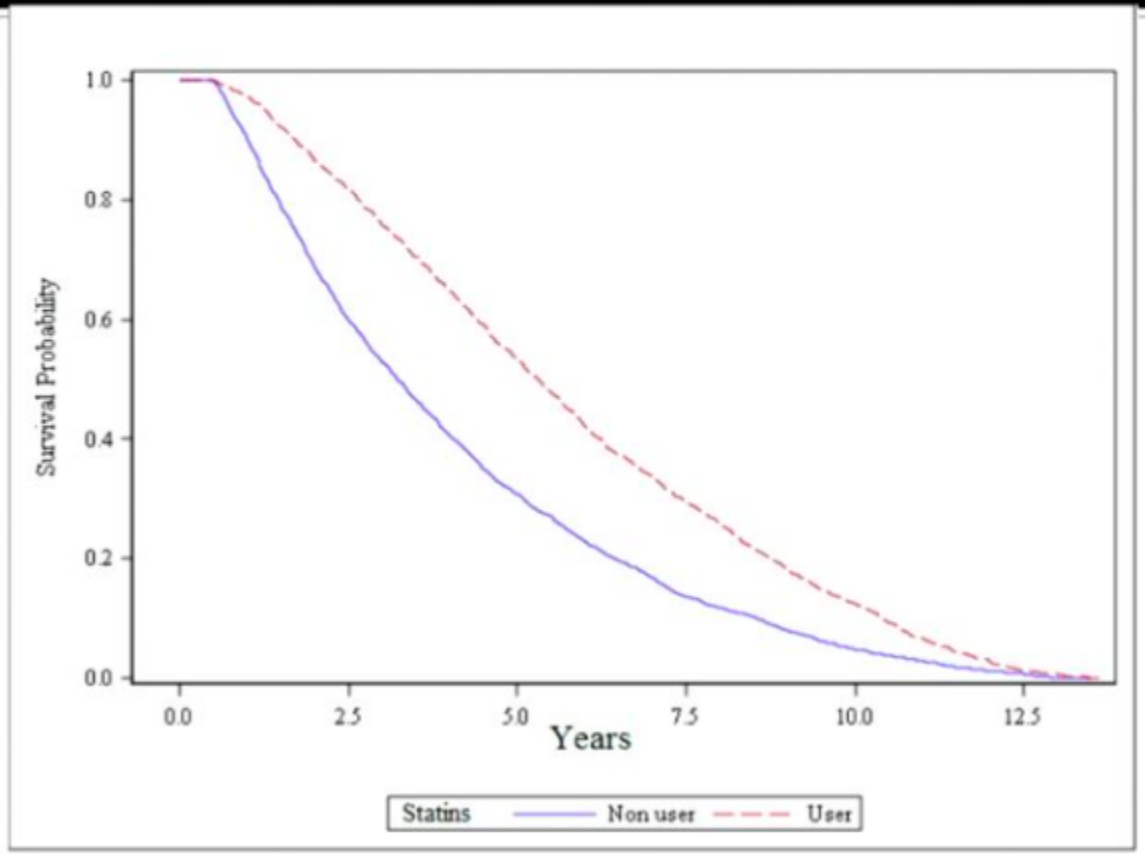
R. Bedimo, 132

Statin Exposure and Risk of Cancer: Non-Virus-Related

Cancer type	All HR (95% CI)	Uninfected HR (95% CI)	HIV + HR (95% CI)	P for interaction
All	0.63 (0.57 – 0.70)	0.67 (0.60 - 0.75)	0.53 (0.39 – 0.70)	0.1
Lung and Bronchus	0.49 (0.37 – 0.64)	0.52 (0.38 - 0.70)	0.56 (0.30 - 1.03)	0.8
Prostate	0.83 (0.71 – 0.97)	0.86 (0.72 - 1.02)	0.66 (0.38 - 1.16)	0.4

R. Bedimo, 132

Statin Exposure and Mortality



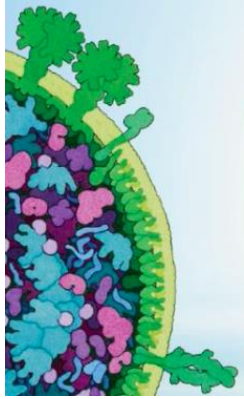
- Incident deaths: n=4,431
- HR for statin use: 0.55 (0.50 – 0.62)

R. Bedimo, 132

Conclusion:

Le traitement par statines est associé à une réduction de la mortalité, dans l'ensemble de la population, HIV+ ou non

Le traitement par statines est associé à risque inférieur de cancer, en particulier viro-induits



HIV-1 PERSISTS IN CSF CELLS IN HALF OF INDIVIDUALS ON LONG-TERM ART

Serena S. Spudich
Yale University
New Haven, CT, USA

Study methods

- Cross sectional CSF and blood from participants with HIV on ART in A5321 at 19 ACTG sites.
- HIV persistence measures:

  HIV RNA from cell free samples: single copy assay sensitivity in CSF supernatant (3-5 ml) and blood plasma (5 ml).[1]

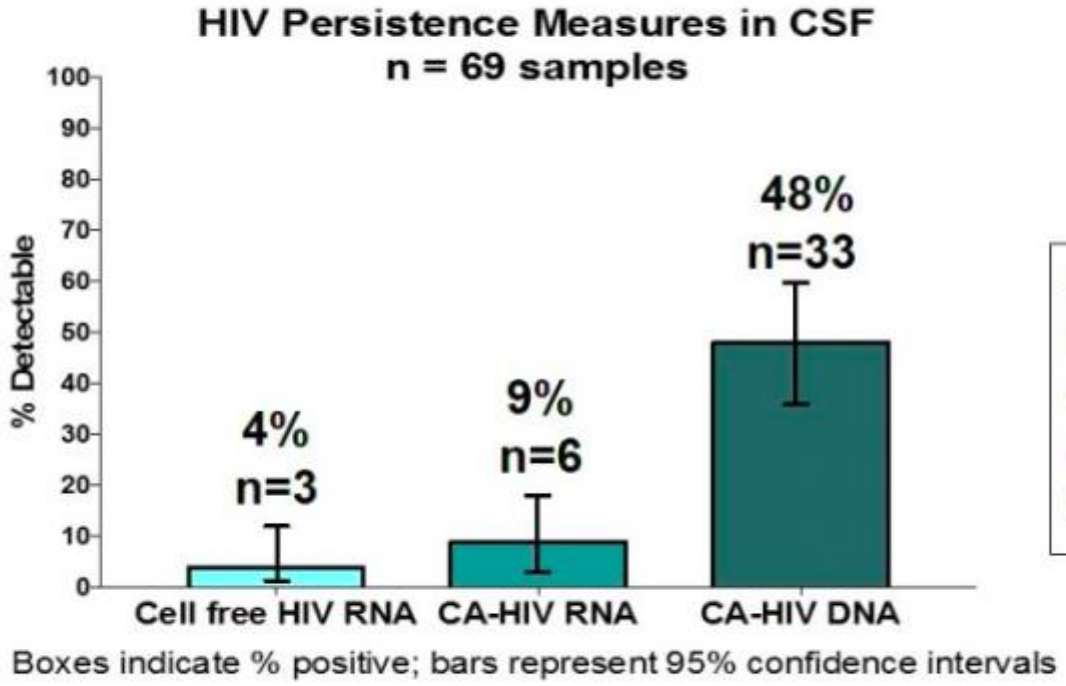
  HIV DNA and **RNA from cells (cell-associated)**: qPCR assays in PBMC and in cell pellets derived from ~13 mls of CSF. Measures were normalized for amplifiable CCR5 copies.[2]

- Inflammation biomarkers: (IL-6, IP-10, neopterin, MCP-1, sCD14, sCD163, TNF-α) by ELISA in cell-free CSF and plasma. Comparison levels were measured from participants without HIV in New Haven, CT, USA.

[1] Cillo AR, et al., *J Clin Microbiol* 2014; [2]Hong F, et al., *J Clin Microbiol* 2016.

HIV-1 persists in CSF cells on ART

HIV detection in CSF in participants on suppressive ART



Boxes indicate % positive; bars represent 95% confidence intervals

Among those with detected CSF cell-associated HIV DNA, median level: 2.1 (range 0.1 - 7.0) copies/10^3 cells.

CA-HIV = cell-associated HIV

S Spudich, 119

HIV-1 persists in CSF cells on ART

HIV DNA detection in CSF cells did not significantly associate with the level of PBMC HIV DNA or persistent viremia

Blood HIV Measures	CSF CA-HIV DNA Not Detected (n=36)	CSF CA-HIV DNA Detected (n=33)	P value*
Blood CA-HIV DNA (cps/10^6 CD4+ T cells)	375 (215-909)	723 (147-1209)	0.33
Blood CA-HIV RNA (cps/10^6 CD4+ T cells)	42 (13-145)	37 (11-156)	0.85
Plasma HIV RNA by iSCA (cps/ml)	<0.4 (<0.4-1.9)	0.4 (<0.4-3.3)	0.46

*Exact Wilcoxon test

- **Detection of CSF CA-RNA also did not associate with blood HIV measures.**

CA-HIV = cell-associated HIV

S Spudich, 119

HIV-1 persists in CSF cells on ART

HIV RNA detection in cell-free CSF did significantly associate with plasma viremia

Blood HIV Measures	CSF HIV by iSCA Not Detected (n=66)	CSF HIV by iSCA Detected (n=3)	P value*
Blood CA-HIV DNA (copies/10^6 CD4+ T cells)	530 (188-1129)	1136 (188-129)	0.62
Blood CA-HIV RNA (copies/10^6 CD4+ T cells)	37 (13-143)	297 (5-503)	0.39
Plasma HIV RNA by iSCA (copies/ml)	<.4 (<0.4-2.2)	5.9 (2.9-23.1)	0.007

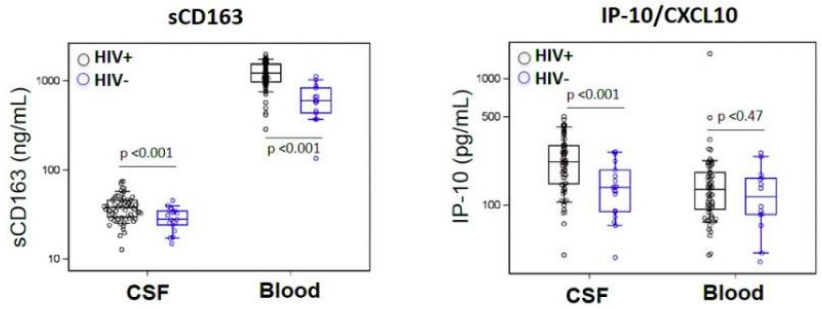
*Exact Wilcoxon test

CA-HIV = cell-associated HIV

S Spudich, 119

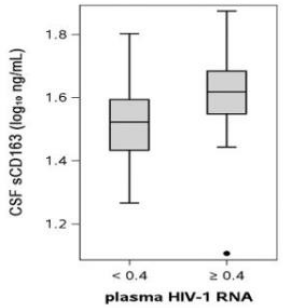
HIV-1 persists in CSF cells on ART

CSF inflammatory biomarkers were elevated despite long-term ART



CSF inflammatory biomarkers did not associate with CSF HIV persistence

- There were no differences in CSF inflammatory measures in those with detected vs undetected CSF CA-HIV DNA, CA-HIV RNA, or cell free HIV RNA by iSCA.
- However, CSF sCD14 and sCD163 did associate with higher levels of plasma HIV RNA by iSCA ($p \leq 0.017$).



CA = cell-associated
iSCA = single copy assay

S Spudich, 119

HIV-1 persists in CSF cells on ART

Conclusions

- Almost half of individuals on long-term ART have HIV-infected cells in CSF.
  - Transcribed HIV RNA is detectable in CSF cells in a small subset of individuals.
- Detection of HIV-infected cells in CSF does not significantly associate with levels of HIV DNA in blood.
  - Levels of plasma HIV RNA detected by single copy assay associates with detection of CSF cell-free HIV RNA.
- Persistence of HIV-infected cells in CSF does not significantly associate with levels inflammation in CSF or blood.

IDENTIFICATION OF BRAIN INJURY USING A NOVEL DEFINITION OF COGNITIVE IMPAIRMENT

Jonathan Underwood[1], James H. Cole[1], Davide De Francesco[2], Caroline Sabin[2], Alan Winston[1] for the The Central nervous system HIV Antiretroviral Therapy Effects Research (**CHARTER**) group

Background

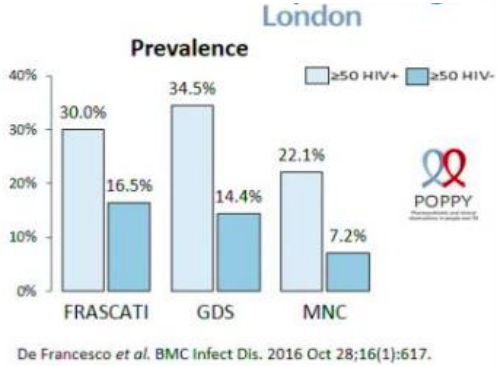
Cognitive impairment reportedly remains prevalent in the cART era.

How do we assess impairment?

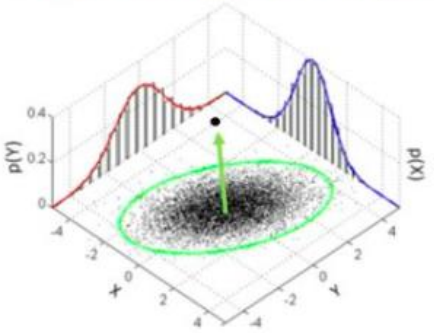
- Neuropsychological tests
- Define a threshold

Novel multivariate method (NMM) using the Mahalanobis distance

- Analogous to a multivariate standard deviation



De Francesco *et al.* BMC Infect Dis. 2016 Oct 28;16(1):617.



Hypotheses tested

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The NMM would be more reliably associated with neuroimaging markers of brain injury than the Frascati and GDS methods:

- Lower grey matter volume
- Lower white matter volume
- Older appearing brains

POPPY

Pharmacokinetic and clinical observations in people over 50

ageivl cohort study

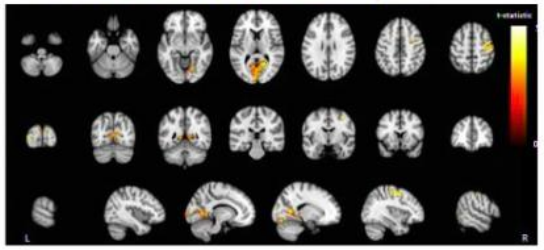
Neurological sub-study

COBRA

CO-MORBIDITY IN RELATION TO AIDS

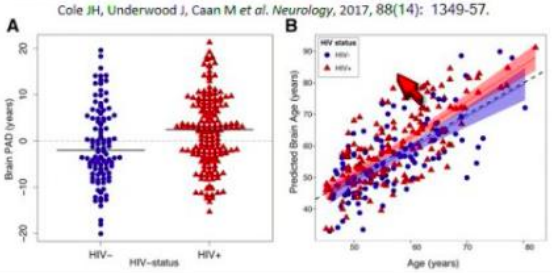
PLWH have lower grey matter volume vs. controls

Underwood J, Cole JH, Caan M et al.. *CLIN INFECT DIS*. April 2017



PLWH have 2.5 years 'added' brain ageing vs. controls

Cole JH, Underwood J, Caan M *et al*. *Neurology*, 2017, 88(14): 1349-57.



Methods – neuroimaging (1.5T)

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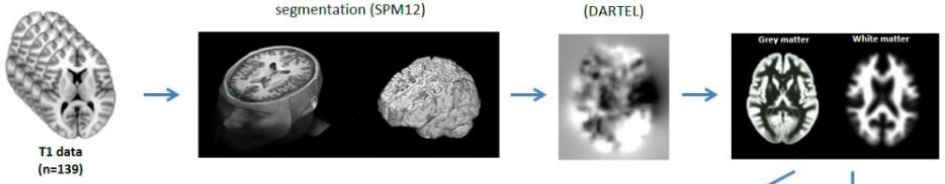
Data acquisition and pre-processing

Bias correction and segmentation (SPM12)

Spatial normalisation

SPM12 (DARTEL)



T1 data (n=139)

T1-weighted MRI data was collected with General Electric 1.5T scanners at

- Johns Hopkins University (n=30)
- Mt. Sinai School of Medicine (n=25)
- University of California at San Diego (n=47)
- University of Texas Medical Branch (n=29)
- University of Washington (n=8)

Extraction of summary statistics (SPM)

Voxelwise analyses with non-parametric permutation testing (using FSL's *randomise*)

Underwood J, Cole JH, Caan M et al.. *CLIN INFECT DIS*. April 2017

Methods – brain age prediction

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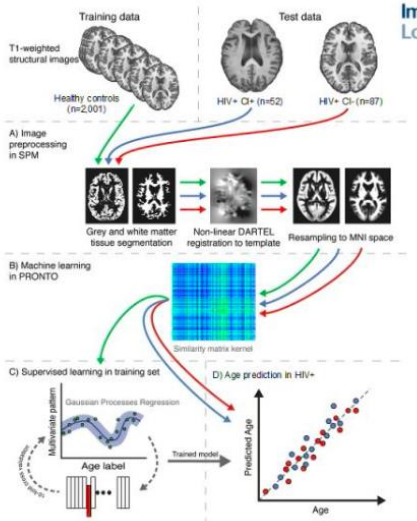
Gaussian processes regression model accurately predicted chronological age in the training set (n=2,001; R^2=0.88)[1]

brain-PAD = predicted age – chronological age

with thanks to Dr James Cole

1. Cole *et al*. *Neurology* (2017) Apr 4;88(14):1349-1357
http://n.neurology.org/content/88/14/1349.long



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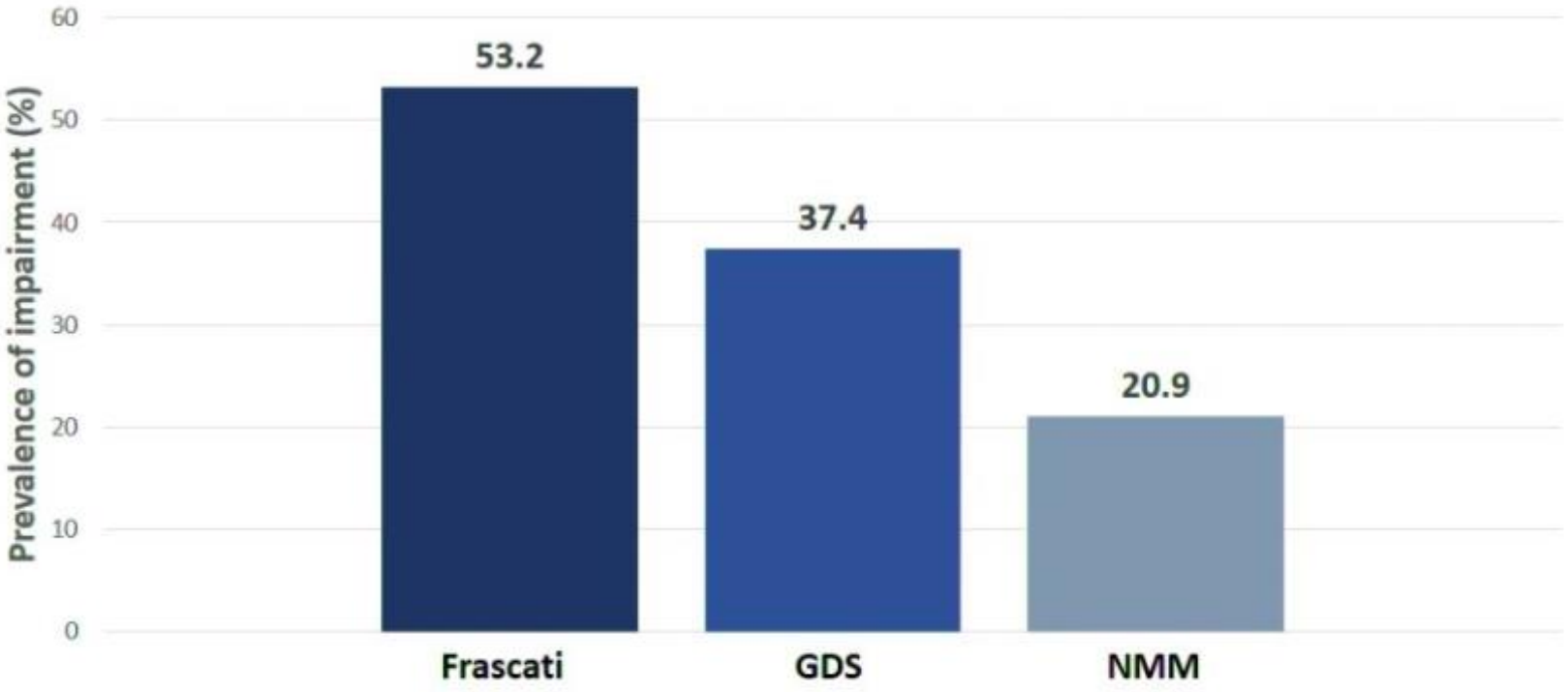
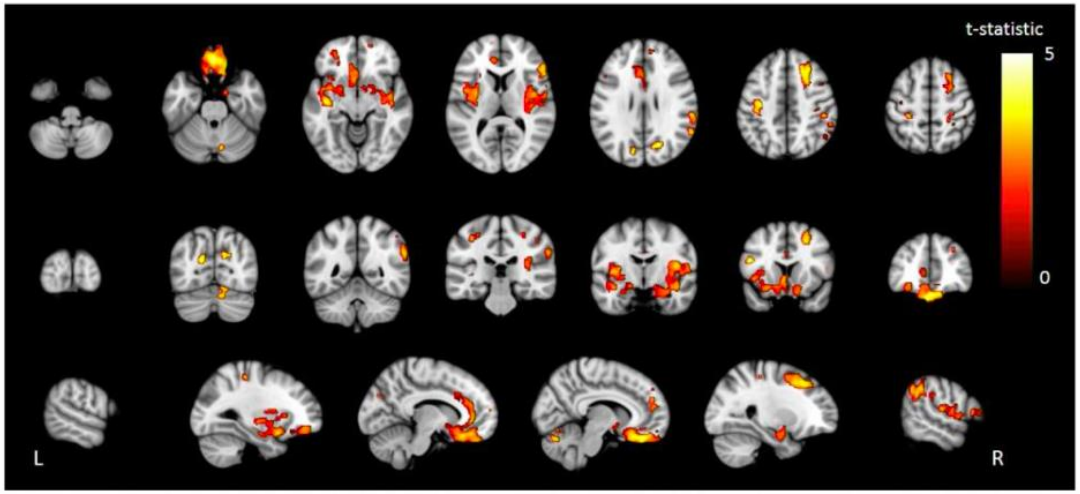
Prevalence of impairment by method



J Underwood, 125

NMM – grey matter voxelwise analysis



Grey matter voxel based morphometry group comparison. Areas with significantly ($p < 0.05$) lower grey matter volume in those with NMM impairment vs. no impairment coloured by the t-statistic - corrected for multiple comparisons (TFCE) and adjusted for age, intracranial volume, scanner and comorbidity status. Statistical image overlaid on MNI 152 T1

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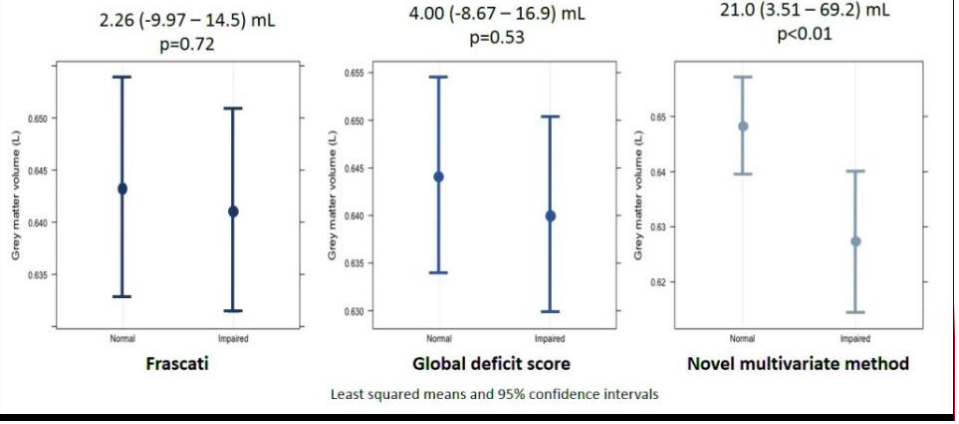
Grey matter volume



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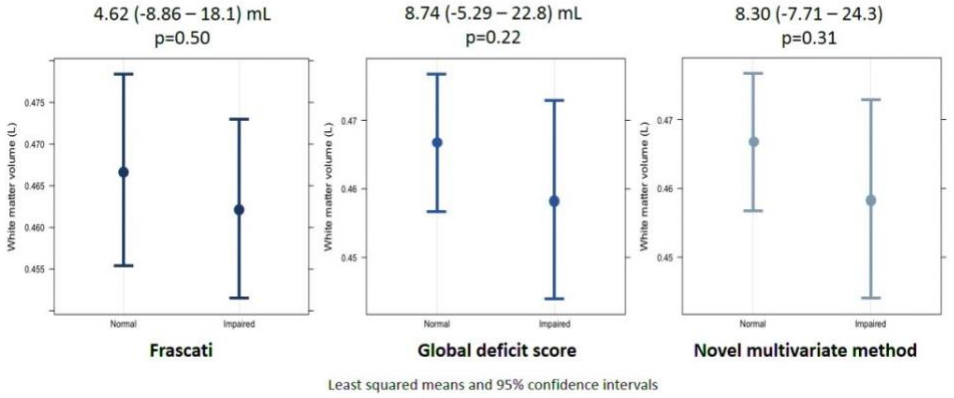
White matter volume



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Brain-predicted age difference

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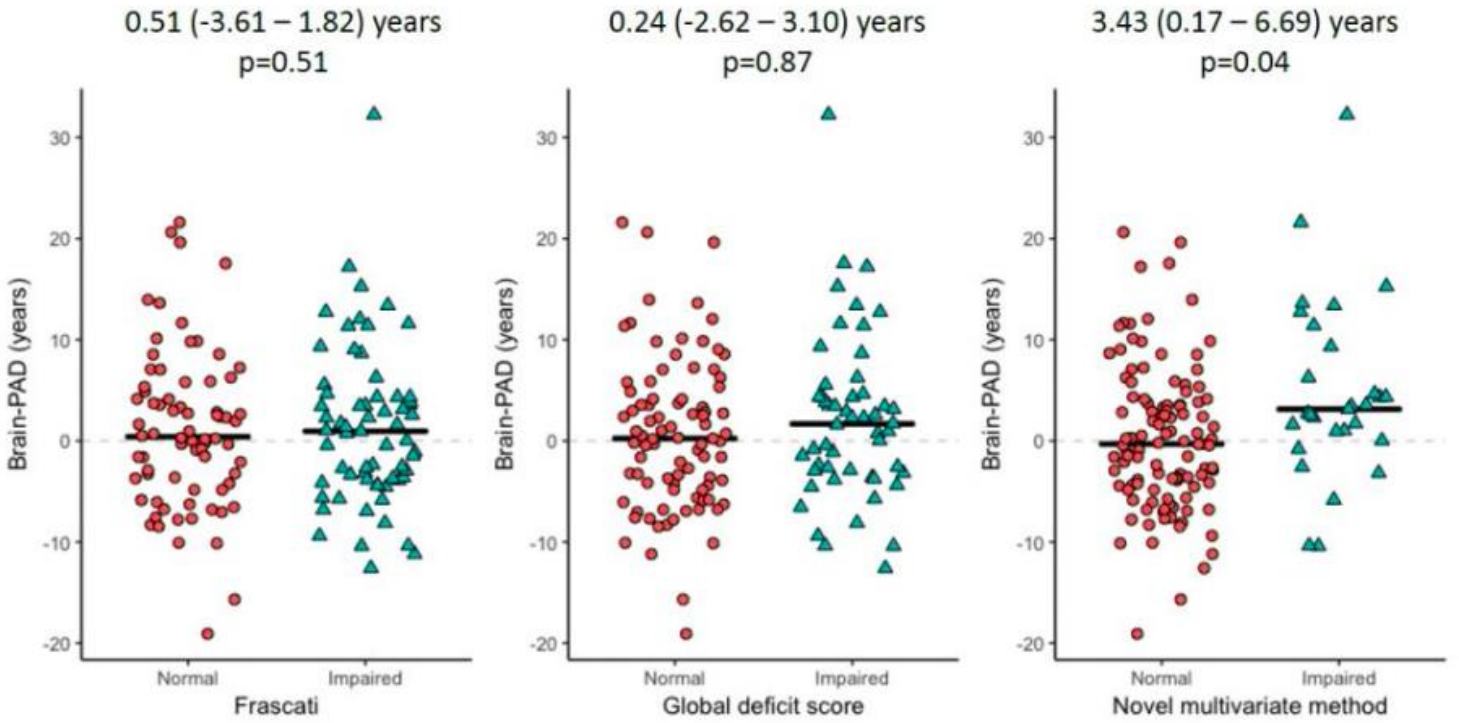


J Underwood, 125

POORER NEUROCOGNITIVE PERFORMANCE ASSOCIATED WITH CSF HIV DNA DESPITE LONG-TERM ART

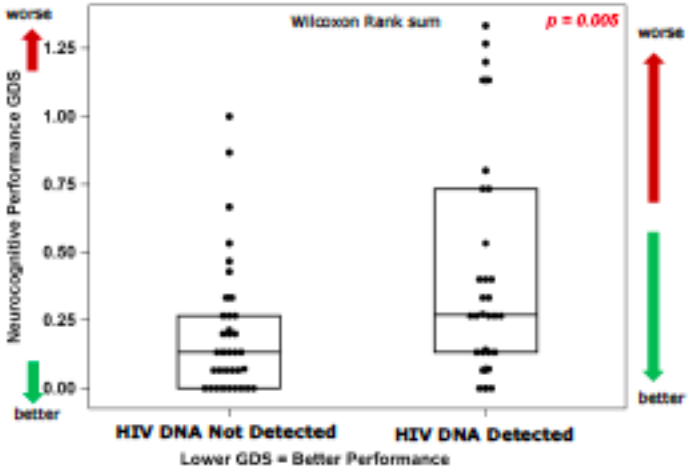
ACTG HIV Reservoirs Cohort study A5321

Kevin Robertson[1], Ronald Bosch[2], Serena S. Spudich[3], Rajesh T. Gandhi[4], Joshua C. Cyktor[5], Hanna Mar[2], Bernard J. Macatangay[5], Christina Lalama[2], Charles Rinaldo[5], Ann Collier[6], Catherine Godfrey[7], Joseph J. Eron[1], Deborah McMahon[5], John W. Mellors[5] for the A5321 Team.
[1]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [2]Harvard University, Boston, MA, USA, [3]Yale University, New Haven, CT, USA, [4]Brigham and Women's Hospital, Boston, MA, USA, [5]University of Pittsburgh, Pittsburgh, PA, USA, [6]University of Washington, Seattle, WA, USA, [7]NIH, Bethesda, MD, USA.

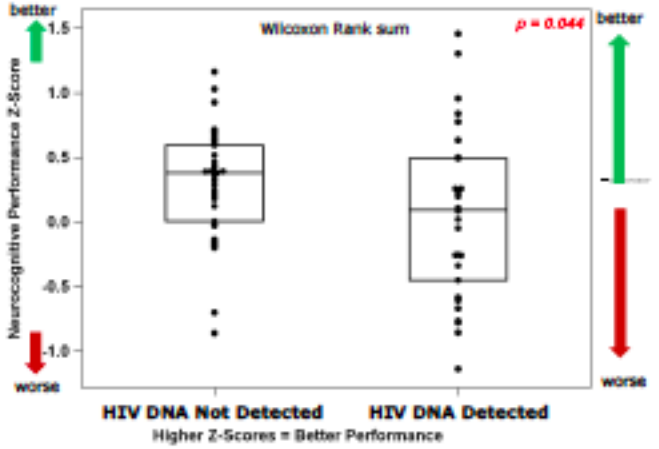
403LB

RESULTS

Poorer NP by GDS in Detected CSF HIV DNA

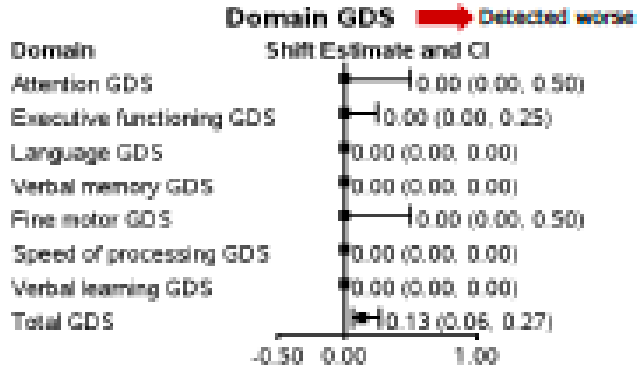


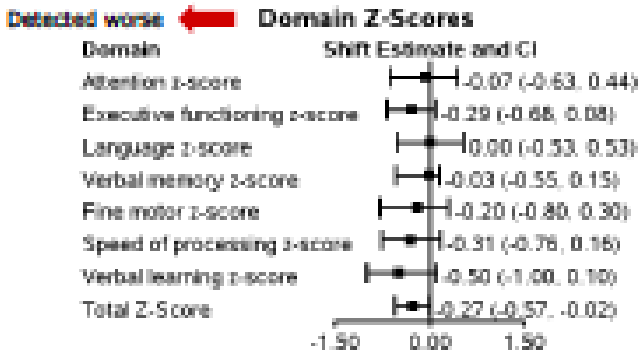
Poorer NP by total z in Detected CSF HIV DNA



RESULTS

Difference between CSF HIV DNA: Detected vs. Not





Hodges-Lehmann method Shift Estimate (Detected – Target Not Detected) and Confidence Intervals

K Robertson, 403LB

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HAND Improvement is Associated with Increase CPE score After ARV Intensification - *Neuro+3 Study*

Contacts:
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G.Force[1], I.Ghout[2], E.Bouaziz-Amar[3], K.Dorgham[4], D.Marigot-Outtandy[5], D.Troisvallet[6], V.Hahn[7], H.Defferrière[5], N.Darchy[1], J.Ropers[2], J.L.Laplanche[3], C. Delaugerre[8], G.Peytavin[9], G.Carcelain[10], P.deTruchis[5]

[1]IHFB Levallois; [2]APHP CHU A.Paré; [3]APHP CHU Lariboisière; [4]APHP CHU Pitié-Salpêtrière; [5]APHP CHU R.Poincaré; [6]CH Gonesse; [7]CH Ste-Anne; [8]APHP CHU St-Louis; [9]APHP CHU Bichat; [10]APHP CHU R.Debré; Paris, France

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Figure 1: Evolution of cognitive results with HAND Classification

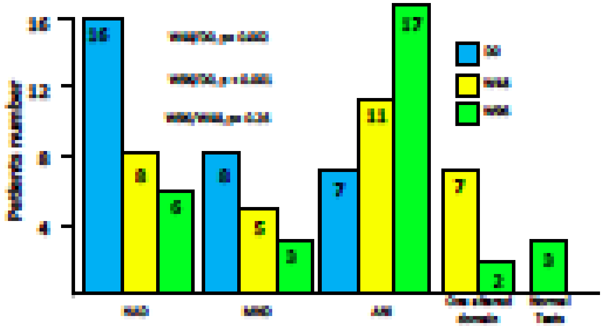


Figure 2: Median cognitive change from D0 to W96:

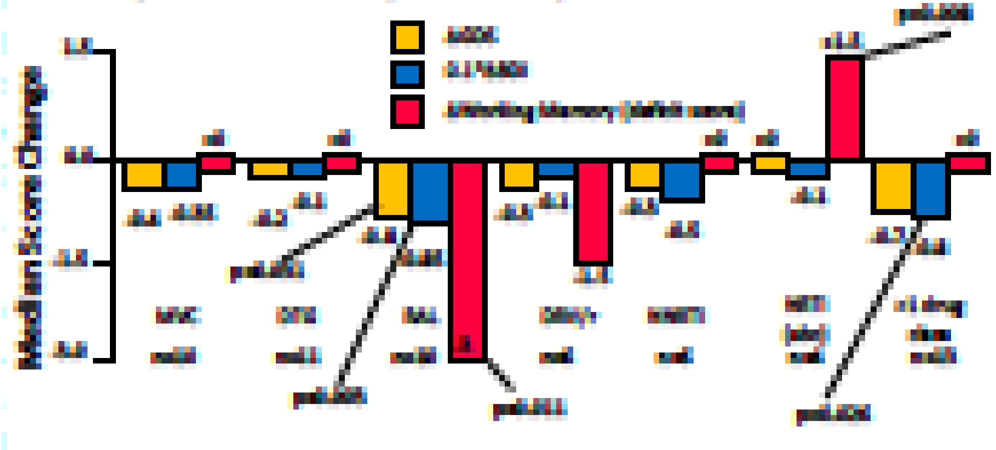


Figure 3: Cognitive Improvement according to ΔCPE score

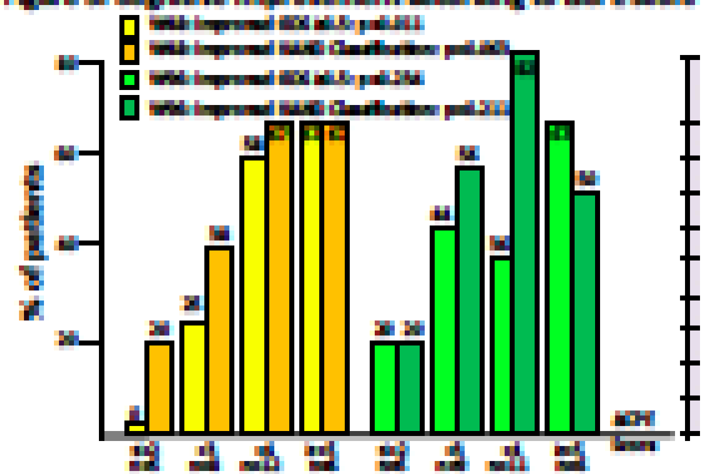


Table 4: Biologic markers evolution according ΔGDS

Median [IQR]	Improved GDS at W96/D0 with ΔGDS >0,1 (n=18)	Failed GDS at W96/D0 with ΔGDS ≤0,1 (n=11)	p
ΔNeopterin [Pl ; CSF]	[illegible]	[illegible]	[illegible]
ΔsCD14 [Pl ; CSF]	[illegible]	[illegible]	[illegible]
ΔMCP-1 [Pl ; CSF]	[illegible]	[illegible]	[illegible]
ΔIP-10 [Pl ; CSF]	[illegible]	[illegible]	[illegible]
ΔNFL [Pl ; CSF]	[illegible]	[illegible]	[illegible]

G. Force, 415

25th CROI 2018, Boston, Massachusetts, March 4–7, 2018, Abstract # 424, P-E3, Mon, 3/5

CNS Toxicity of Dolutegravir Is Not Associated with Psychiatric Conditions or Higher Plasma Exposure

Christian Hoffmann[1,2], Eva Wolf[3], Knud Schewe[1], Michael Sabranski[1], Hans-Jürgen Stellbrink[1], Axel Adam[1], Thomas Buhk[1], Stefan Hansen[1], Stefan Fenske[1], Thomas Brinkmann[4], Harald Ertl[4], Jürgen Hartleb[4], Gerrit Mohrmann[4], and Christian Noah[4]

[1]ICH Study Center Hamburg, [2]Department of Medicine II, University of Schleswig-Holstein, Campus Kiel, [3]MUC Research GmbH, Munich, [4]Labor Lademannbogen, Hamburg, Germany

In total, 861 pts (768 males, median age 47.1 years) had initiated DTG outside RCTs since 2014, among them 151 ART-naive and 710 ART-experienced pts. There were 155 pts (18.0%) with preexisting depressive disorders and 55 pts (6.4%) with other neuropsychiatric diagnoses.

Table 1: Adjusted Relative Hazards (RH) for the covariables of interest, using the Cox model.

Risk factors for NPAEs leading to DTG discontinuation	RH	95 % CI	p
Female, versus male gender	2.31	1.12-4.74	0.03
Older age (> 60 years), versus younger age	2.14	1.10-4.18	0.025
Depressive disorders, versus no	1.00	0.54-1.88	0.952
Other neuropsychiatric diagnoses, versus no	0.93	0.29-3.00	0.896

Figure 3. Reasons (%) for discon
(mean of 2.9 symptoms/NPAEs were reported)

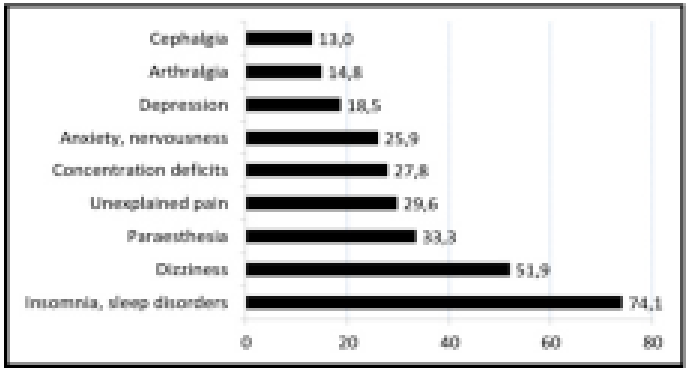
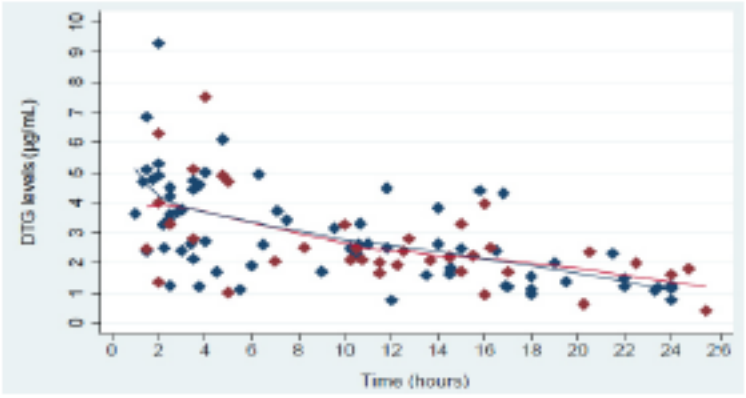


Figure 5. DTG plasma levels in pts discontinuing DTG due to NPAEs (n=37, red dots) and in 71 controls (blue dots), comparable for age and gender. Time after drug intake



Regression lines based on locally weighted scatterplot smoothing ('lowess') using least squares, STATA/SE 13.1

C Hoffmann, 424

HIV-RNA in the Olfactory Mucosa of HIV-positive Patients

Trunfio M[1], Allice T[2], Bertero L[3], Imperiale D[4], Catera S[5], Pirriatore V[1], Di Perri G[1], Amasio E[5], Cassoni P[3], Ghisetti V[2], Bonora S[1], Calcagno A[1]

1 Unit of Infectious Diseases, Amedeo di Savoia hospital, Department of Medical Sciences, University of Turin, Turin, Italy - 2 Laboratory of Microbiology and Virology, Amedeo di Savoia hospital, Turin, Italy
3 Pathology Division, AOU Città della Salute e della Scienza di Torino, Department of Medical Sciences, University of Turin, Turin, Italy - 4 Unit of Neurology, Maria Vittoria hospital, ASL Città di Torino, Turin, Italy
5 Unit of Otorhinolaringoiatry, Maria Vittoria hospital, ASL Città di Torino, Turin, Italy

P 443

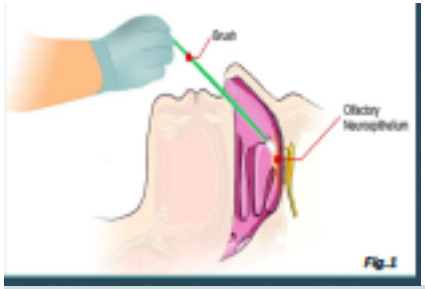


Fig.1

- 47 patients were included. Their demographic and viro-immunovirological features are shown in the table below:

Parameter	Value
Male*	35 (74.5%)
Age, years°	51 (47-57)
Race: Caucasian*	40 (85.1%)
Risk factors*: MSM Previous IDU	21 (44.7%) 9 (12.2%)
Naïve*	19 (40.4%)
PI HIV-RNA <20 cp/mL*	23/28 (82.1%)
PI HIV-RNA, log_{10} cp/ml°	5.0 (3.4-5.4)
CSF HIV-RNA < 20 cp/mL*	20/28 (71.4%)
CSF HIV-RNA, log_{10} cp/ml°	2.6 (1.9-4.2)
CSF viral escape*	5 (10.6%)
CD4+ T-cells, cell/uL°	195 (39-678)
Nadir CD4 T-cells, cell/uL°	114 (40-234)
Type of HAART*: NNRTIs PIs INIs Others	6/28 (21.4%) 5/28 (17.9%) 8/28 (28.6%) 9/28 (32.1%)

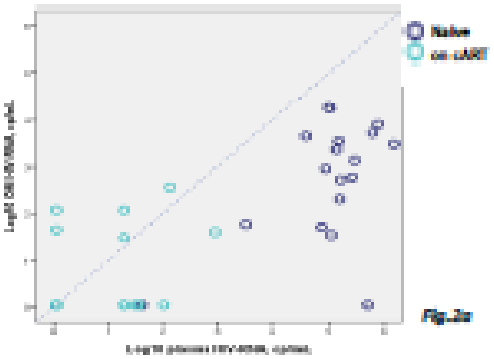


Fig.2a

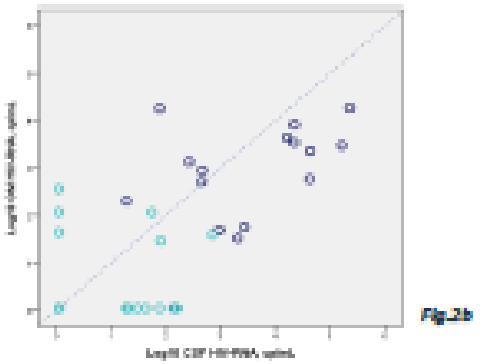


Fig.2b

- An OM escape (OM HIV-RNA more than 1 Log_{10} above pVL) was associated with higher risk of CSF Viral Escape (OR 12.7 [95%CI: 1.3-124.0], p=0.01; Fig.3)

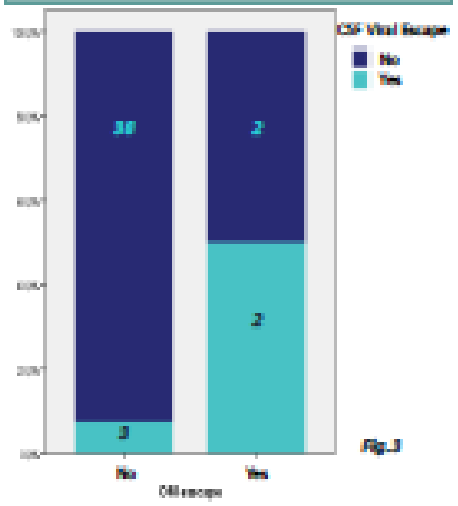


Fig.3

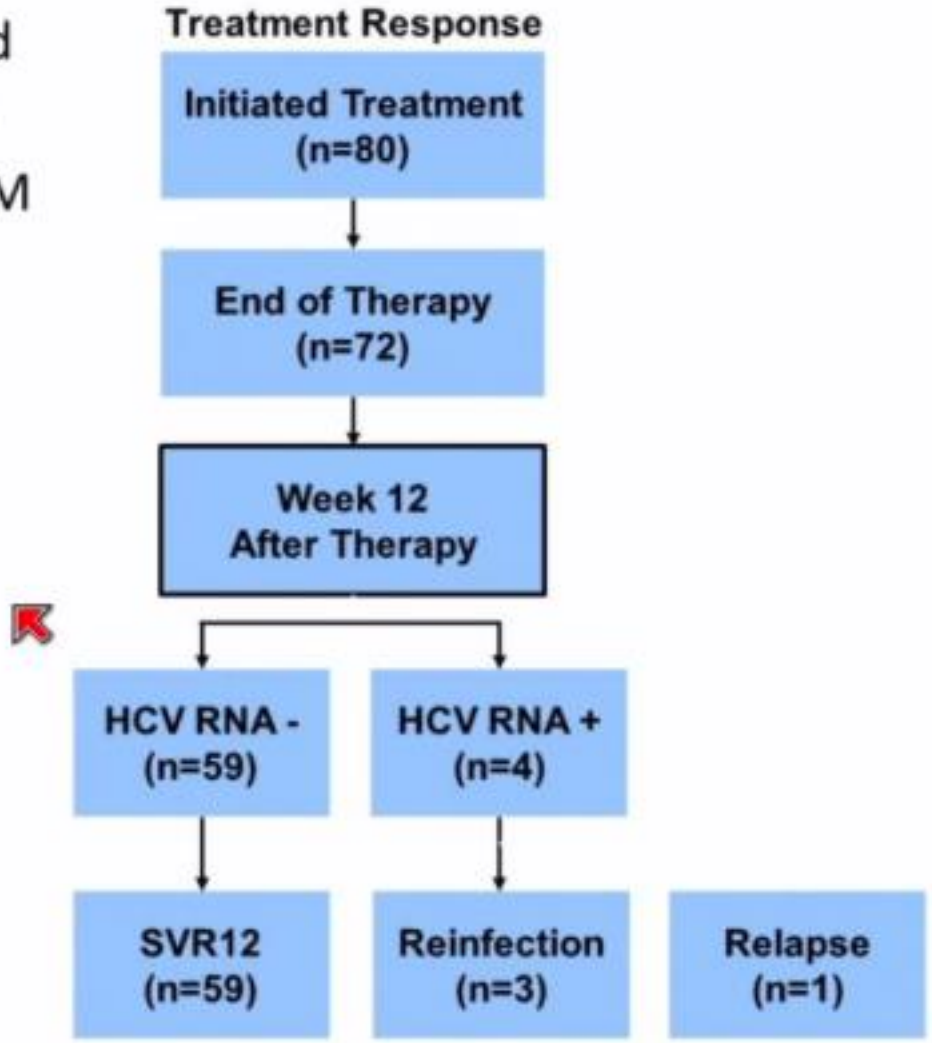
Conclusions & Future Research

- Non-invasive monitoring of HIV tissue replication may have major implications; NB is a safe procedure that allows a non-invasive collection of olfactory mucosa cells, including olfactory neurons
- OM HIV-RNA has been safely measured in around half NB samples. The reported association with HIV-DNA and neopterin is promising as a marker of residual viral burden and immune activation
- Further studies are required to establish whether OM HIV-RNA may be a reliable surrogate of CSF/brain tissue HIV-RNA and whether NB may be used to identify patients experiencing CSF escape

M Trunfio, 443

Short DAA Therapy Feasible in Acute HCV Coinfection

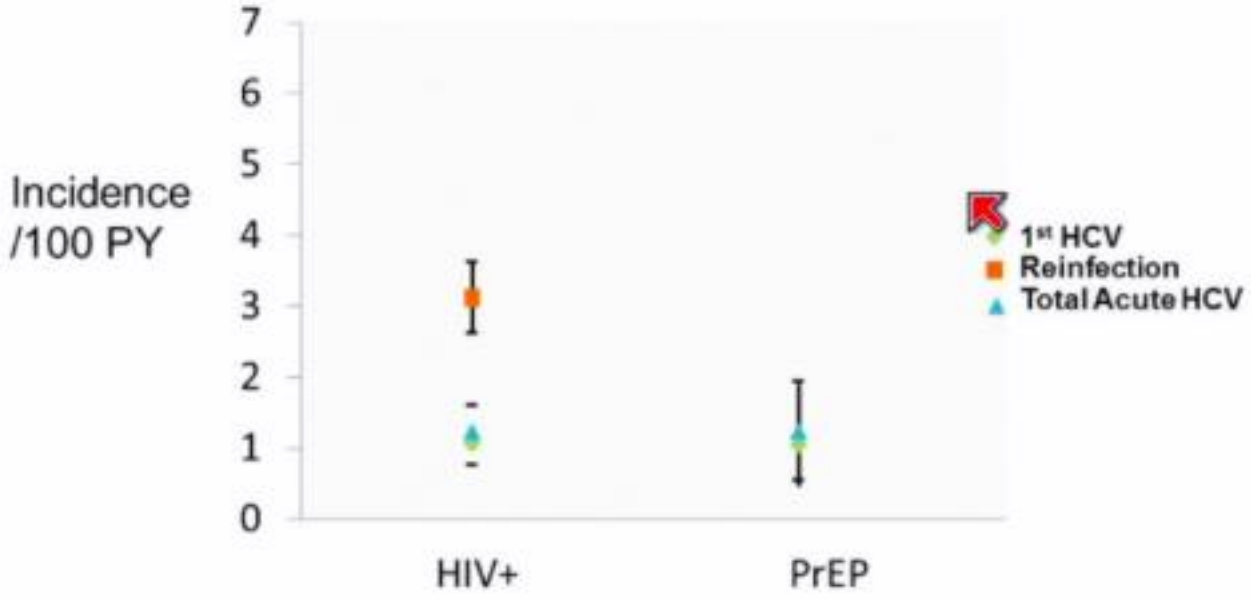
- 9 centres Netherlands and Belgium (DAHHS 2 Study)
- Acute HCV GT 1/4, all MSM
- 24% reinfected
- 95% HIV coinfected
- 8 weeks Grazoprevir/Elbasvir
- Median 4.5 months between
- Estimated infection and DAA start
- SVR 94% (98% incl. reinfections)



Boerekamps A, et al. 25th CROI. Boston, MA; March 4-7, 2018. Abst. 125.

HCV Incidence in HIV-Infected and in PREP-Using MSM from France

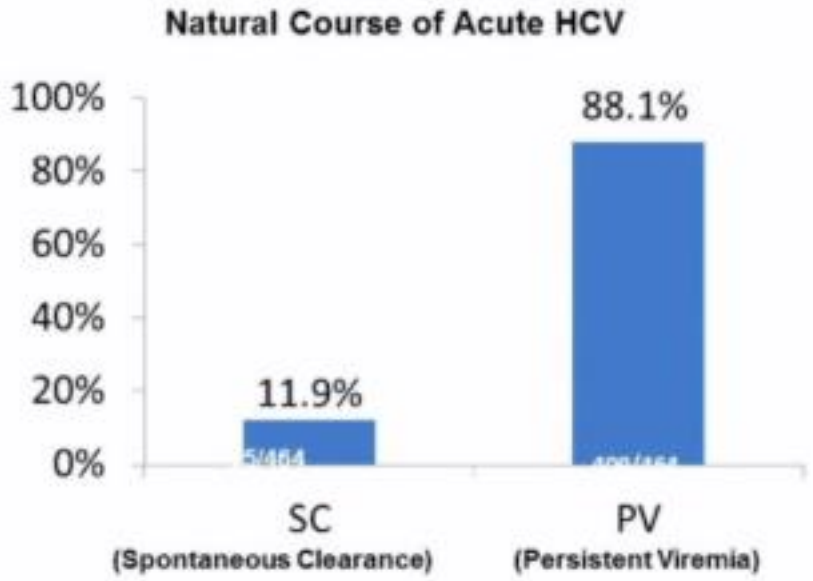
- Incidence of a first HCV infection and of all acute HCV in HIV+ MSM and in PrEP- using MSM was similar in France in 2016-2017
- HIV+ and PrEP-using MSM probably share similar at-risk practices for HCV and should be targeted for preventive interventions



Cotte L, et al. 25th CROI, Boston, MA, March 4-7, 2018. Abst 156.

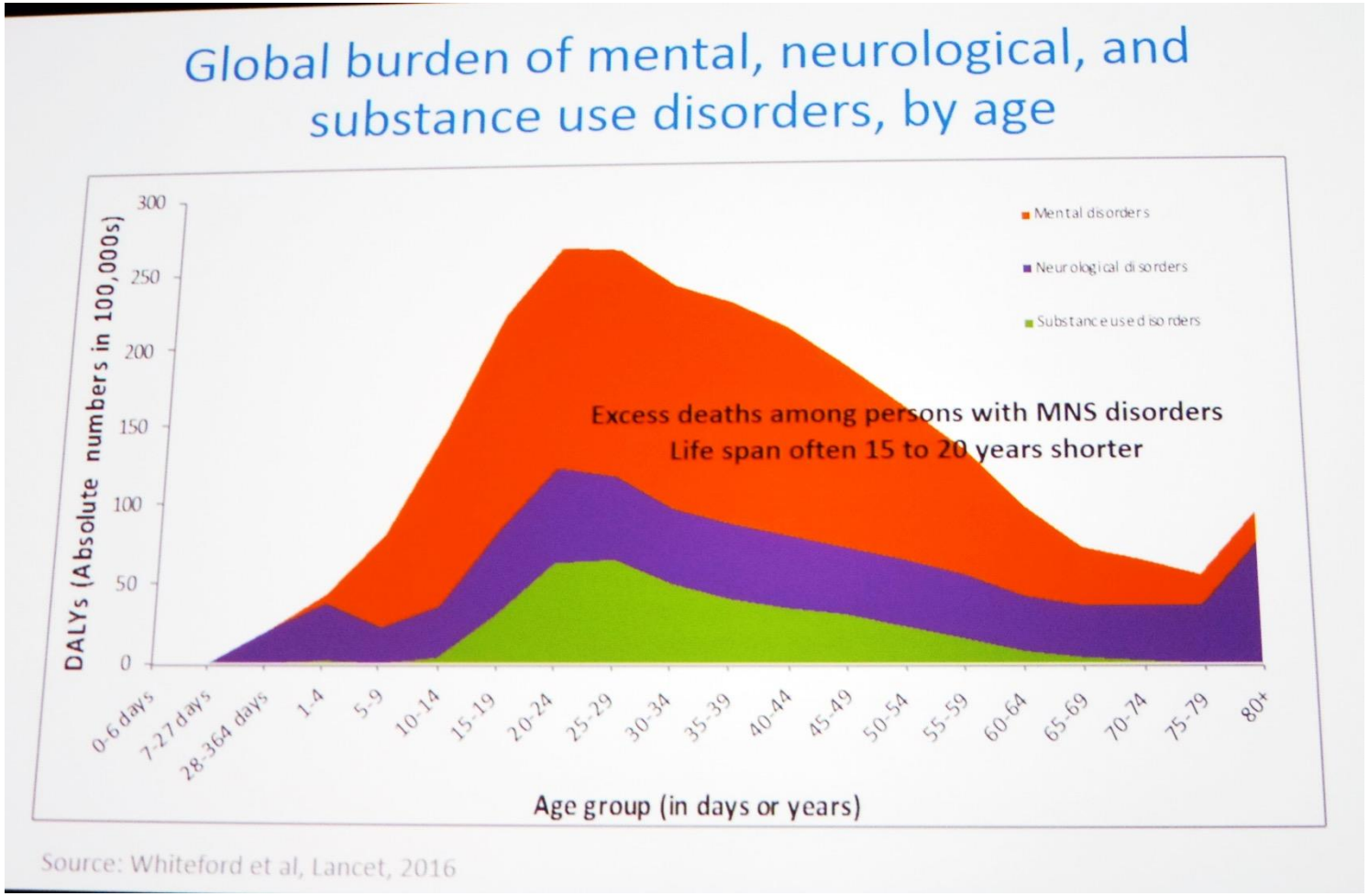
Spontaneous Clearance of HCV after Acute Infection: How Likely is Seroconversion Going to Happen?

- 464 HIV-patients with acute HCV infection (PROBE-C Study)
- 9 countries
- 98,8% MSM
- 78,5% GT1, 18,6% GT4
- SVR: 75.6%
- Reinfections 17%



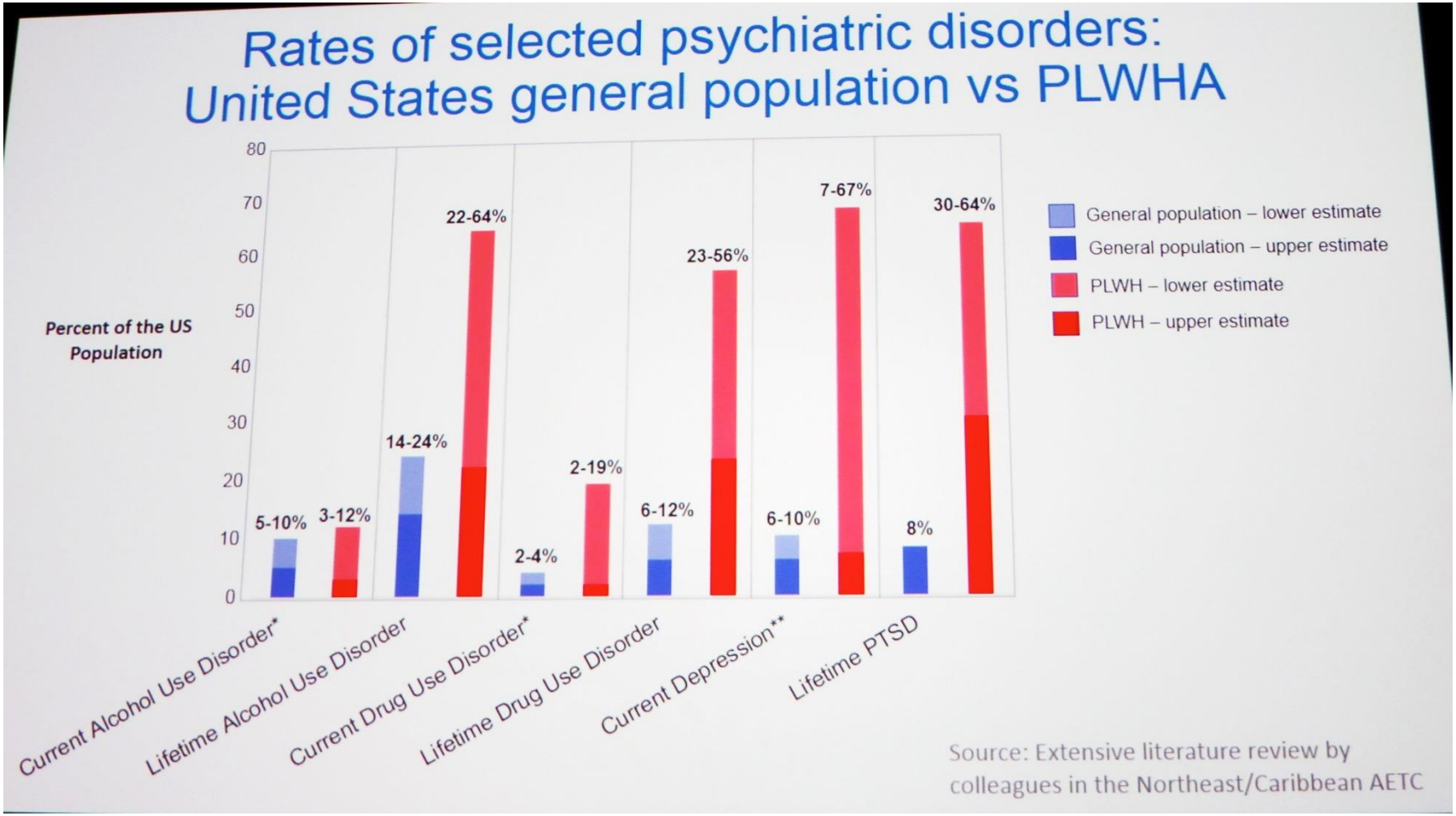
<2log decrease in HCV RNA 4 weeks after initial diagnosis was highly predictive of chronic infection

Mental Health: a crucial component to ending the HIV Epidemic

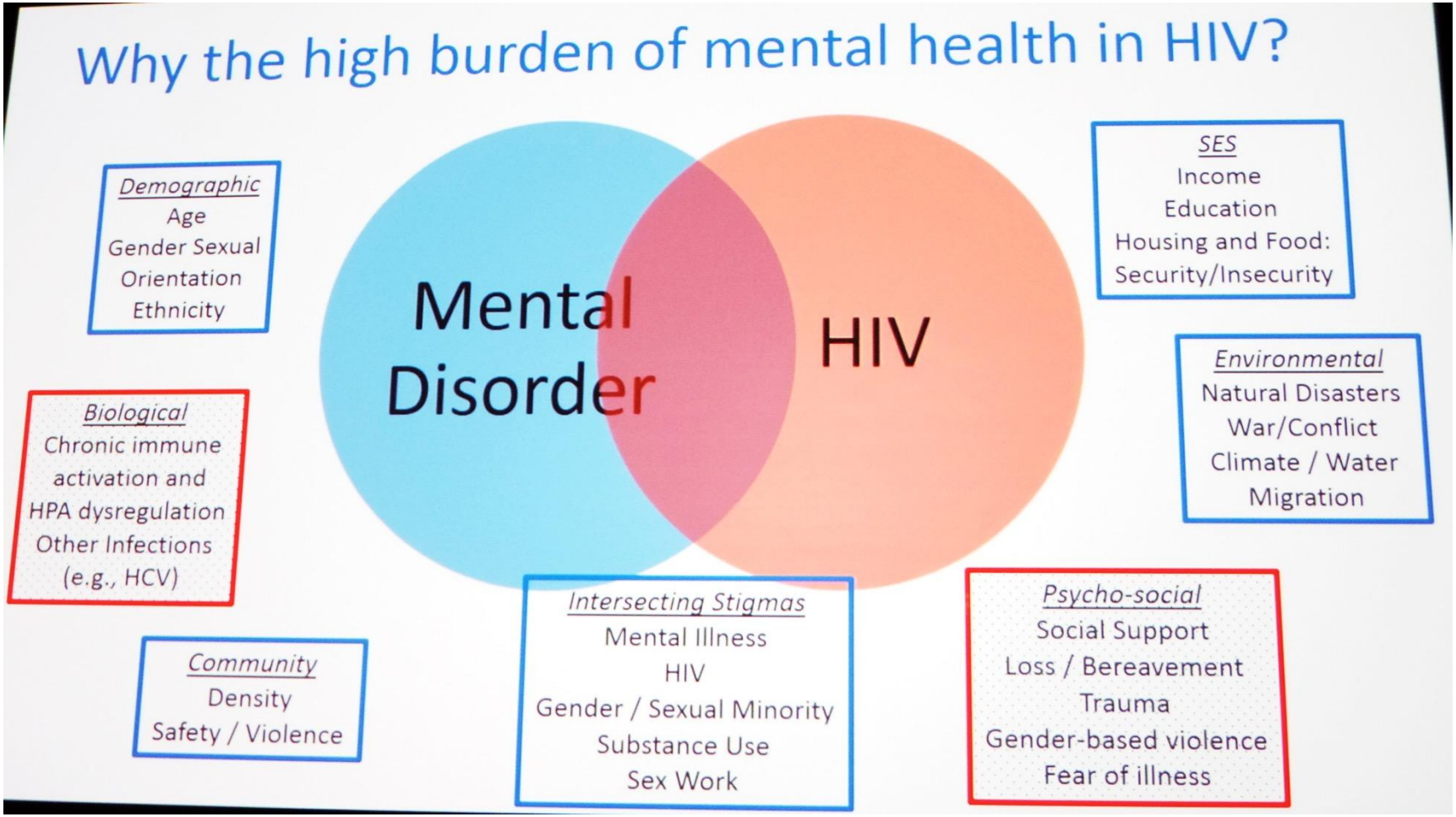


R. Remien

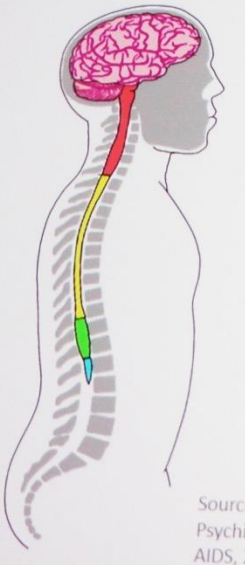
Rates of selected psychiatric disorders: United States general population vs PLWHA



Source: Extensive literature review by colleagues in the Northeast/Caribbean AETC


Why the high burden of mental health in HIV?
Mental Disorder
HIV
Demographic
Age
Gender Sexual Orientation
Ethnicity
SES
Income
Education
Housing and Food: Security/Insecurity
Biological
Chronic immune activation and HPA dysregulation
Other Infections (e.g., HCV)
Environmental
Natural Disasters
War/Conflict
Climate / Water
Migration
Community
Density
Safety / Violence
Intersecting Stigmas
Mental Illness
HIV
Gender / Sexual Minority
Substance Use
Sex Work
Psycho-social
Social Support
Loss / Bereavement
Trauma
Gender-based violence
Fear of illness

What are the potential pathways between mental illness and HIV health outcomes?



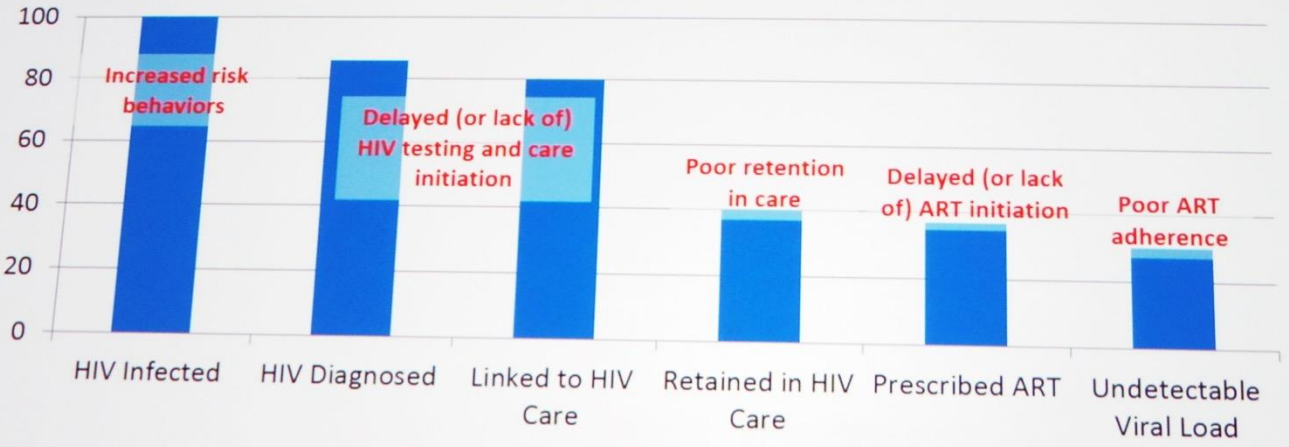
Potential biological mechanisms

- Direct effects of depression → immune system
  - Chronic immune activation, HPA dysregulation
- HIV crosses the blood brain barrier → immune activation in the brain and the CNS
  - Inflammatory proteins → oxidative stress and neuronal injury
- Chronic inflammatory response to HIV infection
  - Elevation in the level of cytokines e.g. Interleukin(IL)-6 and Tumor Necrosis Factor(TNF)-Alpha trigger chain reaction involving Tryptophan depletion through the activation of Indoleamine 2,3-dioxygenase (IDO) enzyme
  - Tryptophan depletion reduces serotonin levels and increases Kynurenine (Kyn) and its metabolites (some are neurotoxic and associated with depression, suicide, and anxiety)

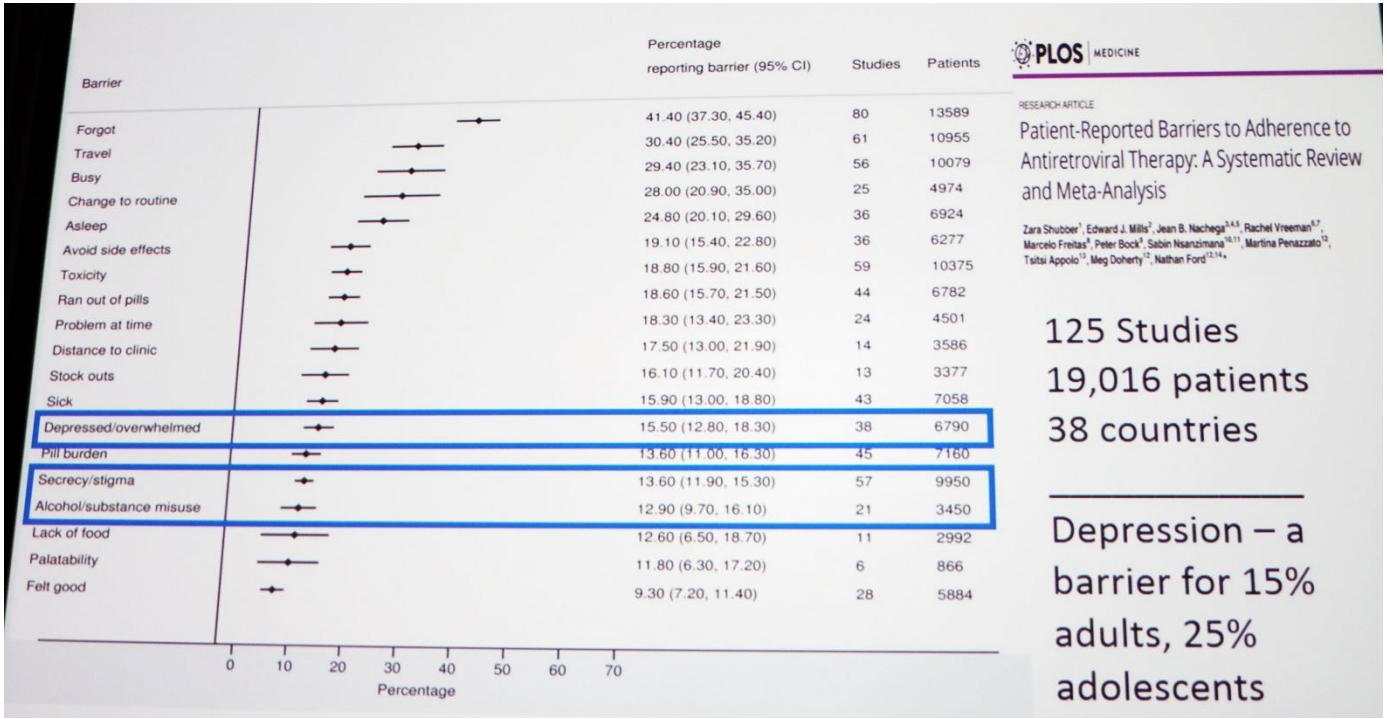
Source: Fu et al, Journal of Neuroinflammation, 2011; Lawson et al, Brain, Behavior, and Immunity, 2011; Capuron et al, Biological Psychiatry, 2011; Castillo-Mancilla et al, Clinical Infections Diseases, 2016; Hunt, Clinical Infections Diseases, 2017; Wada et al, AIDS, 2015; Dantzer, Current Topics in Behavioral Neurosciences, 2016; Martinez et al, JAIDS, 2014

The behavioral pathway is clear

Mental health impairment contributes to:



Dépression

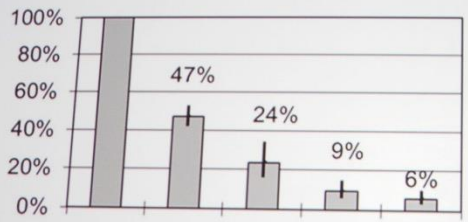


Beyond depression

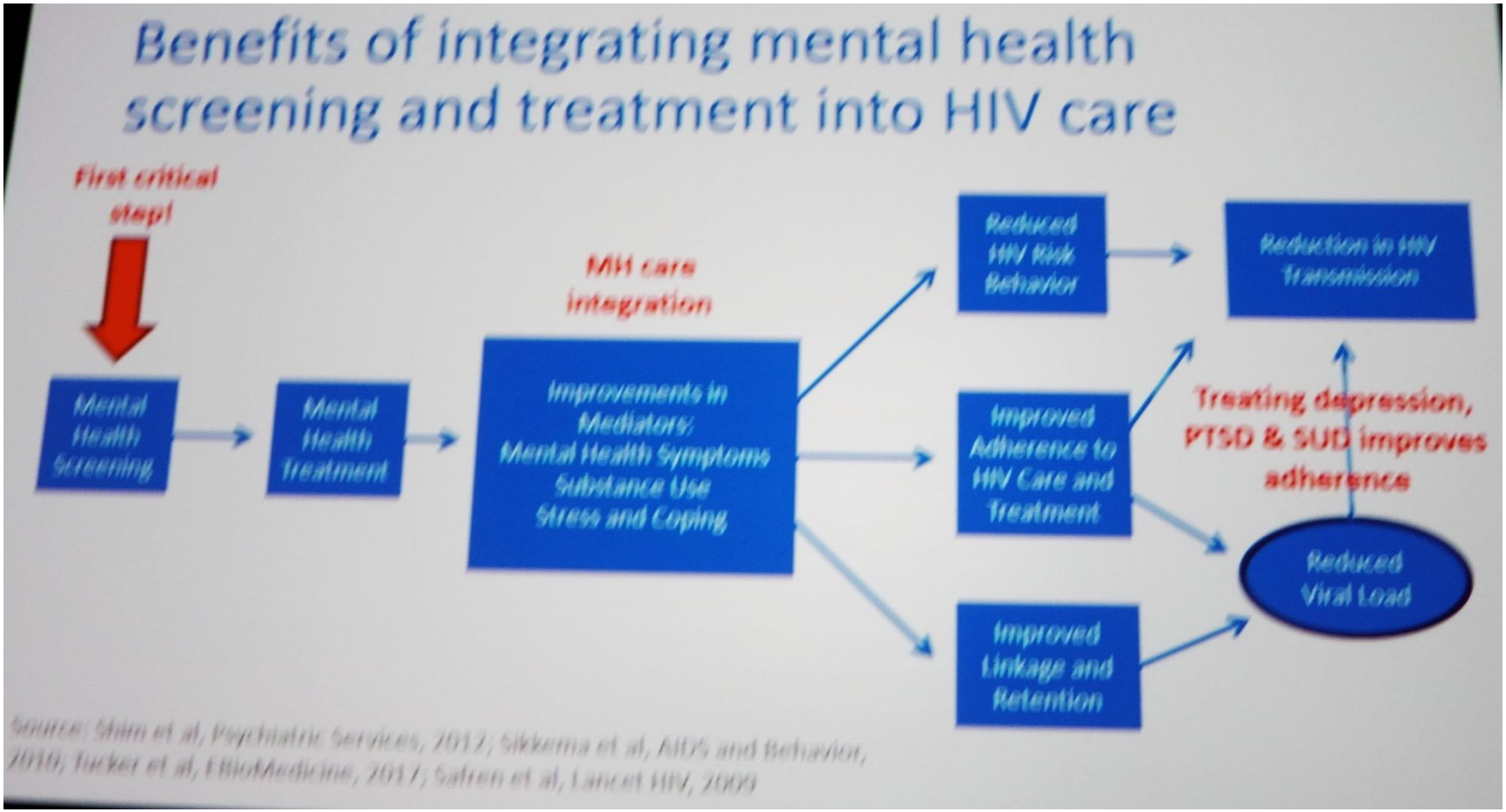
In the context of co-morbid vulnerabilities, such as **unstable housing**, ***food insecurity***, **domestic violence**, **trauma**, **stigma** and **discrimination** a wide range of psychiatric problems are found among PLWHA, including:

- Depressive disorder
- Anxiety disorders
- Alcohol and other substance-use disorders
- Stress disorders, including Post-Traumatic Stress Disorder (PTSD)
- (1) Somatic problems, including insomnia, pain, fatigue, and sexual dysfunction, and (2) Non-somatic problems such as hopelessness and shame

The depression treatment cascade



Source: Pence et al, Psychiatry in Primary Care, 2013; *Zuckerbrot et al, Pediatrics, 2018


Benefits of integrating mental health screening and treatment into HIV care
First critical step!
Mental Health Screening
Mental Health Treatment
MH care integration
Improvements in Mediators: Mental Health Symptoms Substance Use Stress and Coping
Reduced HIV Risk Behavior
Improved Adherence to HIV Care and Treatment
Improved Linkage and Retention
Reduction in HIV Transmission
Treating depression, PTSD & SUD improves adherence
Reduced Viral Load
Source: Shim et al, Psychiatric Services, 2012; Sikkema et al, AIDS and Behavior, 2010; Tucker et al, EBioMedicine, 2017; Safren et al, Lancet HIV, 2009

The scale-up challenge

Task Shifting / Sharing

MH specialists → Non-specialists

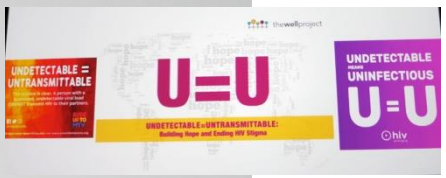
Integrated Care

Referral / Consultative Model

Co-located Model

Integrated Care Model

Source: van Ginneken N et al., Cochrane Database Syst Rev. 2013; WHO, 2007; Verdeli H et al, 2008; Rojas et al, Lancet, 2007; Bass et al, BJP, 2006; Patel et al, Lancet, 2007; Araya et al, Lancet, 2003; Patel and Thornicroft, PLoS Med, 2009; GMHGroup, Lancet, 2007



Evidence-based depression care is feasible with existing HIV clinic staff in LMIC

- INDEPTH-Uganda: NIH-funded comparative, cluster RCT comparing task-shifting approaches to integrating depression treatment into HIV care in Uganda
  - Care provided by **trained nurses** using a structured protocol
  - Care provided by **trained primary care (PC) providers** using "clinical acumen"
- N=1252 clients across 10 public HIV clinics (5 structured protocol, 5 clinical acumen)

	Trained Nurses	Trained PC providers
% Screened with PHQ-2	76%	80%
% Positive screens who received PHQ-9	84%	49%
% Clinically depressed, prescribed antidepressants	69%	56%
Among treated, % with full remission	65%	69%

Source: Wagner et al, PLoS One, 2016; Wagner et al, Research and Advances in Psychiatry, 2016

- **Existing staff (nurses, doctors) can provide quality depression care**
- **Limited funding is needed for training and ongoing supervision by specialists who are available**
- **Both models were widely adopted by providers and depression care reached most depressed clients**