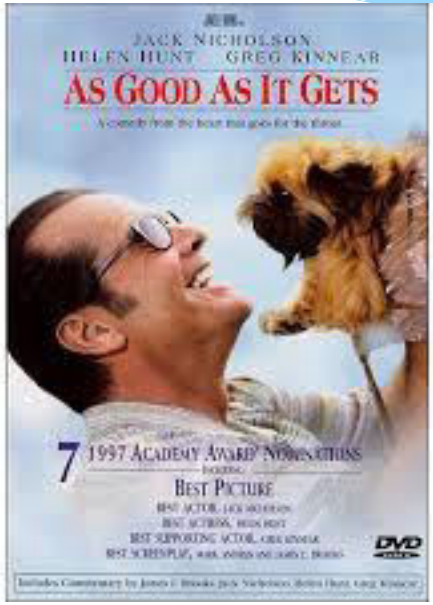
May the best “man” win

Francesca Conradie

As good as it gets



ONE ARV PILL A DAY

New Fixed Dose Combination ARVs

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health

Department:
Health
REPUBLIC OF SOUTH AFRICA

GOALS OF THERAPY

* Durable suppression of HIV viral load to less than 50 copies/mL
* Restoration of immune function (as indicated by the CD4 cell count)
* Prevention of HIV transmission
* Prevention of drug resistance
* Improvement in quality of life

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Improvement in quality of life

Able to get on the with tasks of daily life

Must fit into patient schedule

Twice a day ruled out…..

NNRTI	PI	INSTIs	CCR5 antagonist	Fusion inhibitor
EFV	LPV/r	RTG	MVC	EFT
NVP	ATZ/r	DTG		
ETR	DRV/r	ELVTG		
RPL				

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Our candidates

NNRTI	PI	INSTIs
EFV	LPV/r	RTG
NVP	ATZ/r	DTG
ETR	DRV/r	ELVTG
RPL		

Once a day dosage

NNRTI	PI	INSTIs
EFV	LPV/r Yes but……	RTG
NVP	ATZ/r Yes but……	DTG
ETR	DRV/r	ELVTG
RPL		

Side effect profile

NNRTI	PI	INSTIs
EFV	LPV/r	RTG
NVP	ATZ/r	DTG
ETR	DRV/r	ELVTG
RPL		

EFV vs NVP side effects

* Pillay P, Ford N, Shubber Z, Ferrand RA **Outcomes for efavirenz versus nevirapine-containing regimens for treatment of HIV-1 infection: a systematic review and meta-analysis.** PLoS One. 2013 Jul 22;8(7)
  * Rash
  * Central nervous system side effects.
  * These side effects usually abate within approximately two to three weeks

Summary of sensitivity analysis differentiated by NVP dosages

Outcome	Strict comparison of studies: EFV vs. NVP 200mg twice daily	Comparison of studies of EFV 600mg once dail to all studies of NVP 200mg twice daily and studies of NVP 400mg once daily [1]
Virologic success	RR 1.04 [1.00-1.09] p = 0.05, p for heterogeneity=0.40 I^2=4%.	RR 1.06 [1.00, 1.12] p = 0.06, p for heterogeneity = 0.21 I^2 = 26%
Virologic failure	RR 0.83 [0.73 - 0.94] p = 0.004,p for heterogeneity = 0.98 I^2 = 0%	RR 0.82 [0.73, 0.93] p = 0.0002, p for heterogeneity = 0.96 I^2 = 0%
Mortality	RR 0.94 [0.59, 1.49] p = 0.79, p for heterogeneity = 0.32 I^2=41%	RR 0.79 [0.42, 1.49] p = 0.47, p for heterogeneity = 0.17 I^2 = 12%
Treatment termination	RR0.71 [0.43, 1.17] p = 0.18, p for heterogeneity <0.002 I^2 = 80%	RR 0.76 [0.48, 1.20] p = 0.24, p for heterogeneity = 0.004 I^2 = 74%

EFV vs ATZ

* **Atazanavir** versus **efavirenz** — A randomized trial compared atazanavir 400 mg daily with efavirenz 600 mg daily in 810 treatment-naive patients + AZR, 3TC
* The overall frequency of adverse events was similar in the two groups,
  * with rash and dizziness occurring more frequently with **efavirenz** and
  * jaundice and scleral icterus occurring more frequently with **atazanavir.**
* Overall, **atazanavir** treatment was associated with a more favorable lipid profile with significant differences in the change from baseline in total cholesterol

ACTG A5202-

* **Atazanavir Plus Ritonavir or Efavirenz as Part of a 3-Drug Regimen for Initial Treatment of HIV-1**

Summary of Drug-Resistant Mutations, With Specific Major Mutations of Interest*

Variable	Abacavir–Lamivudine		Tenofovir DF–Emtricitabine	
	Efavirenz (n = 465)	Atazanavir + Ritonavir (n = 463)	Efavirenz (n = 464)	Atazanavir + Ritonavir (n = 465)
Virologic failure				
Events, *n (%)*	72 (15)	83 (18)	57 (12)	57 (12)
Genotype available at failure	71	83	55	57

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Virologic failure				
Events, *n (%)*	72 (15)	83 (18)	57 (12)	57 (12)
NRTI-associated‡	25 (5) [40]§	11 (2) [14]§	11 (2) [23]§	5 (1) [9]§
M184I/V	22	11	5	5
K65R	3	0	4	0
L74I/V	6	0	1	0
Other¶	6	0	1	0
NNRTI-associated‡	41 (9) [65]	1 (<1) [1]	27 (6) [56]	0 (0) [0]
K103N	30	0	19	0
Y181C	2	0	0	0
L100I	4	0	2	0
G190A/E/Q/S	9	0	6	0
Other¶	16	1	6	0
NRTI + NNRTI-associated‡	25 (5) [40]	0 (0) [0]	11 (2) [23]	0 (0) [0]
Protease-associated (N88N/S)‡	0 (0) [0]	1 (<1) [1]	0 (0) [0]	0 (0) [0]

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PI versus NNRTI-based strategy (ACTG 5142, ACTG 5202, ALTAIR)

* The ACTG 5142 trial was a multicenter open-label study of 753 treatment-naive patients who were randomly assigned to receive **lopinavir/ritonavir plus two nucleoside analogs** (NRTIs), or **efavirenz plus two NAs,** or **efavirenz plus lopinavir/ritonavir** alone (a nucleoside-sparing arm)

* Viral suppression (<50 copies/mL) was achieved in a significantly greater proportion of patients on the efavirenz arm (89 percent) compared with either the lopinavir/ritonavir arm (77 percent) or the NRTI-sparing arm (83 percent).

* This trial illustrates different advantages for NNRTI- or PI-based strategies:

PI versus NNRTI-based strategy (ACTG 5142, ACTG 5202, ALTAIR)

* Although virologic efficacy was greater in the efavirenz arm, patterns in the development of drug resistance favoured the lopinavir/ritonavir arm.

* Failure of efavirenz was associated with the **emergence of NNRTI resistance**, whereas failure of lopinavir/ritonavir was not associated with lopinavir/ritonavir resistance mutations.

* **Riddler SA, Haubrich R, DiRienzo AG et al,** Class-sparing regimens for initial treatment of HIV-1 infection N Engl J Med. 2008;358(20):2095.

Table 4. Summary of Resistance Mutations at the Time of Virologic Failure.*

Variable	Efavirenz Group (N=250)		Lopinavir–Ritonavir Group (N=253)		NRTI-Sparing Group (N=250)	
	No. (%)	P Value vs. NRTI-Sparing Group	No. (%)	P Value vs. Efavirenz Group	No. (%)	P Value vs. Lopinavir–Ritonavir Group
Virologic-failure events	60 (24)		94 (37)		73 (29)	
Genotype available at virologic failure	46 (77)		78 (83)		56 (77)	
No sample available or HIV-1 RNA <500 copies/ml	8 (13)		7 (7)		10 (14)	
No sequence available (unable to amplify)	6 (10)		9 (10)		7 (10)	
Any mutation (excluding minor protease mutation)	22 (48)	0.03	16 (21)	0.002	39 (70)	<0.001
NRTI-associated mutation	14 (30)	0.02	15 (19)	0.19	6 (11)	0.23
M184V	8 (17)	0.01	13 (17)	1.00	1 (2)	<0.01
K65R	3 (7)	0.09	0	0.05	0	NA
Thymidine analogue–associated mutation†	2 (4)	1.0	1 (1)	0.56	2 (4)	0.57
NNRTI-associated mutation	20 (43)	0.03	2 (3)	<0.001	37 (66)	<0.001
K103N	11 (24)	0.002	0	<0.001	31 (55)	<0.001
Any protease mutation	39 (85)	0.61	61 (78)	0.48	45 (80)	0.83
Major protease mutation‡	0	0.50	0	NA	2 (4)	0.17
Mutation associated with two drug classes§	12 (26)	0.01	1 (1)	<0.001	4 (7)	0.16

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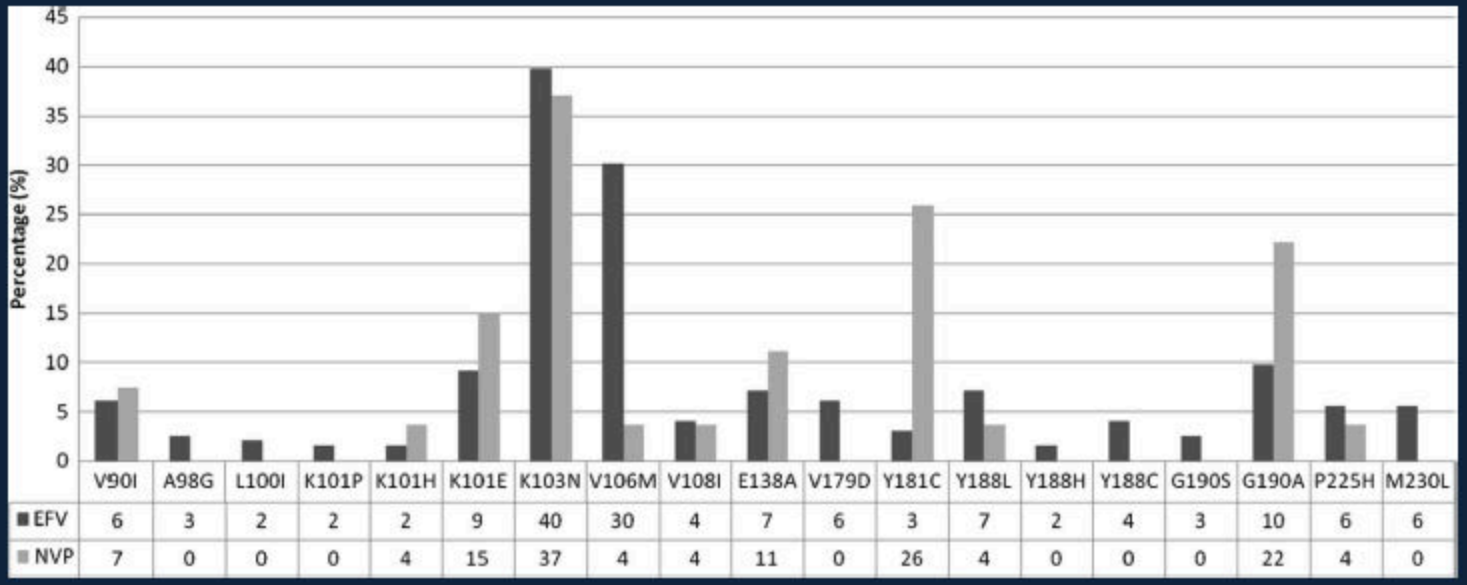
HIVDR in patients failing ARVs in an urban setting

NNRTI mutations



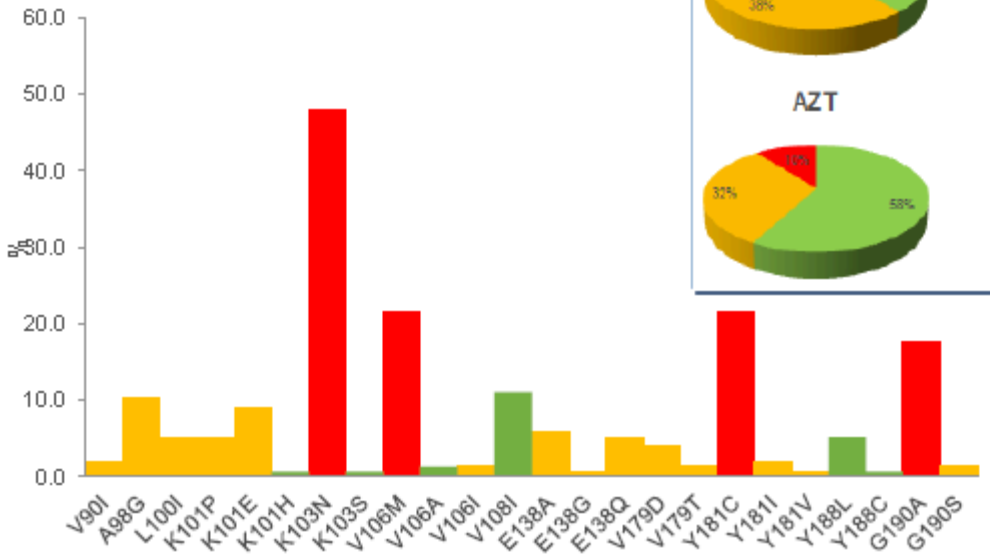
	V90I	A98G	L100I	K101P	K101H	K101E	K103N	V106M	V108I	E138A	V179D	Y181C	Y188L	Y188H	Y188C	G190S	G190A	P225H	M230L
EFV	6	3	2	2	2	9	40	30	4	7	6	3	7	2	4	3	10	6	6
NVP	7	0	0	0	4	15	37	4	4	11	0	26	4	0	0	0	22	4	0

Wallis, Stevens et al.
JAIDS 2010

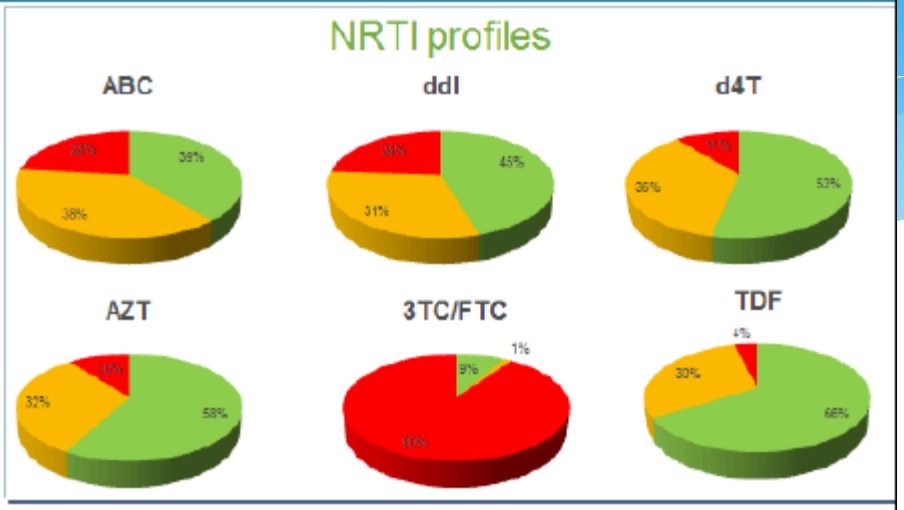
NATIONAL HEALTH LABORATORY SERVICE
National Priority Programmes

HIVDR in patients failing ARVs in a remote setting from the laboratory: NRTI and NNRTI mutations

Steegen et al. INTEREST Workshop 2012



Important single NNRTI mutations
ETR related mutations
Other NNRTI mutations



- High level (23.4%) and intermediate (37.7%) ABC resistance despite limited exposure (n=1)
- Intermediate resistance to TDF in 29.9% of patients
  Only 13 (28.3%) of them were exposed to TDF

And now for a SPRING in your step

* Dolutegravir (DTG) is a newer, potent INSI with low nanomolar activity that is suitable for once-daily, unboosted dosing
* Furthermore, *in vitro*, DTG retains activity against most isolates carrying major integrase resistance mutations to RAL and/or EVG

And now for a SPRING in your step

* In clinical trials conducted to date, DTG was generally well tolerated and effective in a broad range of patients, including those with genotypic resistance to RAL

SPRING-1 was a 96-week, randomized, partially blinded, phase IIb dose-ranging study.

METHODS: Treatment-naive adults with HIV received DTG 10, 25, or 50 mg once daily or efavirenz (EFV) 600 mg once daily (control arm) combined with investigator-selected dual nucleos(t)ide reverse transcriptase inhibitor backbone regimen

Fig. 1

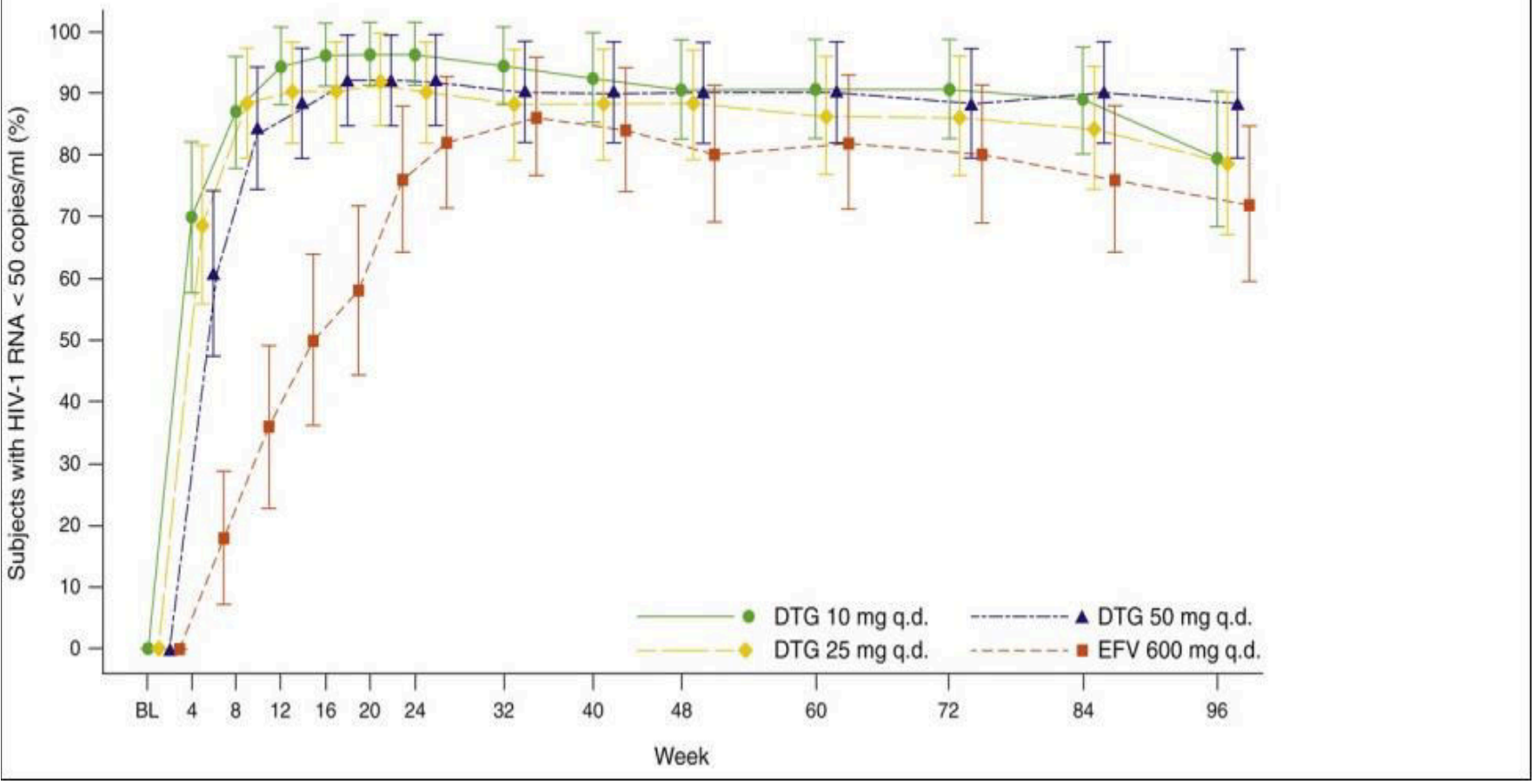
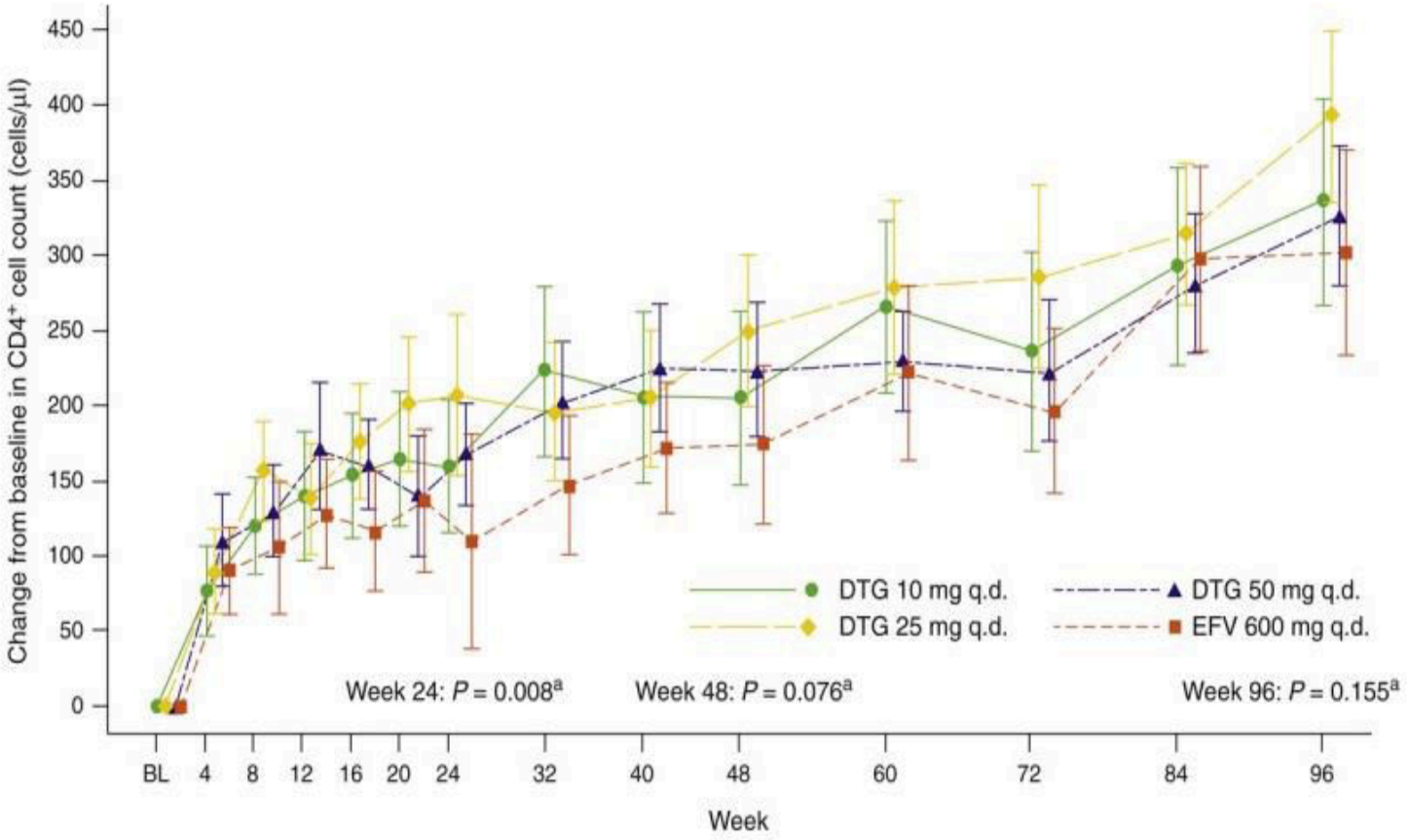

Subjects with HIV-1 RNA < 50 copies/ml (%)
100
90
80
70
60
50
40
30
20
10
0
BL
4
8
12
16
20
24
32
40
48
60
72
84
96
Week
DTG 10 mg q.d.
DTG 25 mg q.d.
DTG 50 mg q.d.
EFV 600 mg q.d.

Fig. 2



Median (95% confidence interval) change from baseline in $CD4^+$ cell counts.

BL, baseline; DTG, dolutegravir; EFV, efavirenz; q.d., once daily. [a]*P* value determined for all DTG doses vs. EFV using the Wilcoxon two-sample test.

Resistance on SPRING 1

* Samples from participants meeting Protocol defined Virological failure criteria were sent for resistance testing.
* No participants on DTG have had emergence of a virus with an INI resistance mutation.
* One participant receiving DTG 10mg developed virus with the mutation M184M/V in reverse transcriptase.

SPRING-2 study.

* Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority

SPRING-2 study

* SPRING-2 was a study evaluating once-daily DLG versus twice-daily raltegravir in 822 HIV-infected, treatment-naïve patients, in each case in combination with a fixed-dose dual-NRTI treatment.
* At week 48, the proportion of study participants who were virologically suppressed (HIV-1 RNA <50 c/mL) was 88% for the regimen containing DLG and 86% for the regimen containing raltegravir, meeting the 10% non-inferiority criteria.

SPRING-2 study

* The tolerability of DLG was similar to that of raltegravir, with adverse events leading to withdrawal at 2% in both arms. There were no treatment-emergent adverse drug reactions of at least moderate intensity (Grades 2 to 4) and ≥2% frequency in the DLG or raltegravir arms in SPRING-2.

SPRING-2 study

* **No treatment-emergent genotypic resistance** to DLG or the background regimen was seen in the DLG arm in SPRING-2.
* The patients with virologic failure who received raltegravir, one (6%) had integrase treatment-emergent resistance and four (21%) had nucleoside reverse transcriptase inhibitors treatment-emergent resistance.

SINGLE

* This was a study evaluating once-daily DLG plus abacavir/lamivudine versus the single tablet regimen Atripla in 833 HIV-infected, treatment-naïve patients.
* At 48 weeks, the proportion of study participants who were virologically suppressed (HIV-1 RNA <50 c/mL) was 88% for the DLG regimen and 81% for Atripla.
* This difference was statistically significant. Overall, 2% of subjects on the DLG-based regimen discontinued due to adverse events versus 10% of those receiving the Atripla regimen.

SINGLE

* No treatment-emergent genotypic resistance that resulted in reduced susceptibility to either DLG or the background regimen was seen in the DLG arm in SINGLE.

SAILING

* This was a study evaluating once-daily DLG versus twice-daily raltegravir in 719 patients with HIV who were failing on current therapy, but had not been treated with an integrase inhibitor,
* At week 24, 79% of patients on the regimen containing DLG were virologically suppressed (HIV-1 RNA <50 c/mL) versus 70% of patients on the regimen containing raltegravir. This difference was statistically significant.
* Overall, the tolerability of DLG was similar to that of raltegravir, with adverse events leading to withdrawal at 2% for the DLG regimen versus 4% for the raltegravir regimen.

SAILING

* There were no treatment-emergent adverse drug reactions of at least moderate intensity (Grades 2 to 4) and ≥2% frequency in the DLG arm. The only treatment-emergent adverse drug reaction of at least moderate intensity (Grades 2 to 4) and ≥2% frequency in the raltegravir arm was diarrhoea (2%).
* Viruses from five of 15 subjects in the DLG arm with post-baseline resistance data had evidence of treatment-emergent genetic changes (integrase substitutions). However, none of these patients had decreases in susceptibility to either DLG or raltegravir

OF course the ever present TB and pregnancy question

* Increase the dose of DLG- poor evidence
* Category B drug.

In summary

* DLG has been combined with both ABC/3TC and TDF/FTC as a once a day dosage.
* Excellent outcomes both virologically and immunologically
* No resistance to the drug itself and only once at a very low dose to one of its companion drugs