Why do we need ARV surveillance studies?

Michelle Moorhouse

27 Oct 2018

Southern African HIV Clinicians Society Conference

University of the Witwatersrand
WITS RHI

Thanks: Andy Hill, Polly Clayden

Disclosures

- Speaker fees and honoraria from Gilead Sciences, AbbVie, Cipla, Mylan, Aspen, Sanofi, Pfizer and Janssen
- Conference sponsorship from BD, Gilead, Janssen, Merck, Cipla and Mylan
- Part of ART optimisation collaborations
- Funding from USAID, Unitaid, SAMRC and study drug donations from ViiV Healthcare and Gilead Sciences for ART optimisation studies

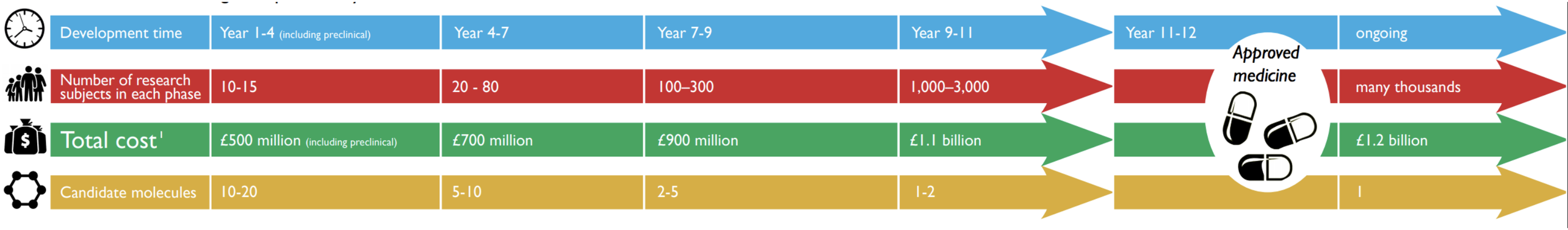
USAID FROM THE AMERICAN PEOPLE

SOUTH AFRICANS AND AMERICANS IN PARTNERSHIP TO FIGHT HIV/AIDS
PEPFAR

saMRC advancinglife

Unitaid

Stages of drug development



12 years

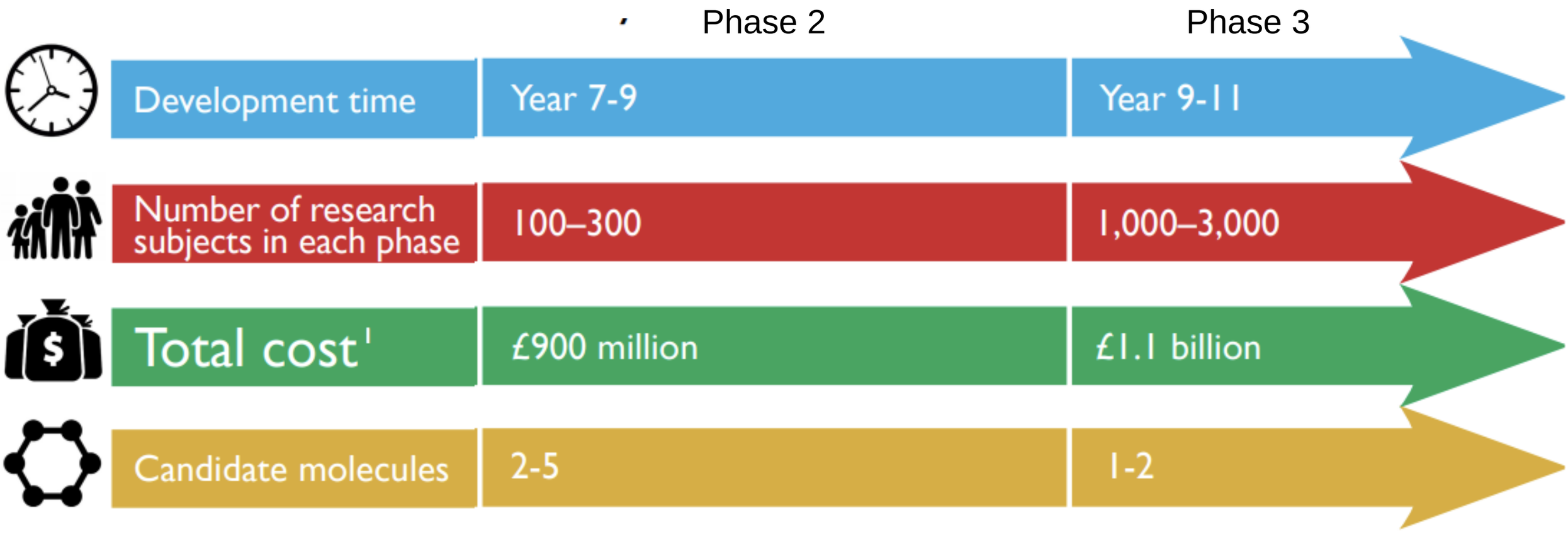
20 molecules → 1

GBP 4.4 billion

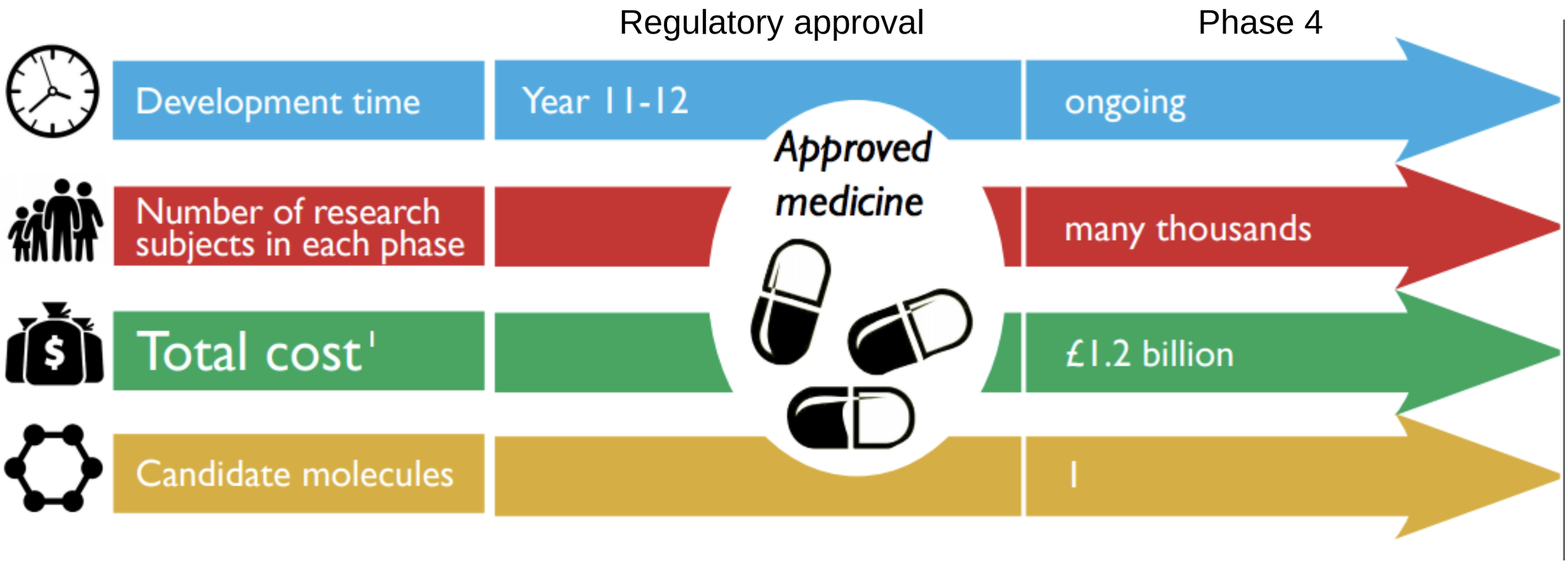
Stages of drug development

	Translational and Phase 0	Phase 1
Development time	Year 1-4 (including preclinical)	Year 4-7
Number of research subjects in each phase	10-15	20 - 80
Total cost[1]	£500 million (including preclinical)	£700 million
Candidate molecules	10-20	5-10

Stages of drug development



Stages of drug development

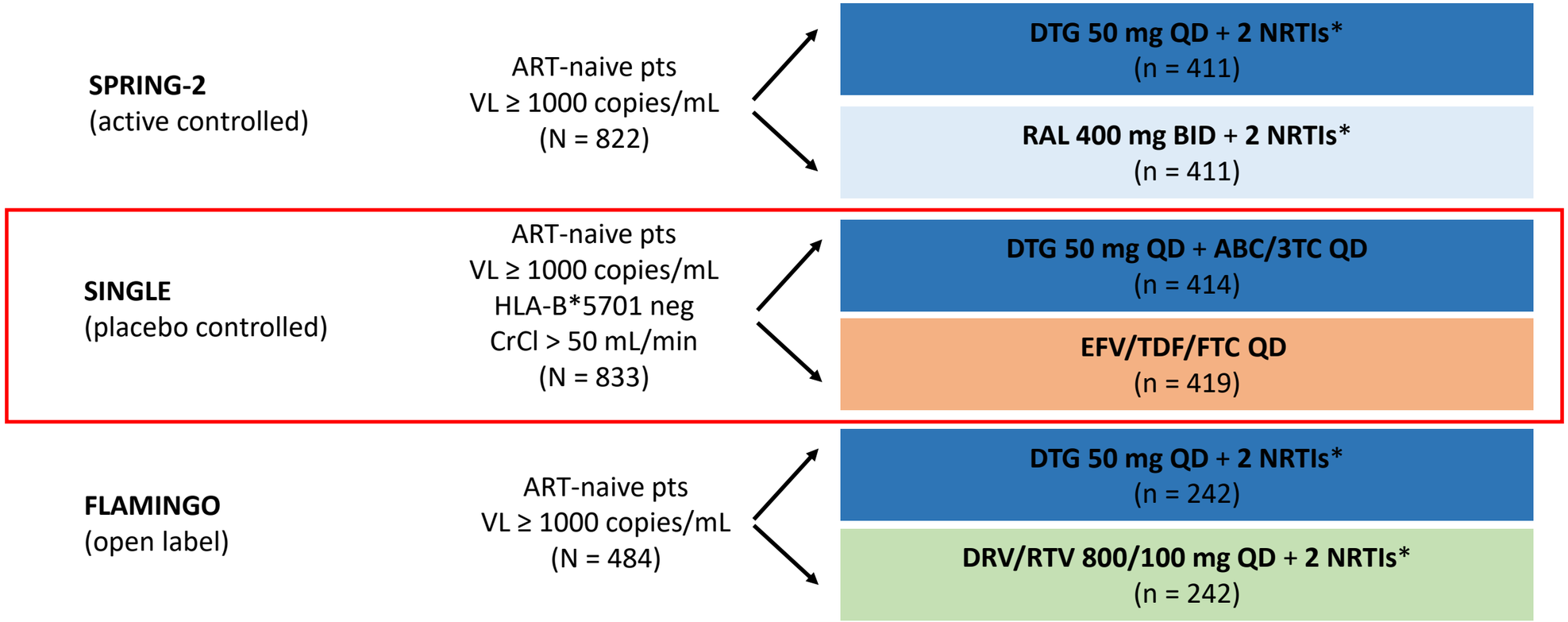


A shiny new molecule…

- Registrational studies are designed to
  - optimise benefits, and
  - minimise risks/adverse events
- Subjects are selected to show these effects

Let’s look at dolutegravir registrational studies

- Randomised, non-inferiority phase 3 studies
- Primary endpoint: HIV-1 RNA < 50 copies/mL at week 48

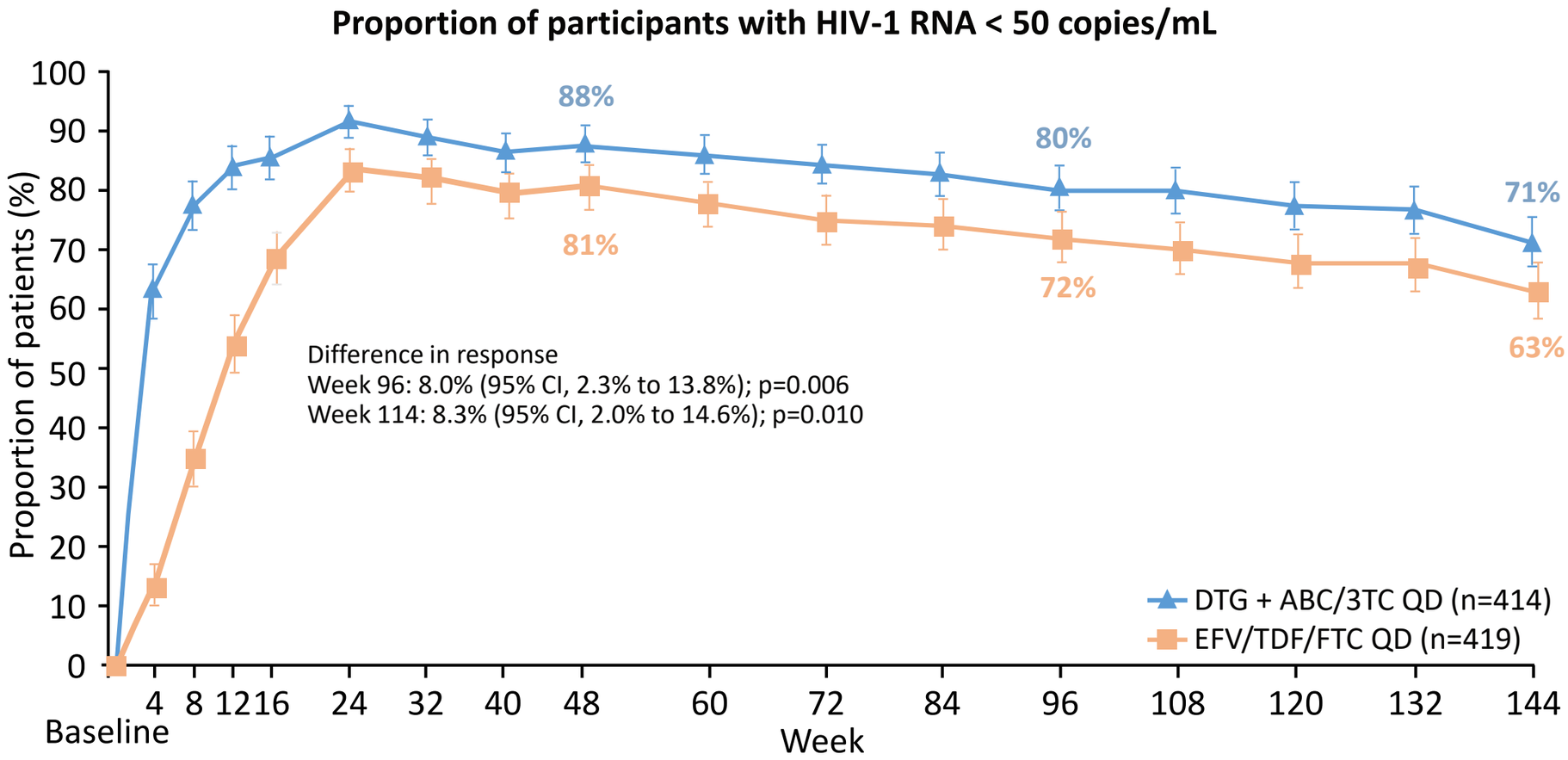


*Investigator-selected NRTI backbone: either TDF/FTC or ABC/3TC.

Clinical Care Options 2014
Raffi et al. Lancet Infect Dis 2013
Walmsley et al. N Engl J Med 2013
Clotet et al. Lancet 2014

SINGLE study: DTG vs. EFV

Better tolerated than EFV (but more insomnia)



Walmsley et al. N Engl J Med 2013
Walmsley et al. J Acquir Immune Defic Syndr 2015

SINGLE study: Safety

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dolutegravir plus Abacavir–Lamivudine for the Treatment of HIV-1 Infection

Sharon L. Walmsley, M.D., Antonio Antela, M.D., Ph.D., Nathan Clumeck, M.D.,

Event	Dolutegravir and Abacavir–Lamivudine (N=414)	Efavirenz–Tenofovir DF–Emtricitabine (N=419)
	no. of participants (%)	
Adverse event leading to discontinuation of study drug†	10 (2)	42 (10)
Psychiatric disorder	2 (<1)	15 (4)
Nervous system disorder	0	13 (3)
Skin and subcutaneous-tissue disorder	2 (<1)	8 (2)
Gastrointestinal disorder	0	8 (2)
General disorder or administration-site condition	0	7 (2)

Study entry criteria: inclusion

- Screening plasma HIV-1 RNA ≥ 1000 copies/mL
- Antiretroviral-naïve (≤ 10 days of prior therapy with any antiretroviral agent following a diagnosis of HIV-1 infection)
- Ability to understand and sign a written informed consent form
- Willingness to use approved methods of contraception to avoid pregnancy (women of child bearing potential only)
- Age equal to or greater than 18 years
- A negative HLAB*5701 allele assessment

Study entry criteria: exclusion

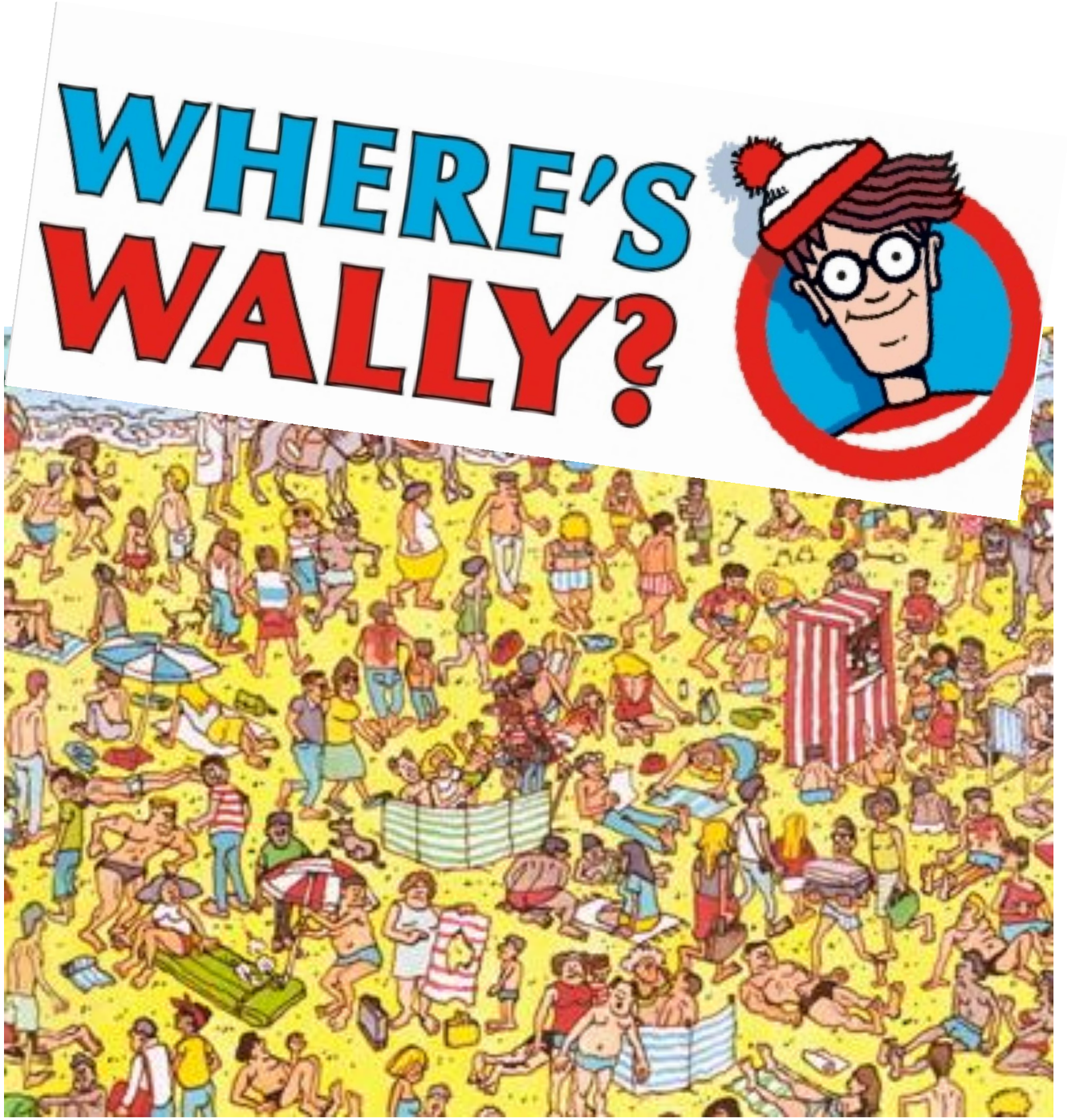
- Women who are pregnant or breastfeeding;
- Active Center for Disease and Prevention Control (CDC) Category C disease
- Hepatic impairment
- HBV co-infection
- Anticipated need for HCV therapy during the study
- Allergy or intolerance to the study drugs or their components or drugs of their class
- Malignancy within the past 5 years
- Treatment with an HIV-1 immunotherapeutic vaccine within 90 days of Screening
- Treatment with radiation therapy, cytotoxic chemotherapeutic agents or any immunomodulator within 28 days of Screening
- Exposure to an agent with documented activity against HIV-1 in vitro or an experimental vaccine or drug within 28 days of first dose of study medication
- Primary viral resistance in the Screening result
- Verified Grade 4 laboratory abnormality
- ALT >5 xULN
- ALT ≥ 3xULN and bilirubin ≥ 1.5xULN (with >35% direct bilirubin);
- Estimated creatinine clearance <50 mL/min
- Recent history (≤3 months) of upper or lower gastrointestinal bleed

clinicaltrials.gov

Who’s missing?

- < 18 years
- Pregnant or breastfeeding women
- HBV coinfection
- Malignancy within last 5 years
- Recent GI bleed
- Various laboratory abnormalities
  - Liver, renal
  - Grade 4

Who is excluded?



Pregnant women in dolutegravir studies

Name	Population	ART	N	No of women on DTG arm
SINGLE	ARV-naive	DTG + ABC/3TC vs EFV/TDF/FTC	144	67
SPRING 2	ARV-naive	2NRTI + DTG vs 2NRTI + RAL	822	63
FLAMINGO	ARV-naive	2NRTI + DTG vs 2NRTI + DRV/r	484	31
SAILING	Experienced	OB + DTG vs OB + RAL	719	107
STRIIVING	Switch	2NRTI/DTG vs current ART	551	77
SWORD 1&2	Switch	RPV + DTG vs current ART	1024	120
ARIA	ARV-naïve women	DTG/ABC/3TC vs ATV/r + TDF/FTC	495	250
DAWNING	Experienced	2NRTI + DTG vs 2NRTI + LPV/r	627	116
INSPIRING	TB	2NRTI + DTG twice daily vs 2NRTI + EFV with RIF-based co-treatment	113	36
		Total:	4979	**867**

Thanks Polly Clayden!

Anyone else missing?

Characteristic	DTG 50 mg +ABC/3TC QD (n=414)	EFV/TDF/FTC QD (n=419)
Median age, years (range)	36 (18-68)	35 (18-85)
Female, n (%)	67 (16)	63 (15)
African American/African Heritage, n (%)	98 (24)	99 (24)
CDC class C, n (%)	18 (4)	17 (4)
Baseline HIV-1 RNA		
Median (log10 copies/mL)	4.67	4.70
> 100,000 c/mL, n (%)	134 (32)	131 (31)
Median CD4 cell count, cells/uL	334.5	339.0
< 200, %	14	14
200 to < 350, %	39	38
350 to < 500, %	32	31
≥ 500, %	15	17

Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18 and supplementary appendix

A shiny new molecule…

- Registrational studies are designed to
  - optimise benefits, and
  - minimise risks/adverse events
- Subjects are selected to show these effects

Honeymoon phase

Drug just launched

Efficacy great

Safety profile looks good

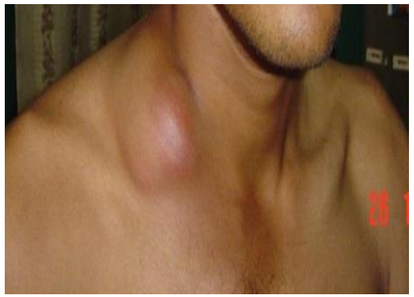
BUT…

- Clinical trials are very different from the **real world** of medical practice and care
- No drug is **safe and effective** for everybody
- Clinical trials are needed to develop labelling instructions on how to use the drug to obtain its **benefits and reduce risks** of harms
- Trials are usually just **large** enough and **long** enough to support efficacy findings

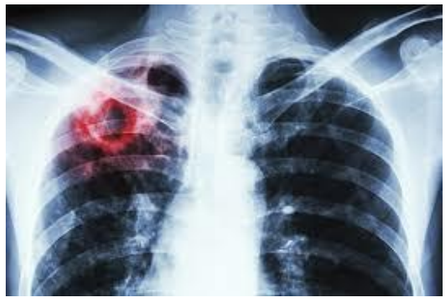
1. Do they really provide full information on how to use ARVs in sicker people living with HIV?
2. Are the results generalisable to all PLWHIV?

Gaps on dolutegravir after registration

Long term tolerability in the real world



Advanced HIV disease



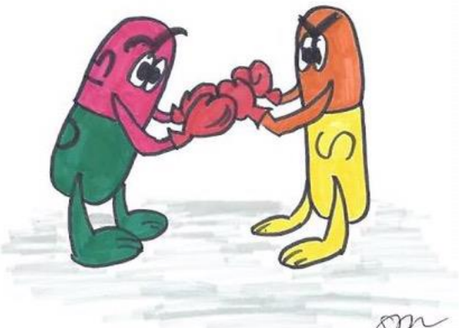
Comorbidity:
TB
HBV
NCDs
etc

Pregnant/BF women

Infants and children

Diverse populations

Elderly/Ageing



Drug interactions

Adapted from: Meg Doherty, WHO 2018

Marriage blues

In the long-term, new evidence emerges…..

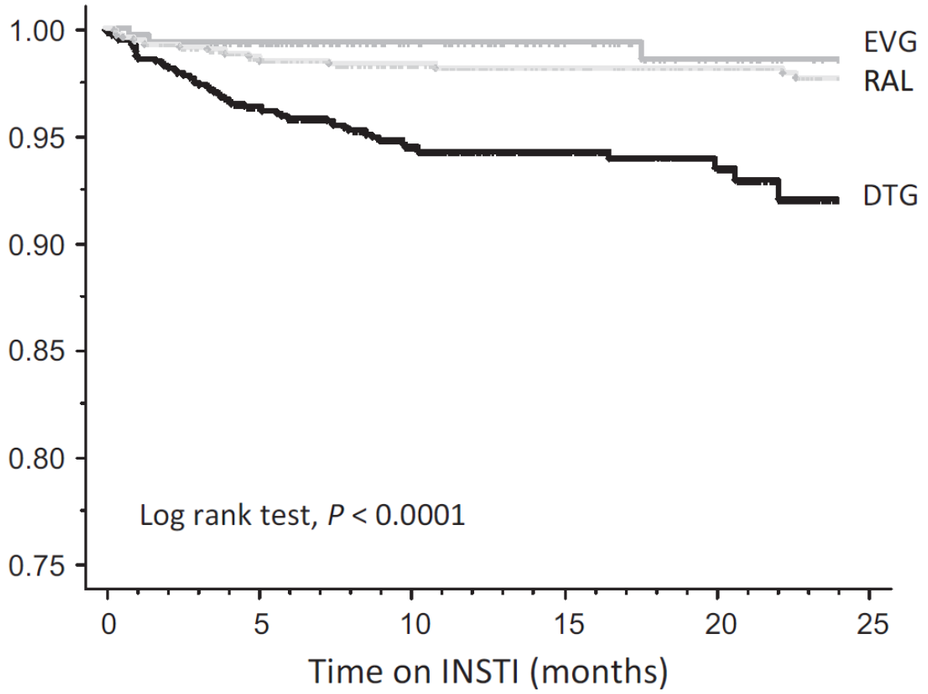
New patient populations, larger sample sizes, new methods to study adverse events

DTG in the real world…

Dolutegravir: discontinuation due to AE

Germany (2 cohorts), 1950 INSTI-based therapies

Discontinuation due to neuropsychiatric AE



Factors associated with DTG discontinuation

	RH	95% CI	*P*
Any AE			
Female, *vs.* male gender	2.81	1.46–5.41	0.002
Older age (> 60 years), *vs.* younger age	2.88	1.56–5.34	< 0.001
ABC with DTG initiated, *vs.* no ABC	2.63	1.61–4.29	0.0001
DTG start in 2016, *vs.* in 2014/2015	8.93	3.76–21.28	< 0.0001
Neuropsychiatric AEs			
Female, *vs.* male gender	2.64	1.23–5.65	0.01
Older age (> 60 years), *vs.* younger age	2.86	1.42–5.77	0.003
ABC with DTG initiated, *vs.* no ABC	2.42	1.38–4.24	0.002
DTG start in 2016, *vs.* in 2014/2015	11.36	4.31–29.41	< 0.0001

ABC, abacavir; CI, confidence interval.

Hoffmann et al. HIV Medicine 2017; Libre et al. CROI 2017 abstract #615;

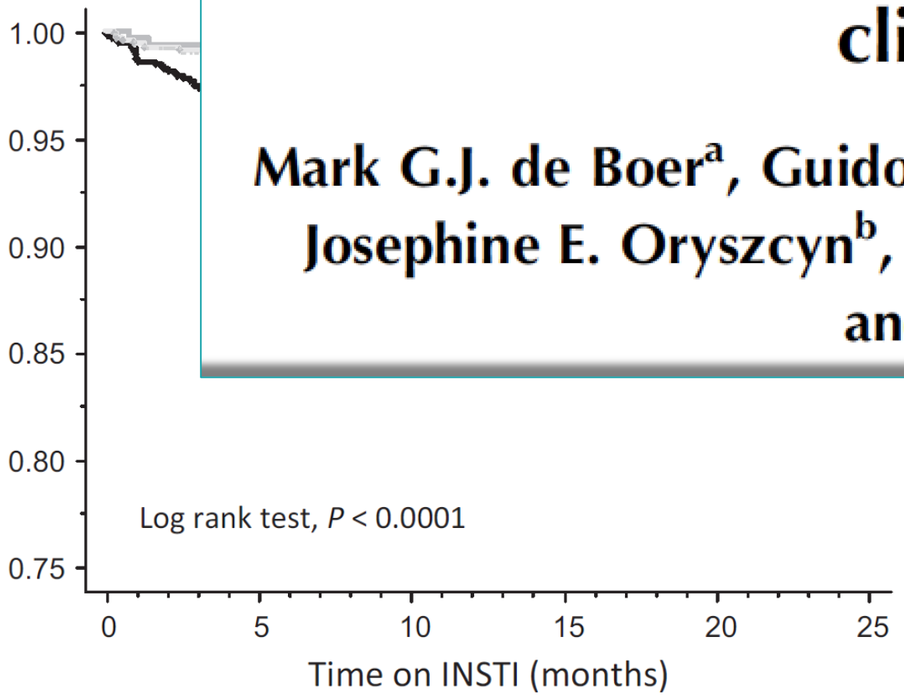
Hsu et al. CROI 2017 abstract #664

DTG in the real world…

Dolutegravir: discontinuation due to AE

Intolerance of dolutegravir-containing combination antiretroviral therapy regimens in real-life clinical practice

Mark G.J. de Boer[a], Guido E.L. van den Berk[b], Natasja van Holten[a], Josephine E. Oryszcyn[b], Willemien Dorama[a], Daoud ait Moha[b] and Kees Brinkman[b]



			P
			0.002
			< 0.001
			0.0001
			< 0.0001
Neuropsychiatric AEs			
Female, *vs.* male gender	2.64	1.23–5.65	0.01
Older age (> 60 years), *vs.* younger age	2.86	1.42–5.77	0.003
ABC with DTG initiated, *vs.* no ABC	2.42	1.38–4.24	0.002
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ABC, abacavir; CI, confidence interval.

Hoffmann et al. HIV Medicine 2017; Libre et al. CROI 2017 abstract #615;

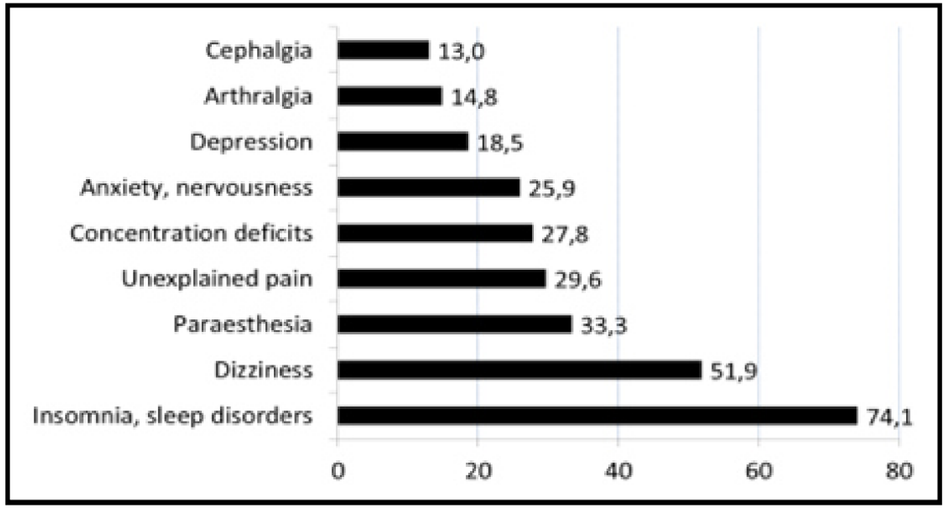
Hsu et al. CROI 2017 abstract #664

From CROI: Risk factors for neuropsychiatric events

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

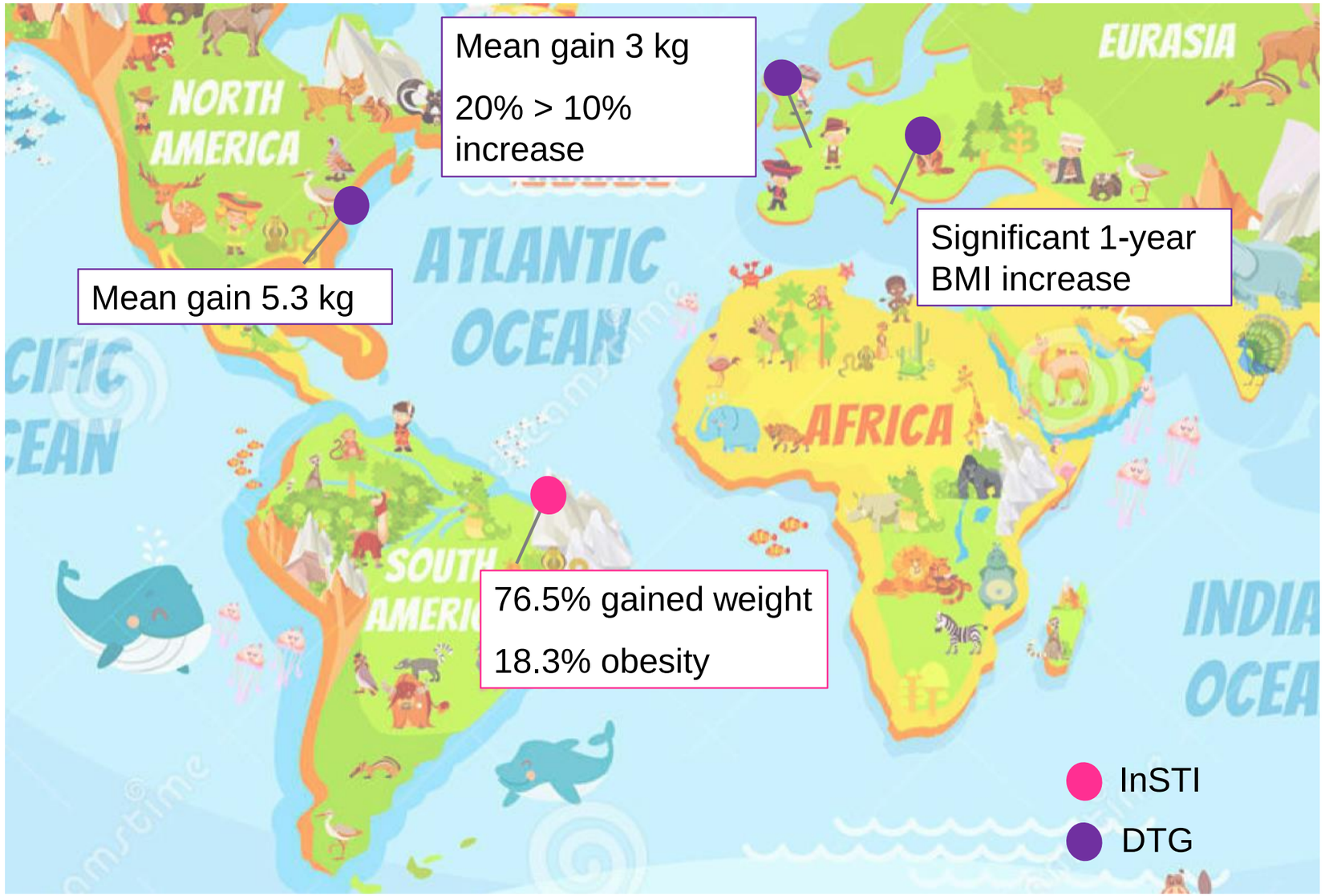
Risk factors for NPAEs leading to DTG discontinuation	RH	95 % CI	p
Female, versus male gender	2.31	1.12-4.74	0.03
Older age (> 60 years), versus younger age	2.14	1.10-4.18	0.025
Depressive disorders, versus no	1.00	0.54-1.88	0.952
Other neuropsychiatric diagnoses, versus no	0.93	0.29-3.00	0.896

Figure 3. Reasons (%) for discontinuing DTG, n=54
(mean of 2.9 symptoms/NPAEs were reported)



Hoffman et al. CROI 2018 abstract #424

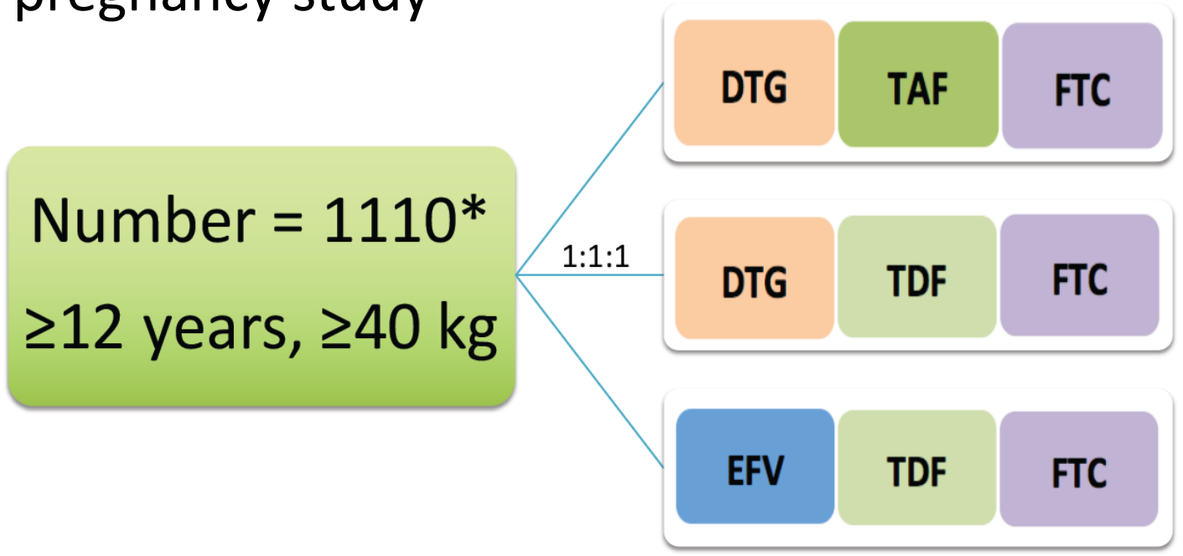
Weight gain?



Menard A et al. AIDS, June 2017; Norwood et al, JAIDS, Aug 2017; Bakal D et al. ID Week 2017; Taramasso et al. Open Forum Infectious Diseases, Nov 2017

REAL “real” world patients on ADVANCE

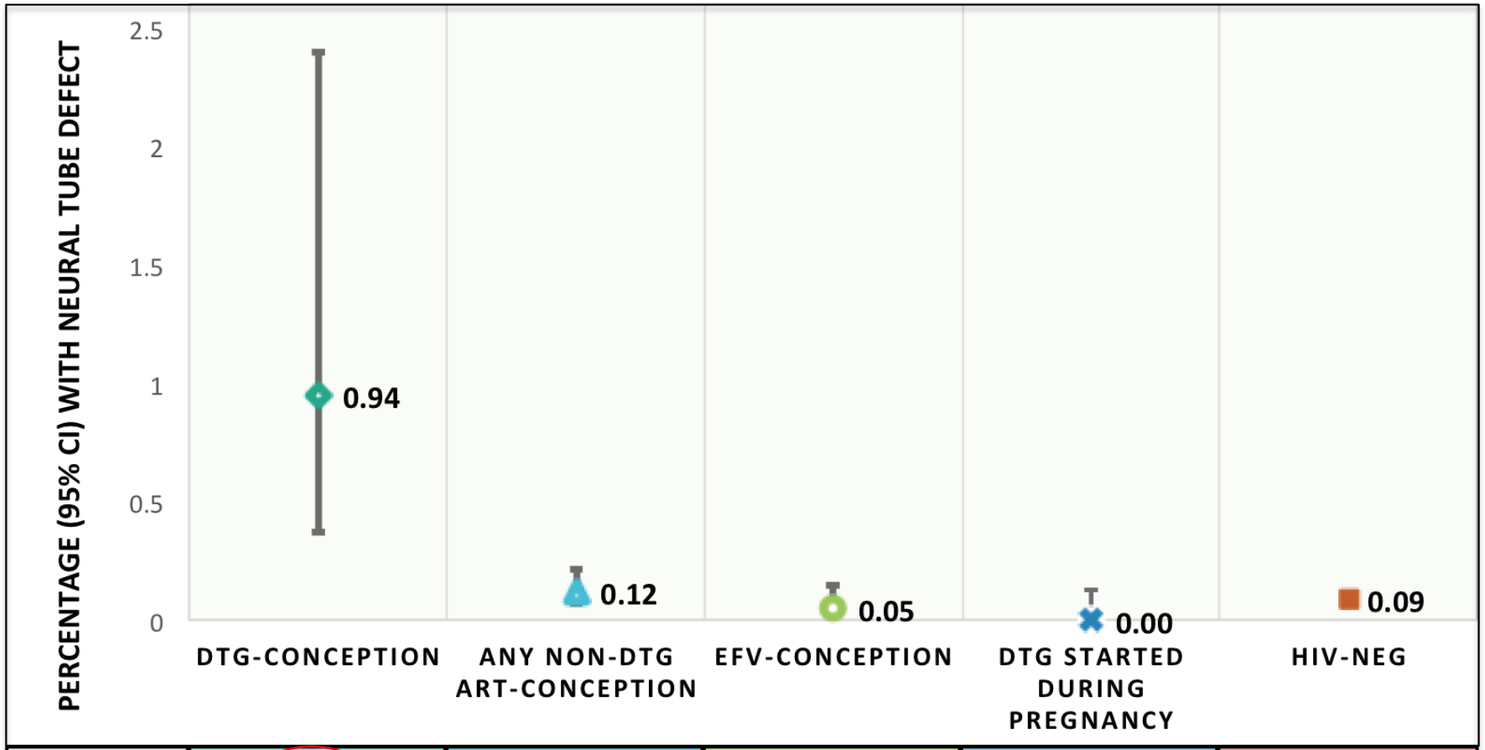
- OPTIMIZE clinical trial DTG to EFV (and TAF to TDF)
- Only RCT providing a head-to-head comparison of the current standard of care
- Aligned with NIH pregnancy study



- Non inferiority of 2 new combinations to current treatment
- Open label, randomised, single site study over 48 weeks
- * n=1110, with 90-120 in age group 12-18 years

Dolutegravir NTD signal

Tsepamo study, Botswana



	DTG-CONCEPTION	ANY NON-DTG ART-CONCEPTION	EFV-CONCEPTION	DTG STARTED DURING PREGNANCY	HIV-NEG
NTDs/Exposures	4/426	14/11,300	3/5,787	0/2.812	61/66,057
% with NTD (95% CI)	0.94% (0.37%, 2.4%)	0.12% (0.07%, 0.21%)	0.05% (0.02%, 0.15%)	0.00% (0.00%, 0.13%)	0.09% (0.07%, 0.12%)
Prevalence Difference (95% CI)	ref	**-0.82% (-0.24%, -2.3%)**	**-0.89% (-0.31%,- 2.3%)**	**-0.94% (-0.35%, -2.4%)**	**-0.85% (-0.27%, -2.3%)**

Neural tube defects in

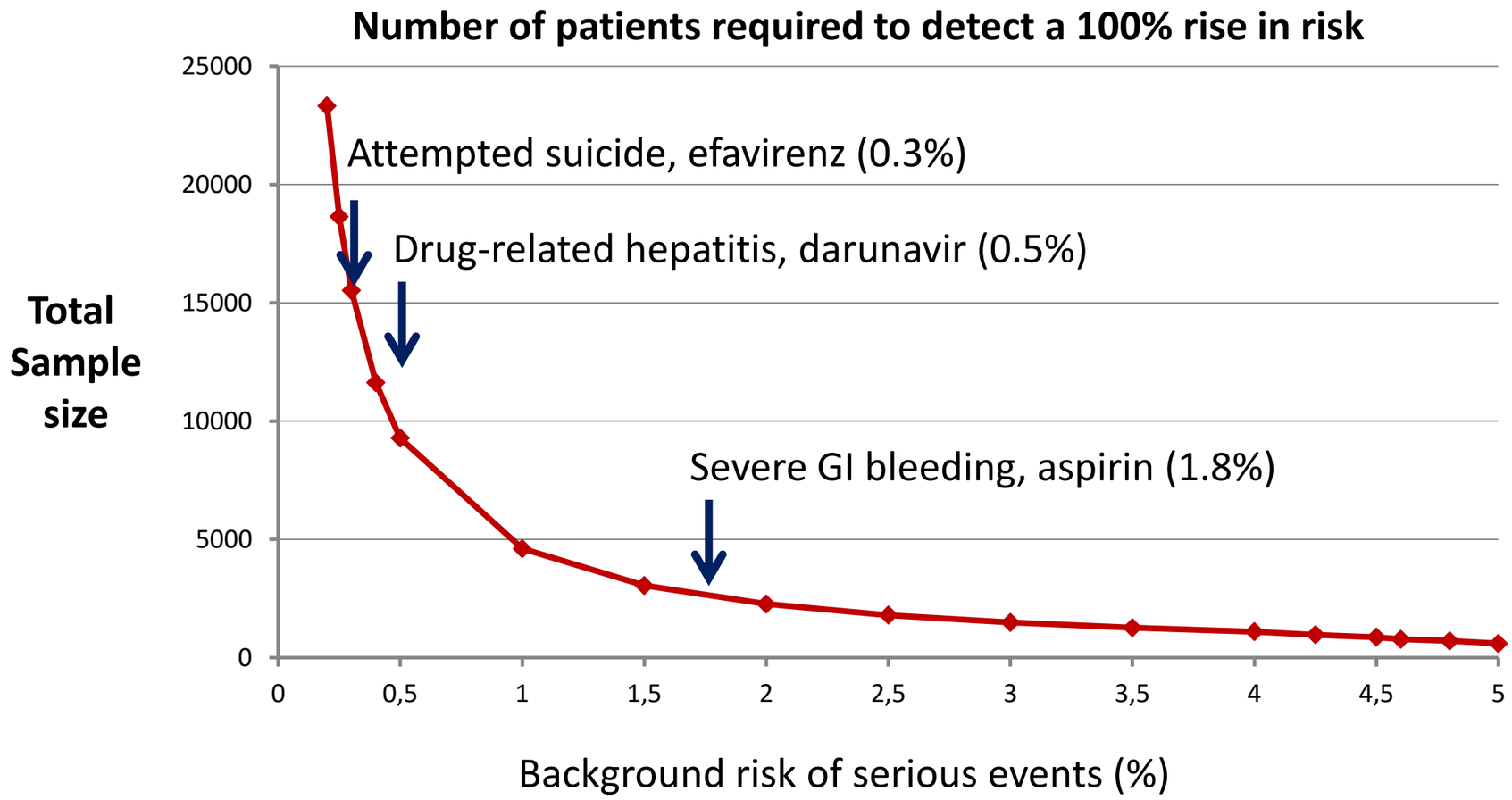
4/426 pregnancies **(0.94%)**

Updated data since 01 May 2018: 4/596 **(0.67%)**

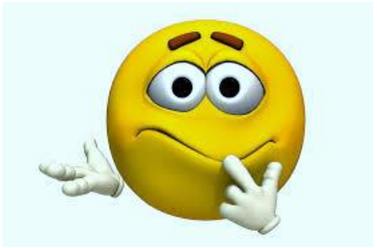
95% CI still does not overlap with other groups

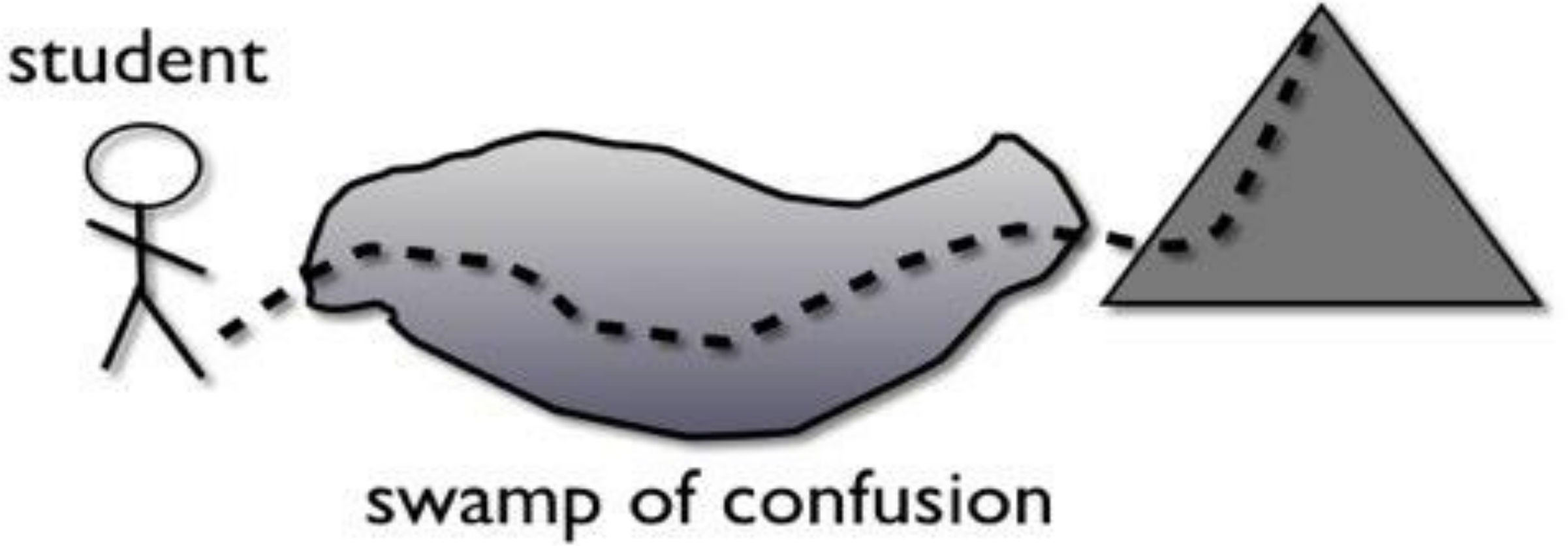
Detecting rare adverse events: numbers

Rare toxicities are often only seen after a drug has been approved: large numbers needed to detect rare but serious events

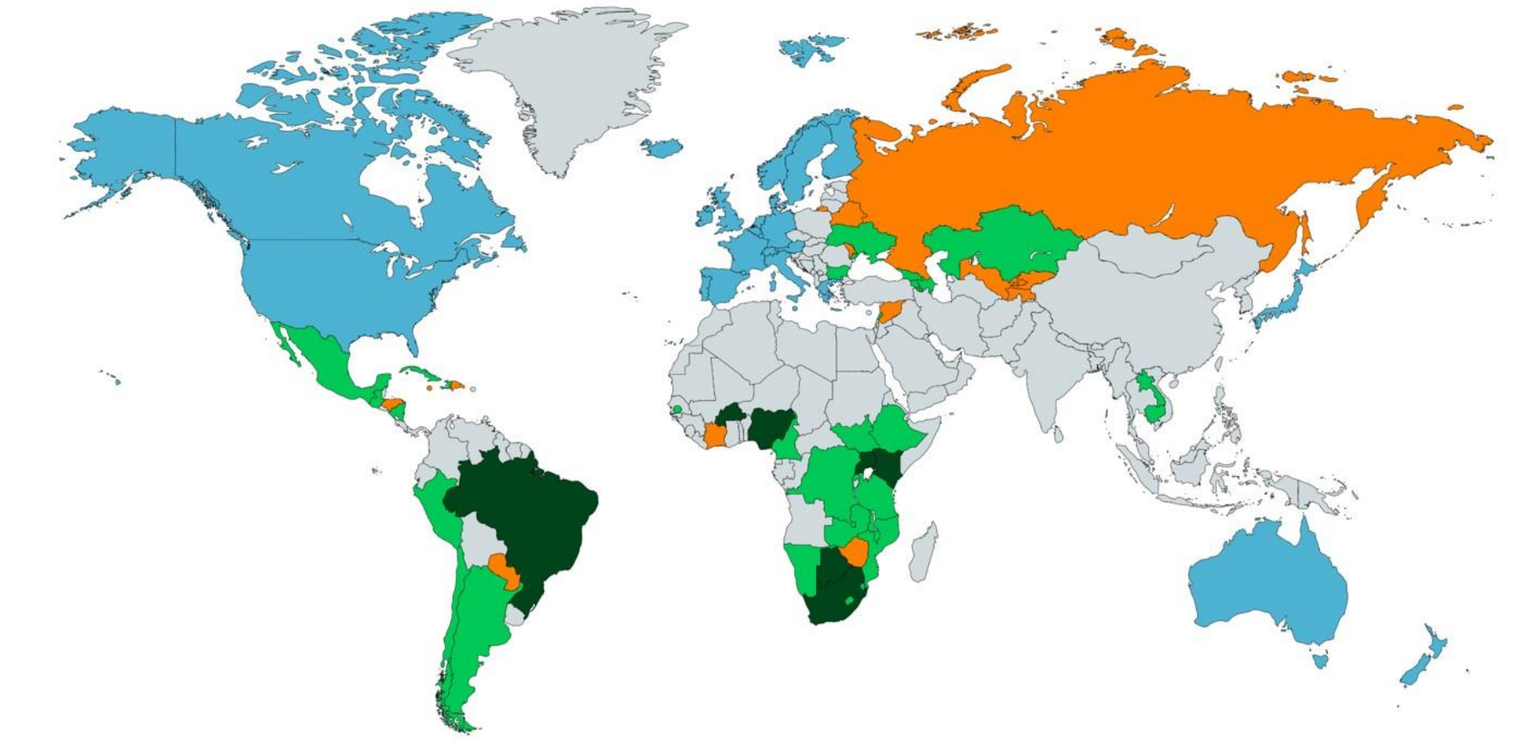


So now what?





Countries are transitioning to DTG



DTG introduced in national guidelines and procurement initiated

DTG introduction in national guidelines planned for 2018/2019

DTG introduced in national guidelines or planned for 2017/2018

High income countries

Should dolutegravir be given to 20 million people in low income countries?

Pros:	**Cons:**
Activity against NNRTI resistant HIV	Safety and efficacy profile mainly from Phase 3 trials in high income countries
Well tolerated versus EFV or DRV/r	Safety in pregnant women and TB coinfection?
Simple low cost co-formulation with TDF/3TC	Reports of IRIS and CNS adverse events?

Thanks Andy Hill!

The consequences of small differences in adverse event profiles

- If a drug is given to 20 million people, and there is an excess risk of 0.5% (1 in 200) for an AE such as CVD, IRIS or suicide
- This could lead to **100,000** people developing this adverse event
- So we need to be very careful when we conduct analyses of safety

Thanks Andy Hill!

Drug safety – keeping it balanced

Too cautious	Too liberal
Overinterpreting trends	Hiding data
Paranoia	Missing important trends
Scare-mongering	Allowing toxicity to happen
New drugs not used	Not updating analyses

Thanks Andy Hill!

Efavirenz controversy: conflicting evidence

Preclinical data

- NTDs in primate study

Clinical data: T1 EFV exposure

- 4 retrospective
- 1 prospective

case report of NTDs in humans

Meta analysis (2011):

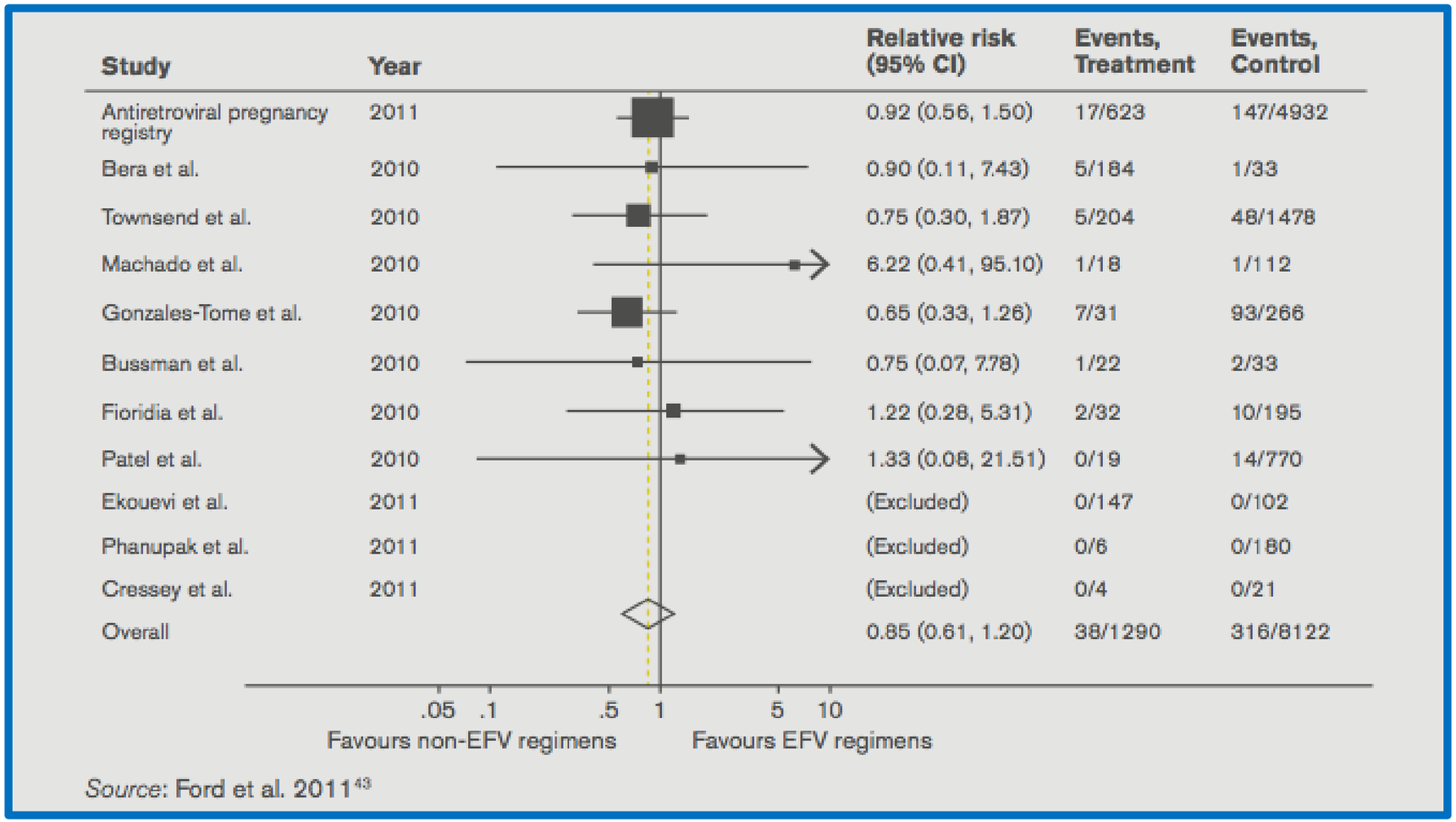
1 NTD

ncidence: 0.7 (95% CI 0.002 – 0.39%

= NO association

1. Ford N, *et al*. AIDS. 2011;25:2301-2304. .

Relative risk of birth defects: EFV vs. non-EFV regimens



Source: Ford et al. 2011[43]

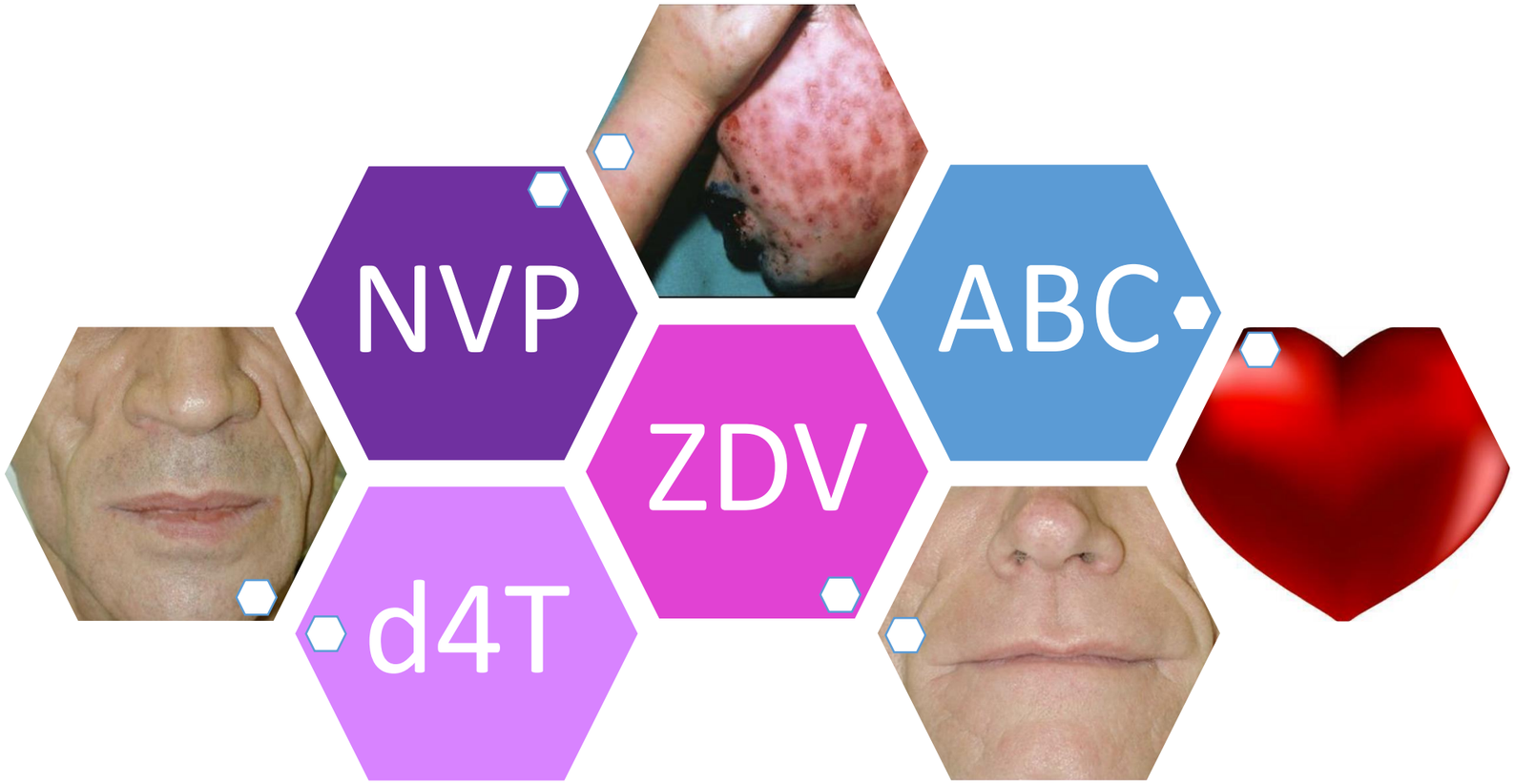
1. Ford N, *et al*. AIDS. 2011;25:2301-2304. .

We have been here before…

… more than once

Drug that appeared to be well tolerated

Toxicity issues appeared several years after the drugs were launched



The need to for ongoing, locally relevant pharmacovigilance

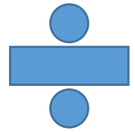
Pharmacovigilance: “Detection, assessment, understanding and prevention of short and long term adverse effects of medicines”

- Clinical studies short
- Comorbidities, concomitant medicines, genetic variability
- Risk versus benefit:
  - early treatment initiation
  - prevention
- Focus on **serious adverse drug reactions (ADRs)**
  - Resulting in hospitalisation and death
  - Treatment limiting ADRs- drug substitutions

Thanks Karen Cohen!

Spontaneous reporting

- Signal detection
  - e.g Interstitial nephritis lopinavir/r
- ADRs that trouble HCWs
  - Guide HCW training and clinical support
  - Nurse-driven services
- Need accessible and responsive systems
  - Telephonic and online reporting in addition to paper-based
  - Prompt, individualised feedback and clinical support
- Does not give prevalence/incidence
  - No denominator; numerator quite dodgy often



Thanks Karen Cohen!

Chugley et al 2015 *AIDS* 29:503. Njuguna et al 2015 *Drug Saf* doi:10.1007/s40264-015-0359-8

The way forward

Well powered prospective observational cohorts of sufficient duration

- Pharmacovigilance
- Identify less frequent AEs / treatment-limiting toxicities
- Enrol populations excluded from registrational studies
- Ideally in parallel to registration studies once a specified level of safety confirmed (phase 3)
  - Included as part of registrational dossiers?

Pharmacovigilance: “Detection, assessment, understanding and prevention of short and long term adverse effects of medicines”

Thanks

- Francois Venter
- Stuart Ali
- Andrew Hill
- Polly Clayden
- Karen Cohen

ARV surveillance

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