- **Looking back**
- **New WHO Guidelines**
- **„newer“ drugs / formulations**

Cornelia Staehelin, Bern

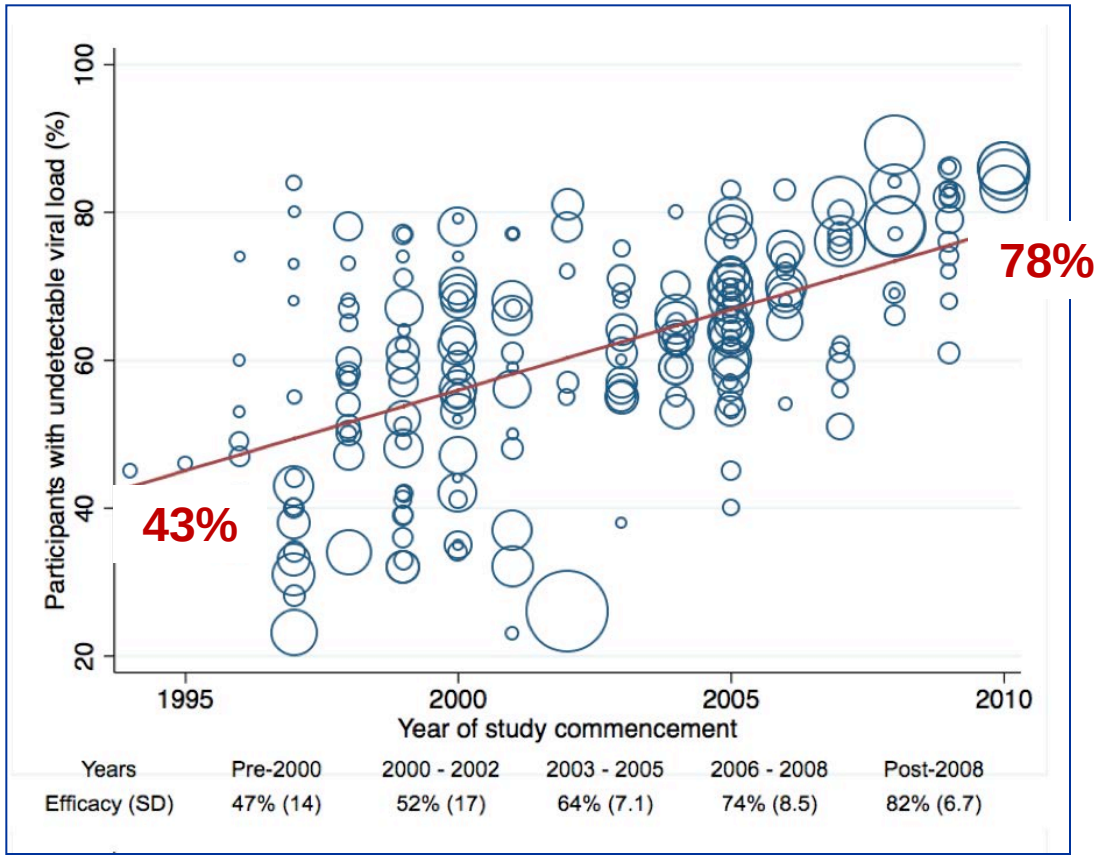
IAS 2013
KUALA LUMPUR, MALAYSIA

Efficacy of initial combination antiretroviral therapy: a meta-analysis

Frederick Lee[1], Janaki Amin[2], Andrew Carr[1]
Centre for Applied Medical Research, St Vincent's Hospital[1]
Kirby Institute, University of New South Wales[2]
Sydney, Australia

Oral abstract session: WEAB0104

Efficacy of ART over time



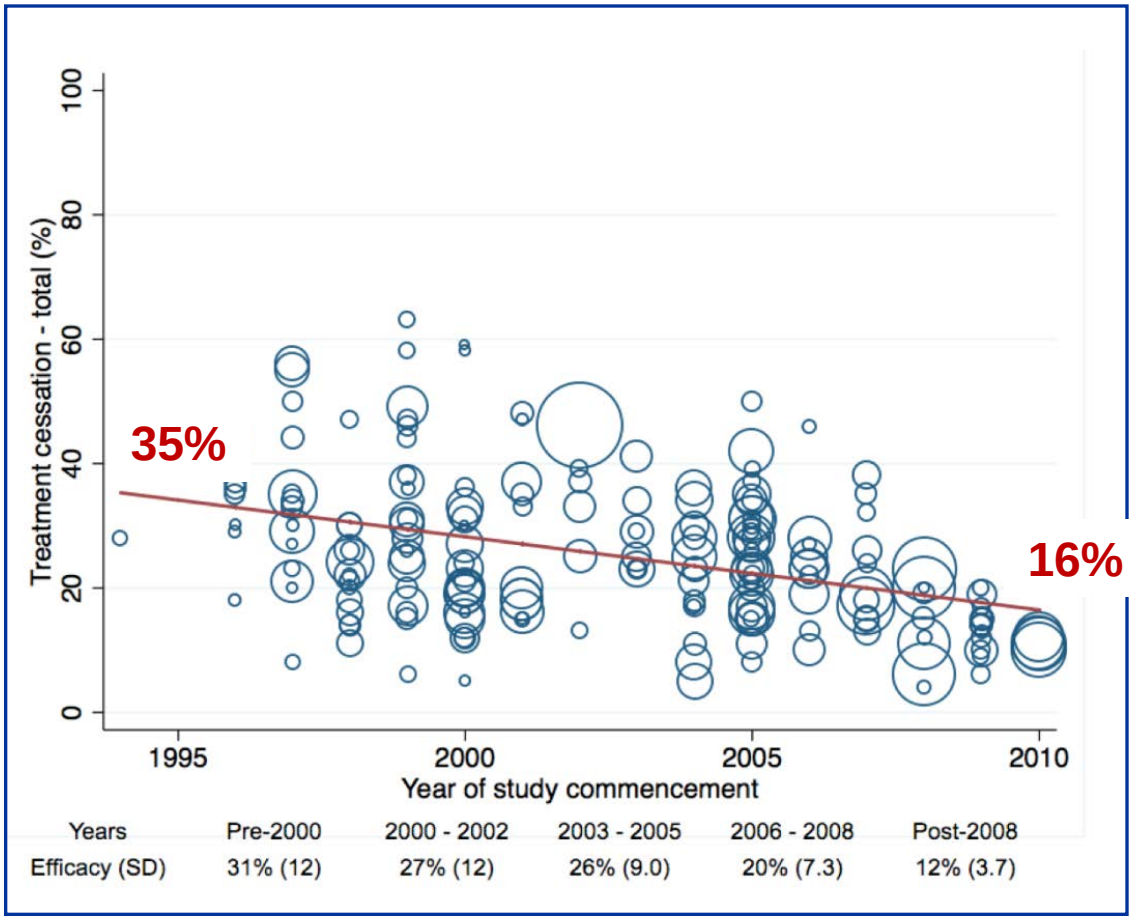
participants: 40’124
studies randomised: 36’534 (91% weight of data)

Inclusion:
- treatment-naive, HIV-1
- Only prospective design
- (no retrosp. / cross-section)
- Min. 48 weeks
- ITT

Exclusion:
- Non-recommended regimens (ie. PI-mono/dual NRTI)
- DOT

Oral abstract session: WEAB0104

Cessation – changes over time

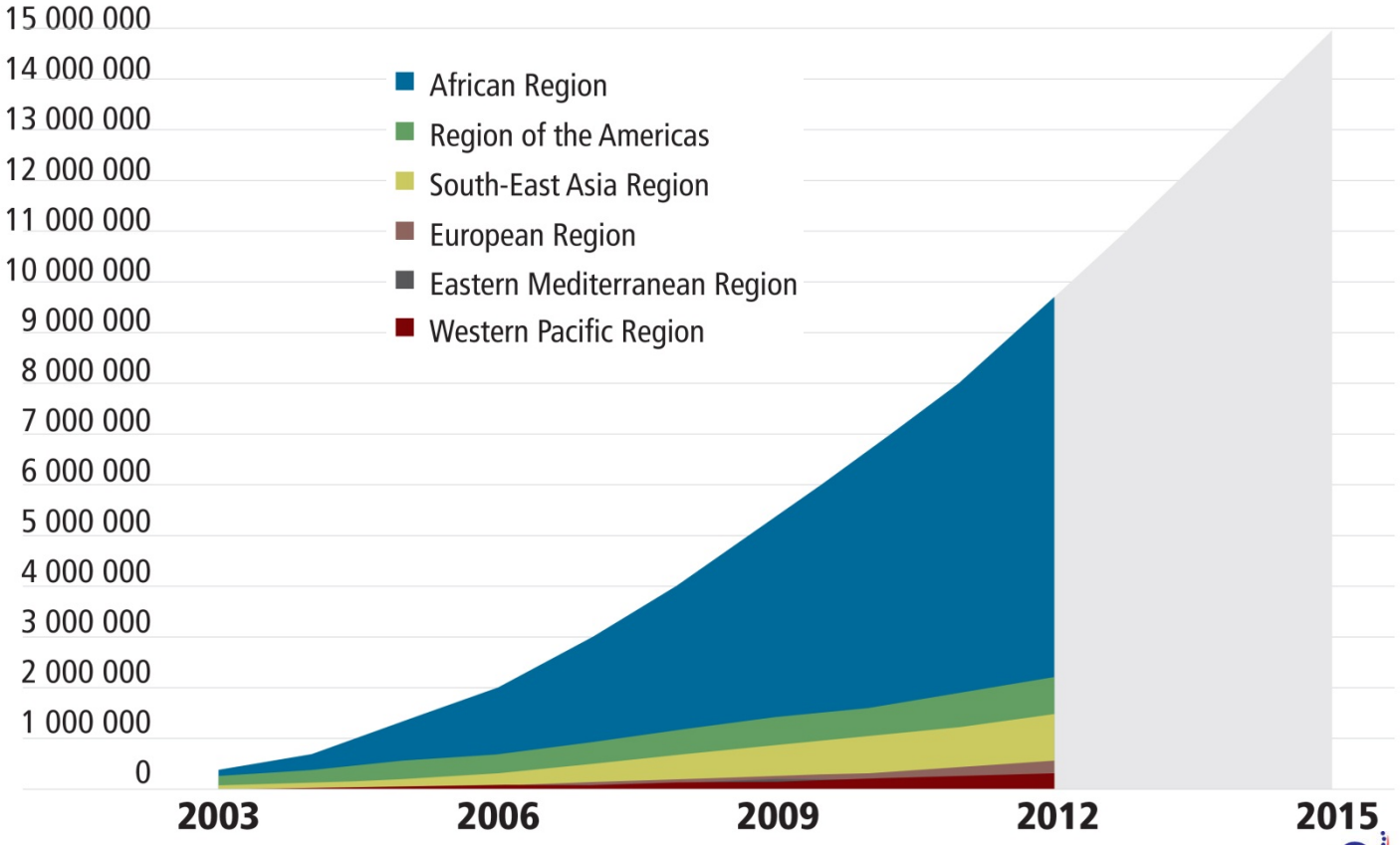


Years	Pre-2000	2000 - 2002	2003 - 2005	2006 - 2008	Post-2008
Efficacy (SD)	31% (12)	27% (12)	26% (9.0)	20% (7.3)	12% (3.7)

And for more: http://pag.ias2013.org/session.aspx?s=17#4

9.7 million people on ART by end of 2012 – 1.6 million more than at the end of 2011

Actual and projected numbers of people receiving antiretroviral therapy in low- and middle-income countries, and by WHO Region, 2003–2015



Source: 2013 Global AIDS Response Progress Reporting (WHO/UNICEF/UNAIDS).

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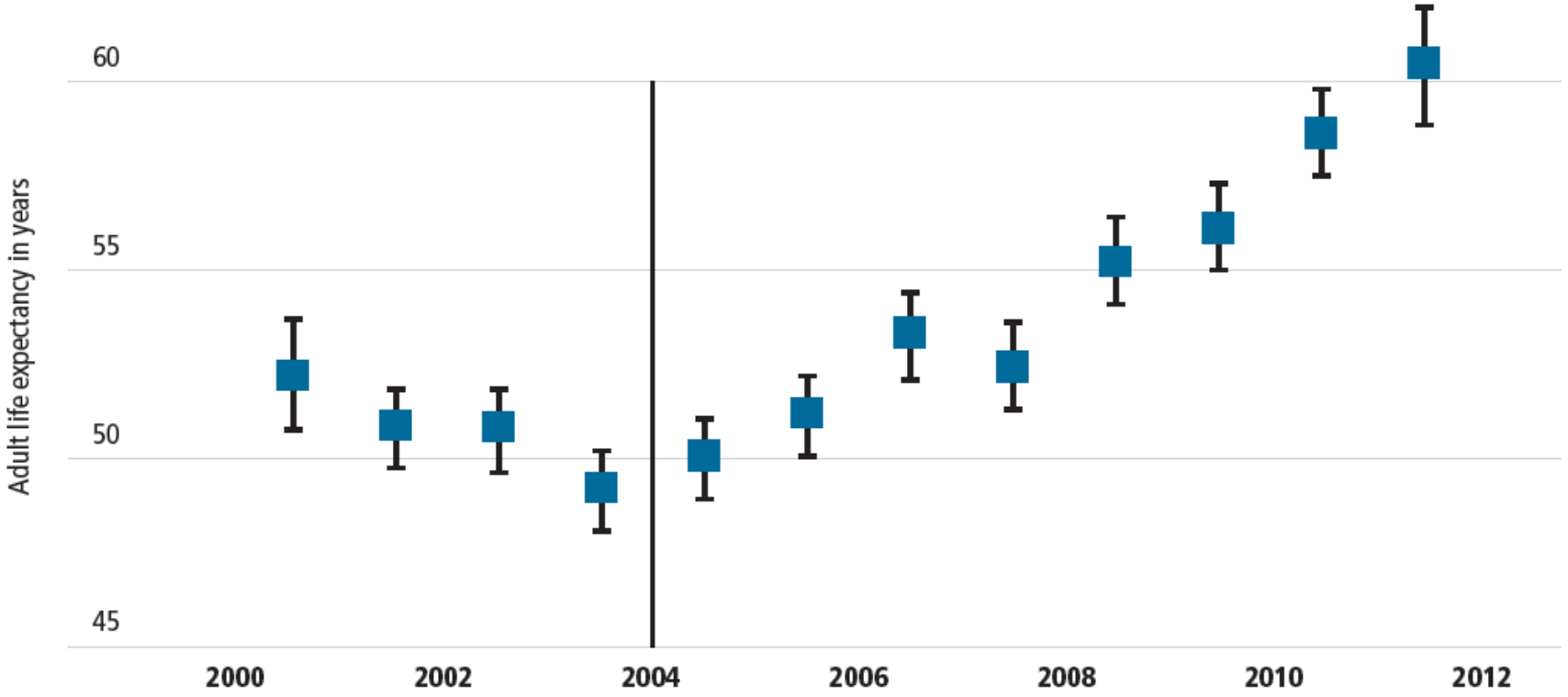
World Health Organization

Life expectancy increase in rural South Africa

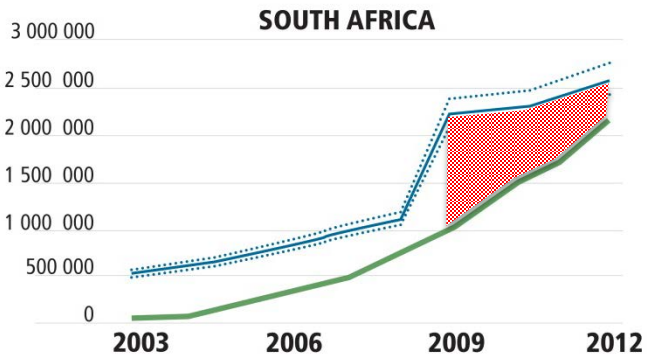
Average adult life expectancy, rural South Africa, 2000–2011

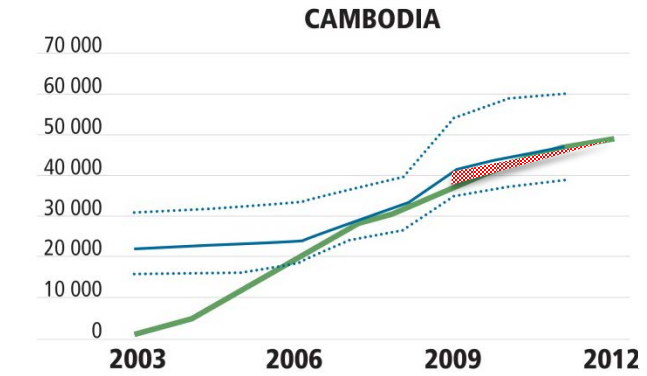


Source: Bor et al. Increases in adult life expectancy in rural South Africa: valuing the scale-up of HIV treatment. Science, 2013, 339:961–965.

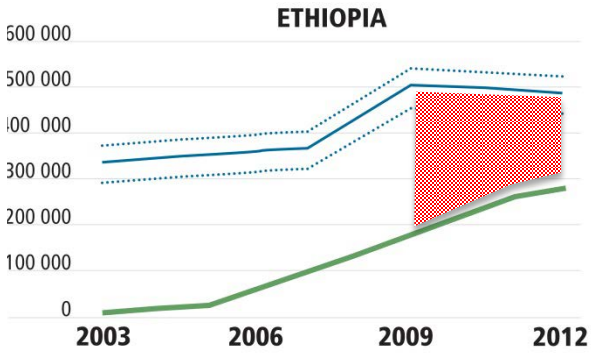
Countries are at different stages of scale-up

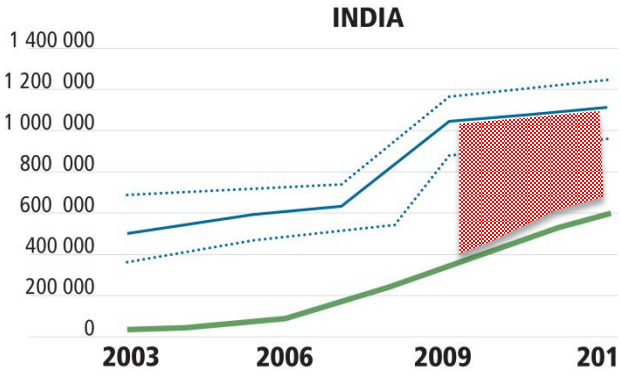
Gap closed



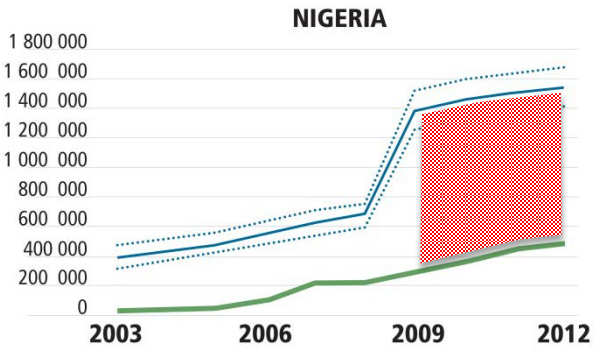


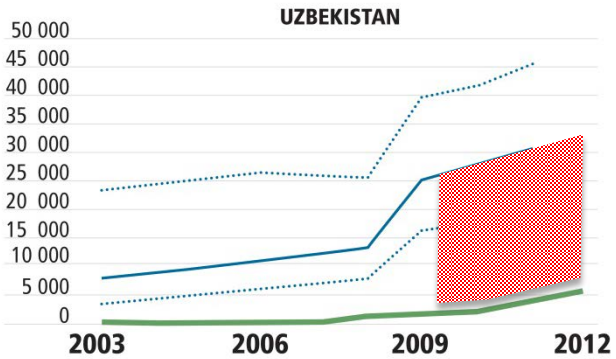
Gap closing





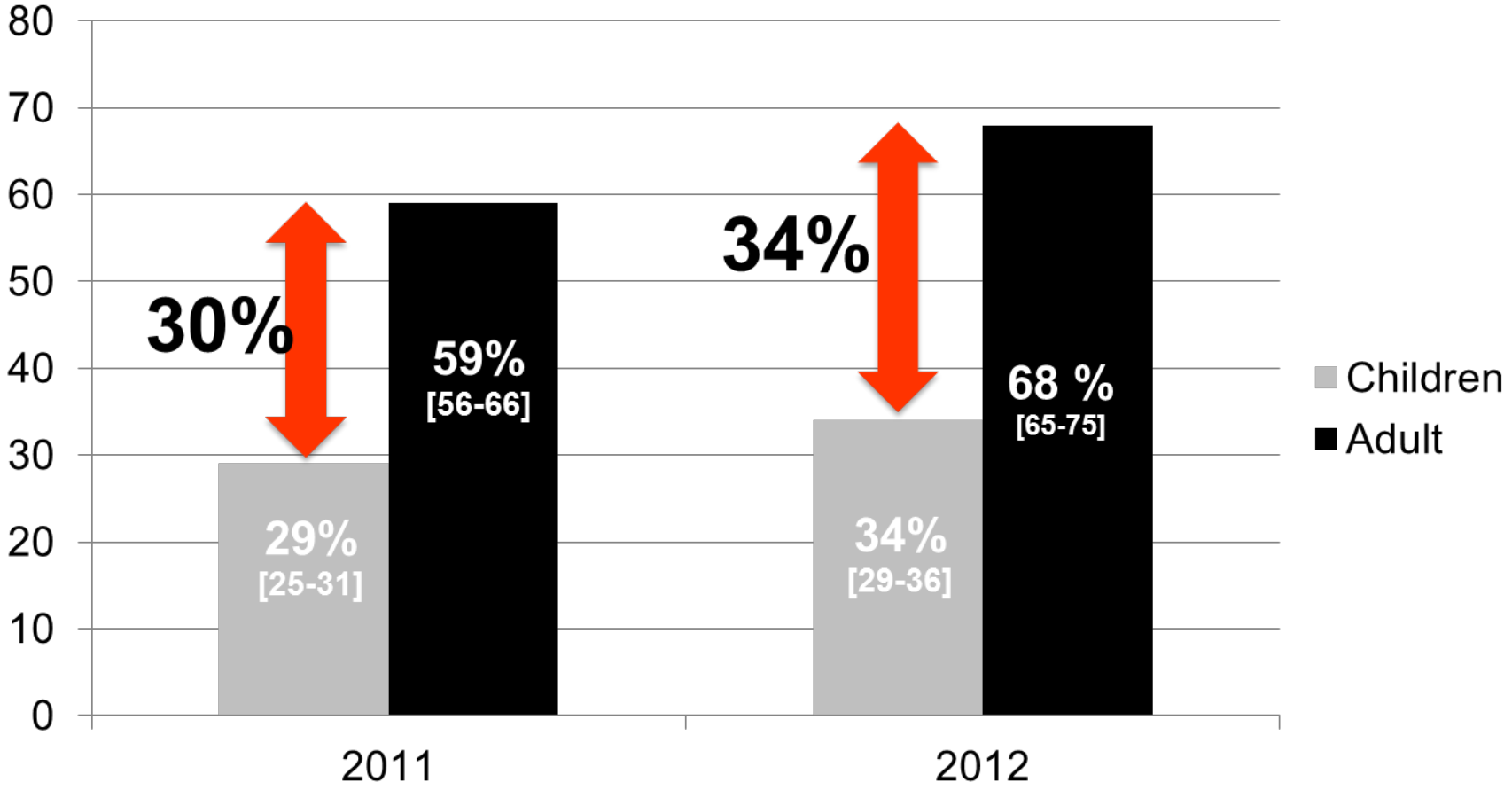
Gap constant or widening





Source: 2013 Global AIDS Response Reporting (WHO/UNICEF/UNAIDS) and 2012 UNAIDS/WHO estimates.

The gap between adult and child ART coverage in 20 high burden countries is widening



Source: Global AIDS Response Progress Reporting (WHO/UNICEF/UNAIDS) and 2013 UNAIDS estimates.

HIV TREATMENT

Summary of Changes in Recommendations When to Start in Adults

TARGET POPULATION *(ARV-NAIVE)*	2010 ART GUIDELINES	2013 ART GUIDELINES	STRENGTH OF RECOMMENDATION & QUALITY OF EVIDENCE
HIV+ ASYMPTOMATIC	CD4 ≤350 cells/mm^3	**CD4 ≤500 cells/mm^3 (CD4 ≤ 350 cells/mm^3 as a priority)**	***Strong, moderate-quality evidence*** NEW
HIV+ SYMPTOMATIC	WHO clinical stage 3 or 4 regardless of CD4 cell count	No change	***Strong, moderate-quality evidence***

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PREGNANT AND BREASTFEEDING WOMEN WITH HIV	CD4 ≤350 cells/mm^3 or WHO clinical stage 3 or 4	**Regardless of CD4 cell count or WHO clinical stage**	***Strong, moderate-quality evidence*** NEW

HIV TREATMENT

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PREGNANT AND BREASTFEEDING WOMEN WITH HIV	CD4 ≤350 cells/mm^3 or WHO clinical stage 3 or 4	**Regardless of CD4 cell count or WHO clinical stage**	***Strong, moderate-quality evidence*** NEW
HIV/TB CO-INFECTION	Presence of active TB disease, regardless of CD4 cell count	No change	***Strong, low-quality evidence***
HIV/HBV CO-INFECTION	Evidence of chronic active HBV disease, regardless of CD4 cell count	**Evidence of severe chronic HBV liver disease, regardless of CD4 cell count**	***Strong, low-quality evidence*** NEW

HIV TREATMENT

Summary of Changes in Recommendations When to Start in Adults

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PREGNANT AND BREASTFEEDING WOMEN WITH HIV	CD4 ≤350 cells/mm^3 or WHO clinical stage 3 or 4	**Regardless of CD4 cell count or WHO clinical stage**	***Strong, moderate-quality evidence*** NEW
HIV/TB CO-INFECTION	Presence of active TB disease, regardless of CD4 cell count	No change	***Strong, low-quality evidence***
HIV/HBV CO-INFECTION	Evidence of chronic active HBV disease, regardless of CD4 cell count	**Evidence of severe chronic HBV liver disease, regardless of CD4 cell count**	***Strong, low-quality evidence*** NEW
HIV+ PARTNERS IN SD COUPLE	No recommendation established	**Regardless of CD4 cell count or WHO clinical stage**	***Strong, high-quality evidence*** NEW

Summary of Changes in Recommendations: What to Start in Adults

FIRST-LINE REGIMENS (PREFERRED ARV REGIMENS)			
TARGET POPULATION	**2010 ART GUIDELINES**	**2013 ART GUIDELINES**	**STRENGTH & QUALITY OF EVIDENCE**
HIV+ ADULTS	AZT or TDF + 3TC (or FTC) + EFV or NVP	**TDF + 3TC (or FTC) + EFV** (as fixed dose combination)	***Strong, moderate-quality evidence*** NEW
HIV+ PREGNANT WOMEN	AZT + 3TC + NVP or EFV		
HIV/TB CO-INFECTION	AZT or TDF + 3TC (or FTC) + EFV		
HIV/HBV CO-INFECTION	TDF + 3TC (or FTC) + EFV		

HIV TREATMENT

Summary of changes to recommendations: What ART to Switch to

HIV/AIDS Department

TARGET POPULATION	WHAT TO SWITCH IN ADULTS (PREFERRED REGIMENS)			
	2010 ART GUIDELINES		2013 ART GUIDELINES	STRENGTH & QUALITY OF EVIDENCE
HIV+ ADULTS AND ADOLESCENTS	If d4T or AZT used in first-line	TDF + 3TC (or FTC) + ATV/r or LPV/r	No change	*strong, moderate-quality evidence*
	If TDF used in first-line	AZT + 3TC + ATV/r or LPV/r	No change	*strong, moderate-quality evidence*
HIV+ PREGNANT WOMEN	Same regimens recommended for adults		No change	*strong, moderate-quality evidence*
HIV/TB CO-INFECTION	If rifabutin available	Same regimens as recommended for adults	No change	*strong, moderate-quality evidence*
	If rifabutin not available	NRTI backbone plus LPV/r or SQV/r with adjusted dose of RTV (i.e., LPV/r 400mg/400mg BID or SQV/r 400mg/400mg BID)	No change	*strong, moderate-quality evidence*
HIV/HBV CO-INFECTION	AZT + TDF + 3TC (or FTC) + (ATV/r or LPV/r)		No change	*strong, moderate-quality evidence*

HIV TREATMENT

Summary of Adult Guidelines

Topic	2002	2003	2006	2010	2013
When to start	CD4 ≤200	CD4 ≤ 200	CD4 ≤ 200 - Consider 350 - CD4 ≤ 350 for TB	CD4 ≤ 350 -Irrespective CD4 for TB and HBV	**CD4 ≤ 500** -Irrespective CD4 for TB, HBV, PW and SDC - **CD4 ≤ 350 as priority**
1st Line	8 options - AZT preferred	4 options - AZT preferred	8 options - AZT or TDFpreferred - d4T dose reduction	6 options &FDCs - AZT or TDF preferred - d4T phase out	**1 preferred option & FDCs** - TDF and EFV preferred across all populations
2nd Line	Boosted and non-boosted PIs	Boosted PIs -IDV/r LPV/r, SQV/r	Boosted PI - ATV/r, DRV/r, FPV/r LPV/r, SQV/r	Boosted PI - Heat stable FDC: ATV/r, LPV/r	**Boosted PIs** - Heat stable FDC: ATV/r, LPV/r
3rd Line	None	None	None	DRV/r, RAL, ETV	**DRV/r, RAL, ETV**
Viral Load Testing	No	No (Desirable)	Yes (Tertiary centers)	Yes (Phase in approach)	**Yes** (preferred for monitoring, use of PoC, DBS)

Earlier initiation

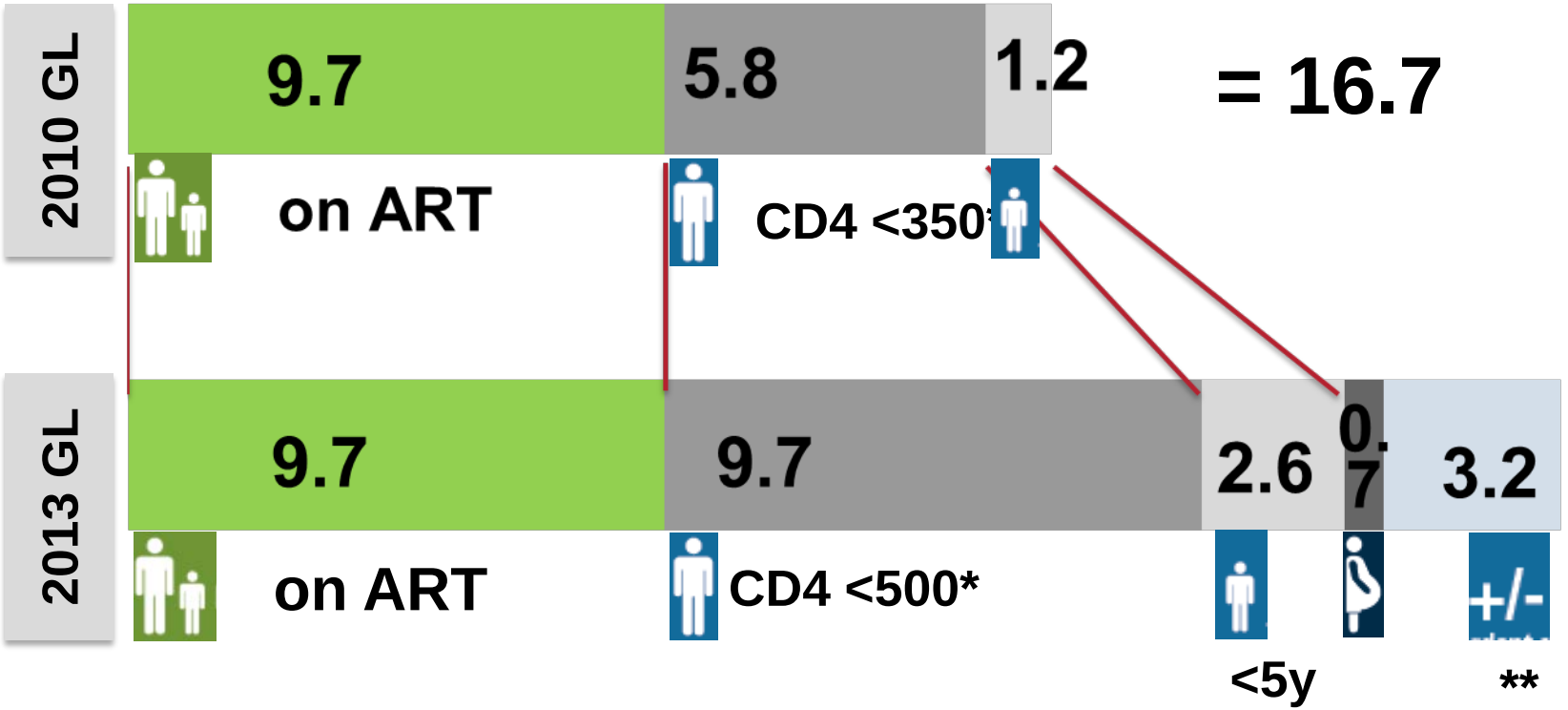
Simpler treatment

Less toxic, more robust regimens

Better monitoring

Switch to 2013 guidelines will increase eligibility from 16.7 to 25.9 million people globally

Figures based on end of 2012 epidemic situation



* incl. co-infected with TB or HBV

** only CD4>500, others included in adults

What's new?

First study of repeat dose co-administration of GSK1265744 and TMC278 long-acting parenteral nanosuspensions: pharmacokinetics, safety, and tolerability in healthy adults

W. Spreen[1], P. Williams[2], D. Margolis[1], S. Ford[1], H. Crauwels[2], Y. Lou[1], E. Gould[1], M. Stevens[2], S. Piscitelli[1]

[1]GlaxoSmithKline, Infectious Diseases Research & Development, Research Triangle Park, United States, [2]Janssen Infectious Diseases BVBA, Beerse, Belgium

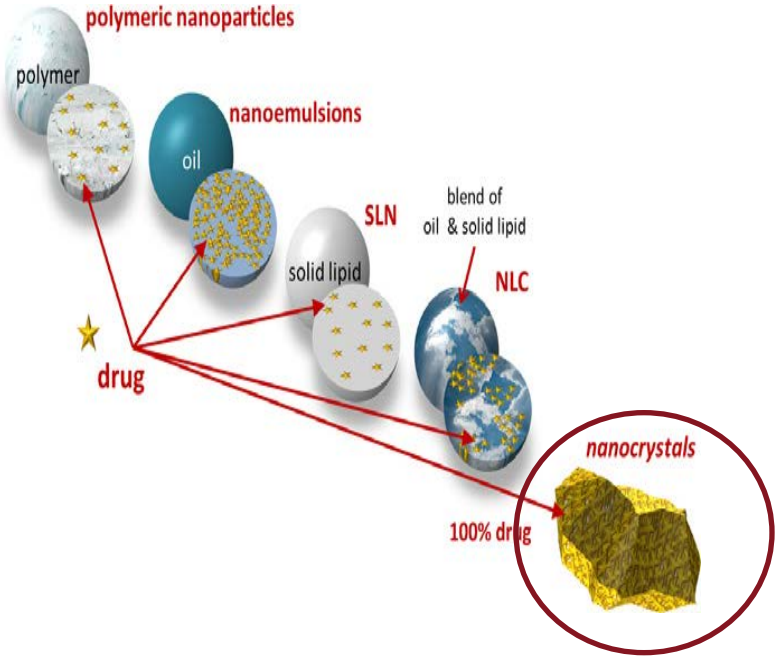
- GSK744:
  - INI, analogue of dolutegravir
  - P.o. at 5mg and 30mg/d: >2.2log$_{10}$ reduction in 10 day monotherapy study

- TMC278 = Rilpivirine as long-acting (LA) nanosuspension

- Possible applications:
  - HIV-treatment if need for LA substances
  - PrEP?

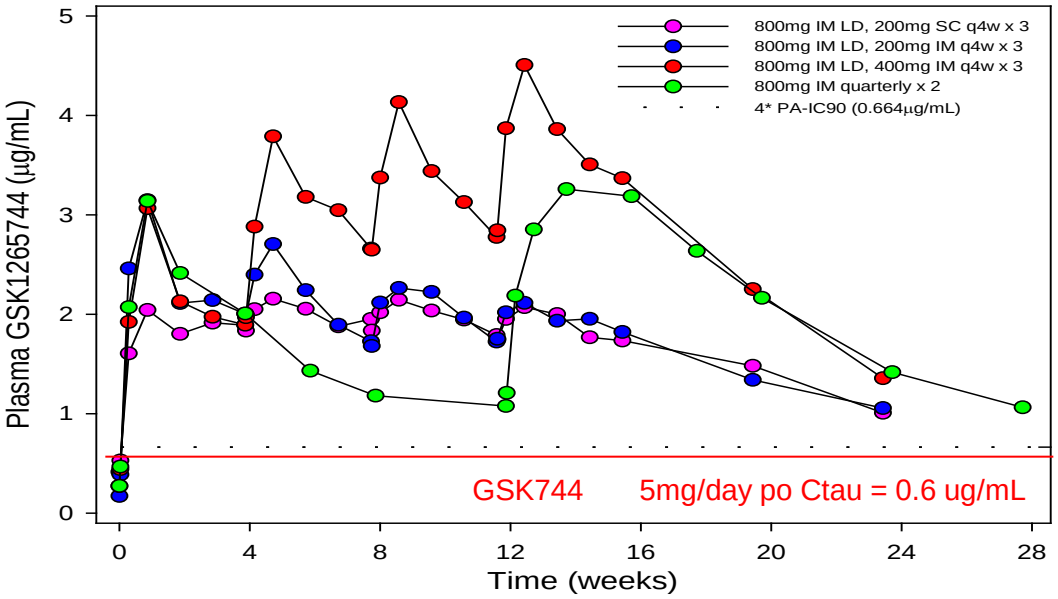
GSK744 and TMC278 Nanosuspensions

- Drug nanocrystal suspended in liquid = nanosuspension
- Nanomilled to increase surface area and drug dissolution rate
- Allows ~100% drug loading (vs. matrix approaches) for lower inj. volumes



R H. Müller, et al. European Journal of Pharmaceutics and Biopharmaceutics 78 (2011) 1-9

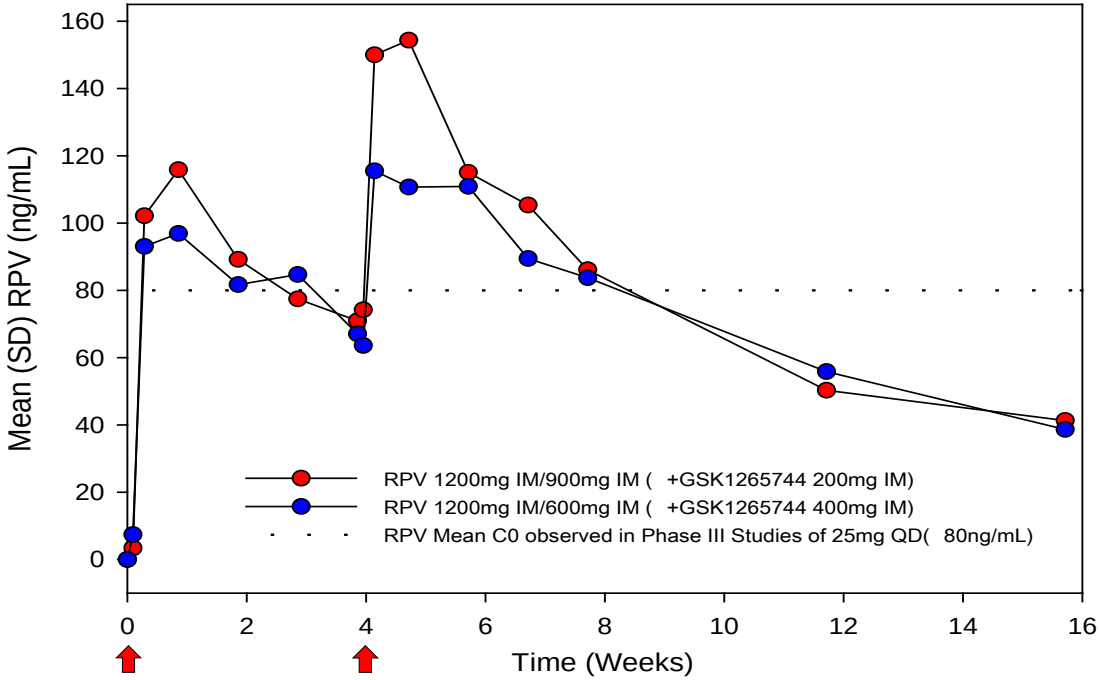
Mean GSK744 plasma concentration-time profiles



= q 28 day injection

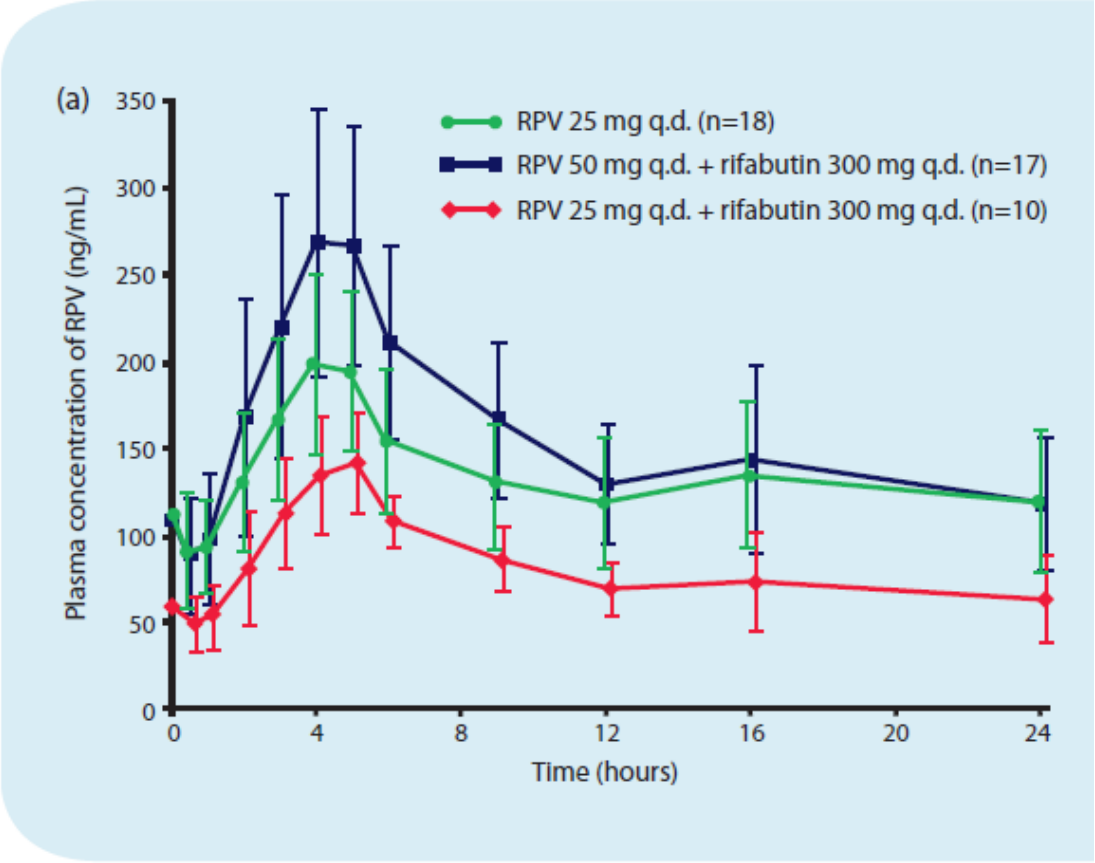
= q 84 day injection

Mean RPV plasma concentration-time profiles



= q 28 day injection

Pharmacokinetics of Rilpivirine with Rifabutin - Phase I trial

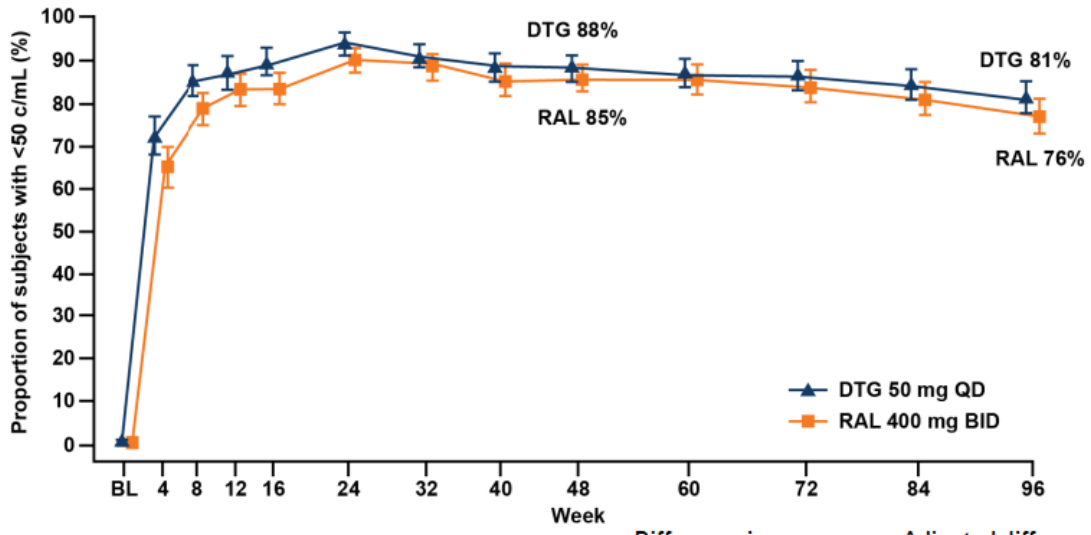


Rilpivirin 50mg with Rifabutin 300mg gives adequate plasma levels of RPV

Poster MOPE030, IAS 2013

SPRING-2: Dolutegravir vs. RGV

Figure 2. Virologic Success (HIV-1 RNA <50 c/mL) Over 96 Weeks



Treatment	Number of responders/ total assessed, n (%)	Difference in proportion (95% CI) (DTG - RAL)	Adjusted difference in proportion (95% CI) (DTG - RAL)
DTG 50 mg QD	332/411 (81)	4.4% (-1.2%, 10.0%)	4.5% (-1.1%, 10.0%)
RAL 400 mg BID	314/411 (76)		

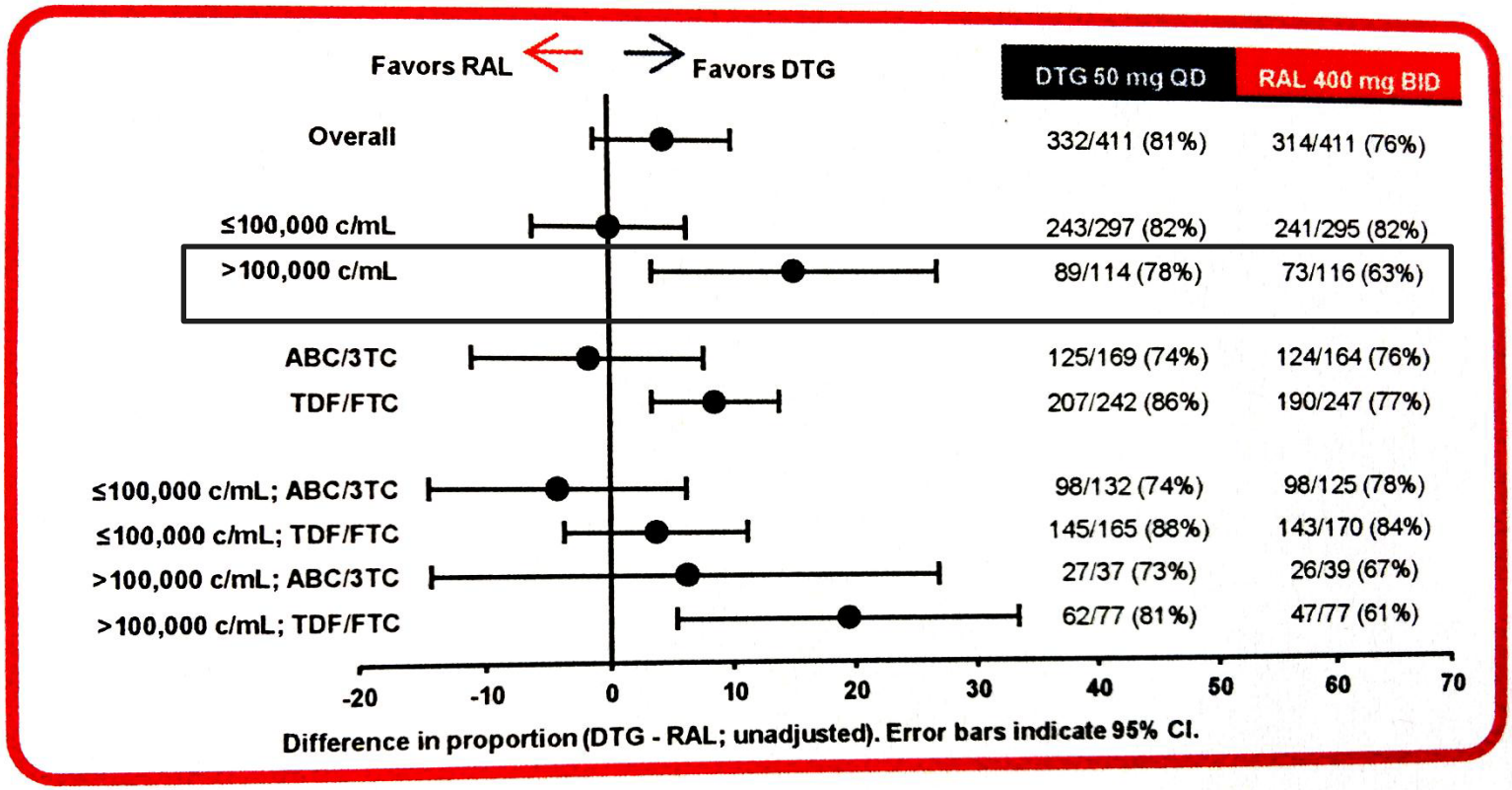
Error bars indicate 95% CI

- The lower end of the 95% CI (-1.1%) is greater than -10%, indicating that DTG remains non-inferior to RAL at 96 weeks.
- Non-inferiority was supported by secondary analyses.
  - Per protocol population, HIV-1 RNA <50 c/mL: DTG 83% vs RAL 80%
  - Proportion without PDVF (treatment-related discontinuation = failure): DTG 93% vs RAL 91%
- Median increase (interquartile range [IQR]) in CD4 cells/mm^3 was similar through W96: DTG, +276 cells/mm^3 (159, 402); RAL, +264 cells/mm^3 (155, 396).

Abstract TULBPE17

DTG besser bei hoher Viruslast

Figure 3. Proportion of Patients With Virologic Success



Abstract TULBPE17

…und bei Resistenzen zu 1st Gen INI?

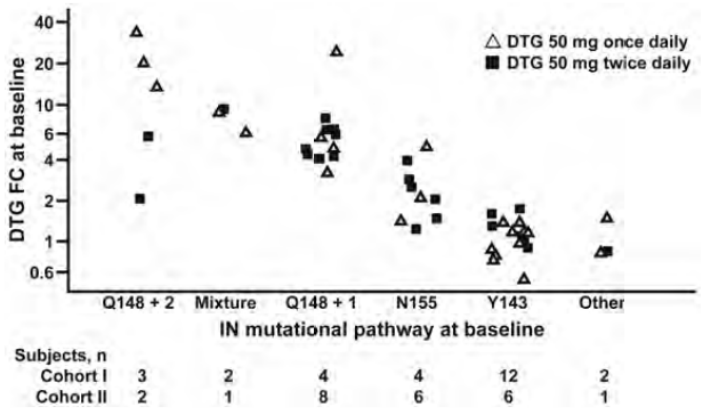


Figure 2. Dolutegravir (DTG) fold-change (FC) in 50% inhibitory concentration at baseline, by integrase (IN) mutational pathway at baseline.

Eron; JID 2013, VIKING

Q148 key mutation for DGV

MUTATIONS IN THE INTEGRASE GENE ASSOCIATED WITH RESISTANCE TO INTEGRASE STRAND TRANSFER INHIBITORS

Dolutegravir[aa]										E	G					Q			
										138	140					148			
										A	S					H			
										K	A								
Elvitegravir[bb]		T				E	T								S	Q		N	
		66				92	97								147	148		155	
		I				Q	A								G	R		H	
		A				G										H			
		K														K			
Raltegravir[cc]			L		E	T		E	G	Y					Q			N	
			74		92	97		138	140	143					148			155	
			M		Q	A		A	A	R					H			H	
								K	S	H					K				
										C					R				

??

IAS-USA
March 2013

Dolutegravir in prior INI-resistance, VIKING-3

- Inclusion: resistance to RGV / Elvitegravir

- VIKING, Cohort I, n=24: DTG 50mg **OD** → 41% response (VL <50c/ml at 24 weeks)
- VIKING, Cohort II, n=27: DTG 50mg **bid** → 75% response

- VIKING-3: DTG 50mg **bid**

Abstract TULBPE19

Table 1. Baseline Characteristics (ITT-E, N=183)

Median CD4+, cells/mm^3 (range)	140 (19-1110)
CDC class C (%)	56%
Median prior ART, y (range)	13 (0.3-25)
Median prior ARVs, n (range)	14 (3-23)
DRV/r	73%
ETR	56%
T20	49%
MVC	32%
Resistance (%)	79%
≥2 NRTIs	75%
≥1 NNRTI	70%
≥2 PIs	62%
INI resistance (%)*	100%
At screening	68%
Documented from prior INI failure	32%
Women (%)	23%
HBV and/or HCV (%)	21%
African American/African heritage (%)	27%

*INI resistance = presence of T66A/I/K, E92Q/V, Y143C/H/R, Q148H/K/R, N155H or a RAL FC >1.5 or EVG FC >2.5

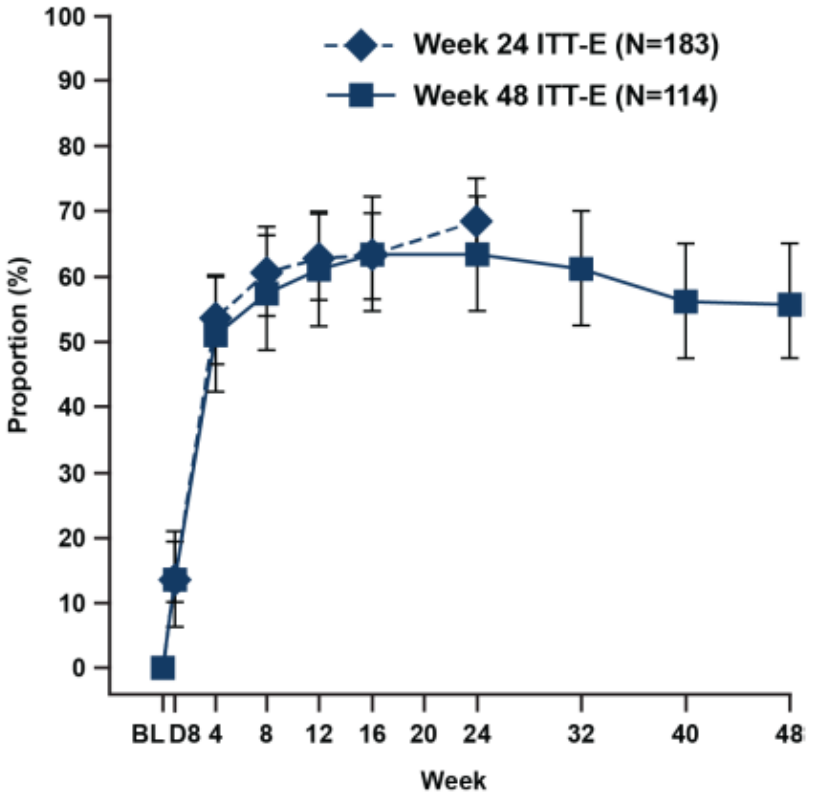
Heavily pre-treated population:

- Median yrs on ART: 13
- Low median CD4: 140 (range 19 – 1110)
- 60-80% resistance to common ART components

Abstract TULBPE19

Proportion with VL<50c/ml

Snapshot outcome	DTG 50 mg BID	
	Wk 24 ITT-E (N=183)	Wk 48 ITT-E (N=114)
Virologic success	126 (69%)	64 (56%)
Virologic non-response	50 (27%)	44 (39%)
No virologic data at data cut	7 (4%)	6 (5%)
Discontinued due to AE or death	5 (3%)	5 (4%)
Discontinued for other reasons	2 (1%)	1 (<1%)



Abstract TULBPE19

Response to DGV depends on INI baseline mutations

Table 4. Day 8 and Week 24 Responses by Baseline Resistance

Primary INI resistance mutations at BL	N	Mean HIV-1 RNA (log_{10}) change from BL (SD) at Day 8	% With <50 c/mL HIV-1 RNA at Week 24
Total	183	-1.4 (0.61)	69%
No primary mutations	60	-1.6 (0.55)	78%
T66	1	-1.9	100%
Y143	28	-1.7 (0.42)	75%
N155	33	-1.4 (0.51)	88%
≥2 Primary mutations	8	-1.4 (0.76)	50%
Q148 + 1 secondary mutation*	32	-1.1 (0.51)	59%
Q148 + ≥2 secondary mutations*	21	-1.0 (0.81)	24%

*Key secondary mutations were G140A/C/S, L74I and E138A/K/T.

- In multivariate analyses, Q148 + ≥2 mutations and increasing DTG FC were each highly correlated with smaller reductions in HIV-1 RNA (P<0.001).

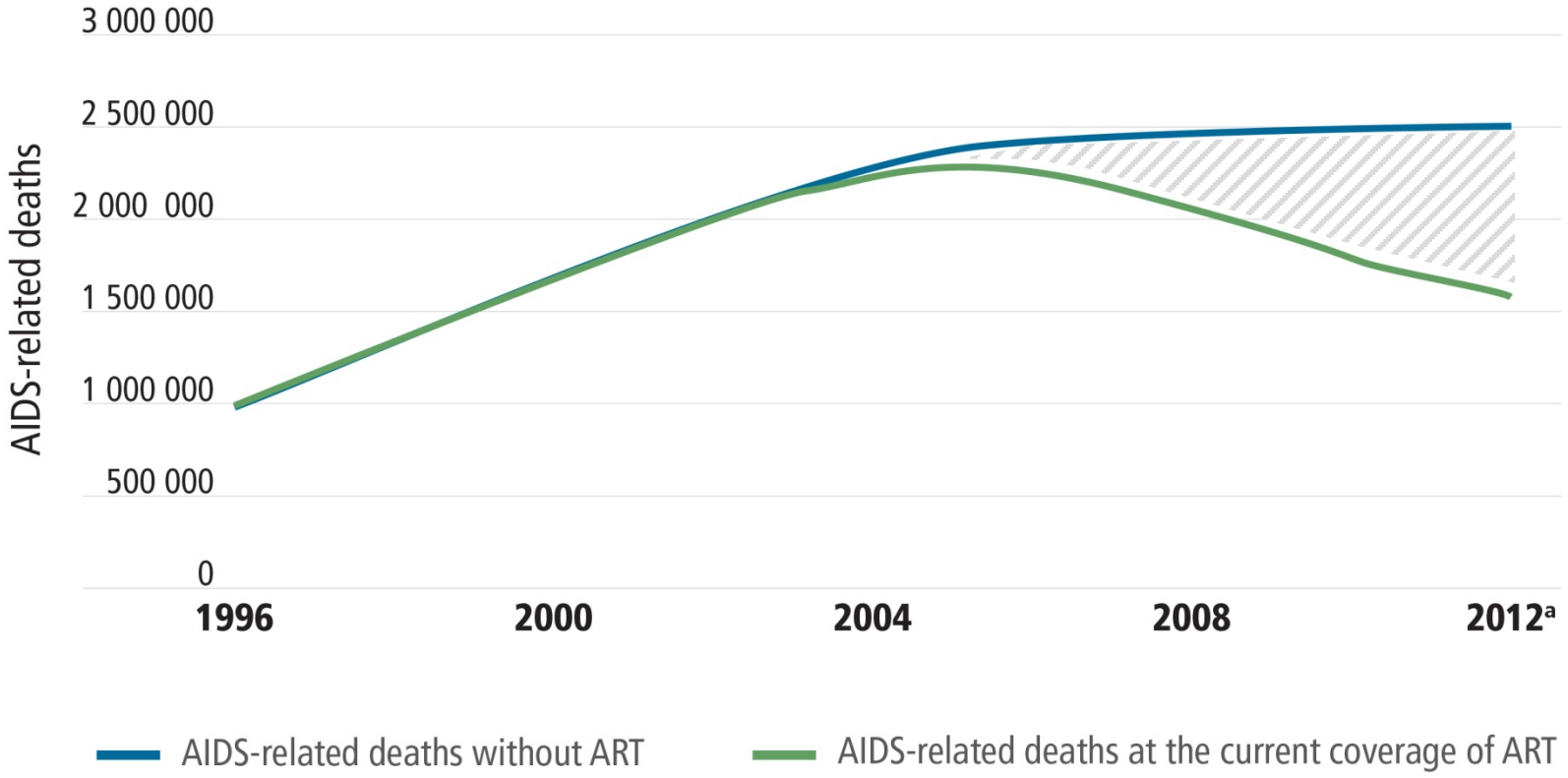
Abstract TULBPE19

That was it, thank you

HIV
CUP

ART averted 4.2 million deaths

Annual number of people dying from AIDS-related causes in low- and middle-income countries globally compared with a scenario of no antiretroviral therapy, 1996–2012



[a] The data points for 2012 are projected based on the scaling up of programmes in 2009–2011 and do not represent official estimates of the number of annual AIDS-related deaths.

Summary of Adult Guidelines

Topic	2002	2003	2006	2010	2013
When to start	CD4 ≤200	CD4 ≤ 200	CD4 ≤ 200 - Consider 350 - CD4 ≤ 350 for TB	CD4 ≤ 350 -Irrespective CD4 for TB and HBV	
1st Line	8 options - AZT preferred	4 options - AZT preferred	8 options - AZT or TDF preferred - d4T dose reduction	6 options &FDCs - AZT or TDF preferred - d4T phase out	
2nd Line	Boosted and non-boosted PIs	Boosted PIs -IDV/r LPV/r, SQV/r	Boosted PI - ATV/r, DRV/r, FPV/r LPV/r, SQV/r	Boosted PI - Heat stable FDC: ATV/r, LPV/r	
3rd Line	None	None	None	DRV/r, RAL, ETV	
Viral Load Testing	No	No (Desirable)	Yes (Tertiary centers)	Yes (Phase in approach)	

Earlier initiation

Simpler treatment

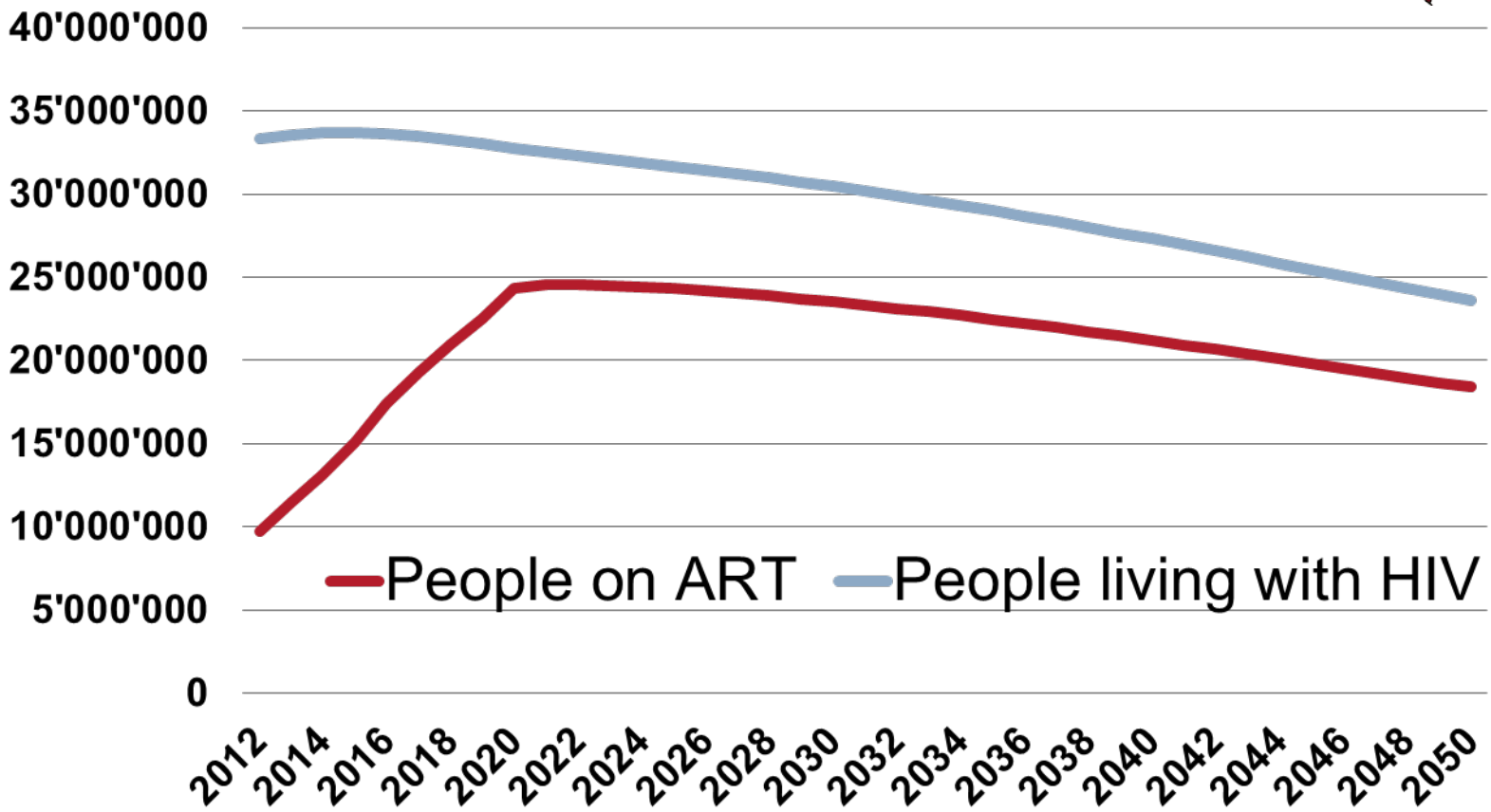
Less toxic, more robust regimens

Better monitoring

Recommendations:
CD4 Independent Conditions

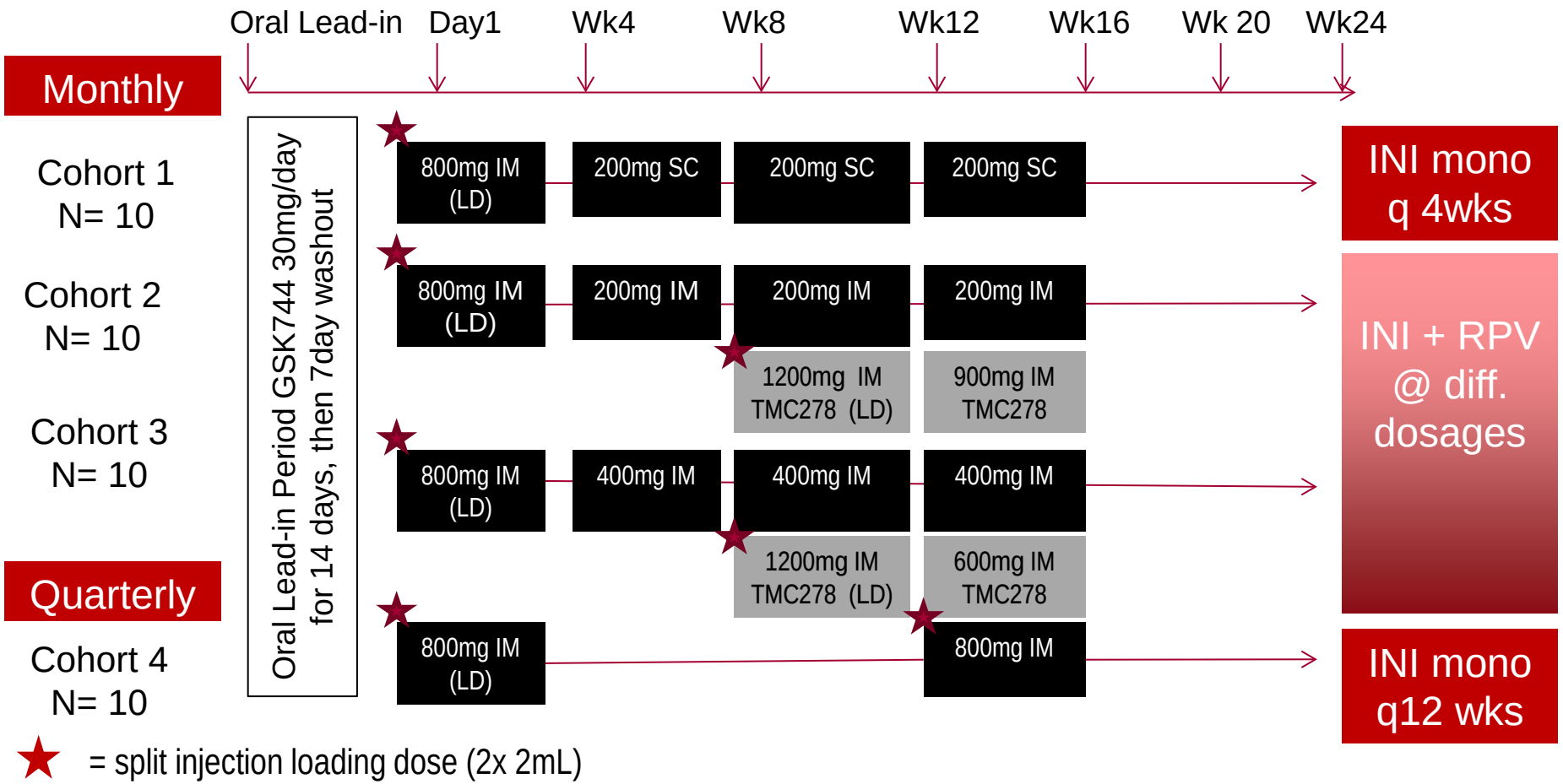
INITIATE ART REGARDLESS OF CD4 COUNT OR CLINICAL STAGE		RECOMMENDATION
ADULTS WITH HIV…	…and active TB disease	*Strong, low-quality evidence*
	…and HBV co-infection with severe liver disease	*Strong, low-quality evidence* NEW
	…who are pregnant or breastfeeding	*Strong, moderate-quality of evidence* NEW
	…in a HIV serodiscordant partnership	*Strong, high-quality evidence* NEW
CHILDREN < 5 YEARS OLD WITH HIV	Infants diagnosed in the first year of life	*Strong, moderate-quality of evidence*
	Children infected with HIV between one and below five years of age	*Conditional, very-low-quality evidence* NEW

Looking ahead: In the long term, ART scale-up will contribute to decreasing ART need



Source: Special analysis conducted by Futures Institute, 2013

Study Design



Pharmacokinetics of Rilpivirine with Rifabutin

- Rilpivirin 150 mg + Rifampin 600mg →
  - AUC: – 80%
  - C_{max}: – 69%
  - C_{min}: – 89%

- RPV 150mg + Rifabutin 300mg →
  - AUC: – 46%
  - C_{max}: – 35%
  - C_{min}: – 49%

→ Can a different dosing of RPV overcome this induction?

Poster MOPE030, IAS 2013

Conclusions

- These results confirm the role of CYP3A in the metabolism of RPV.
- The potent CYP3A enzyme inducer, rifabutin, significantly decreases plasma concentrations of RPV.
- Doubling the RPV dose (50 mg q.d.) was able to overcome the interaction with rifabutin, relative to RPV 25 mg q.d. alone.
- No new safety issues were identified for RPV alone or in combination with rifabutin, taking into account the known safety and tolerability profiles of both rifabutin and RPV.

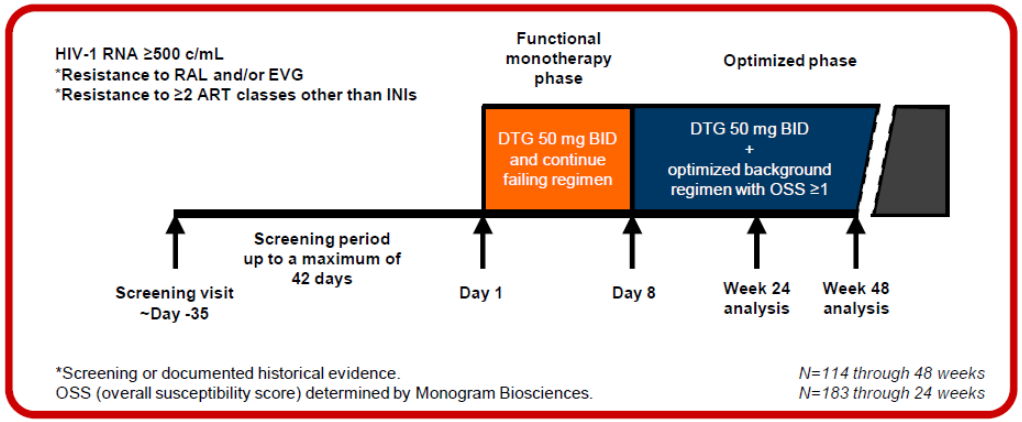
Dolutegravir in prior INI-resistance, VIKING-3

- Inclusion: resistance to RGV / Elvitegravir
- VIKING, Cohort I, n=24: DTG 50mg **OD** → 41% response (VL <50c/ml at 24 weeks)
- VIKING, Cohort II, n=27: DTG 50mg **bid** → 75% response
- VIKING-3: DTG 50mg **bid**

Rationale and Study Design

- DTG 50 mg QD is effective for INI-susceptible, HIV-infected patients.
- Patients with INI resistance benefit from DTG 50 mg BID.
- VIKING-3 was designed to demonstrate activity in INI-resistant patients.

Figure 1. Study Design



d1- d8: functional monotherapy (cont. failing regimen)

d8 forward: optimize backbone

24 weeks: n=183
48 weeks: n=114

Abstract TULBPE19

A daily dose of 400 mg efavirenz (EFV) is non-inferior to the standard 600 mg dose: week 48 data from the ENCORE1 study, a randomised, double-blind, placebo controlled, non-inferiority trial

encore 1

Rebekah Puls for the ENCORE1 Study Group

Kirby Institute

Reduced dose antiretroviral drugs (ARV)

GFATM/WHO/PEPFAR plans to expand treatment to 15 million people by 2015 will come at significant cost

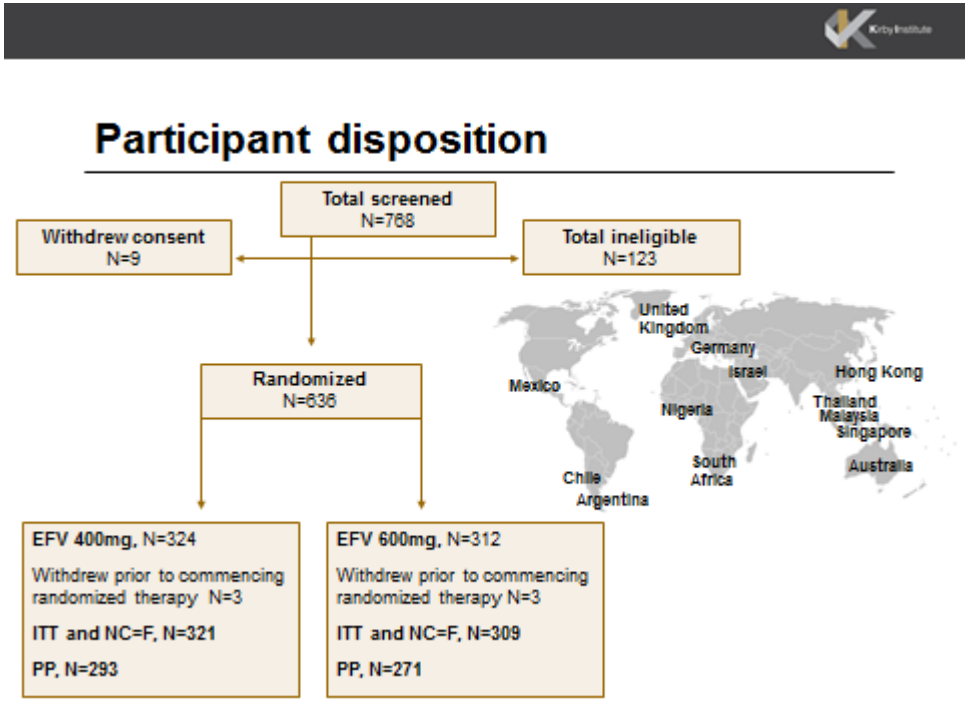
Although reduced, the cost of ARV remains substantial

Dose reduction may be a means to reduce drug costs

Efavirenz (EFV) is a globally important ARV

WHO guidelines recommend EFV for first line

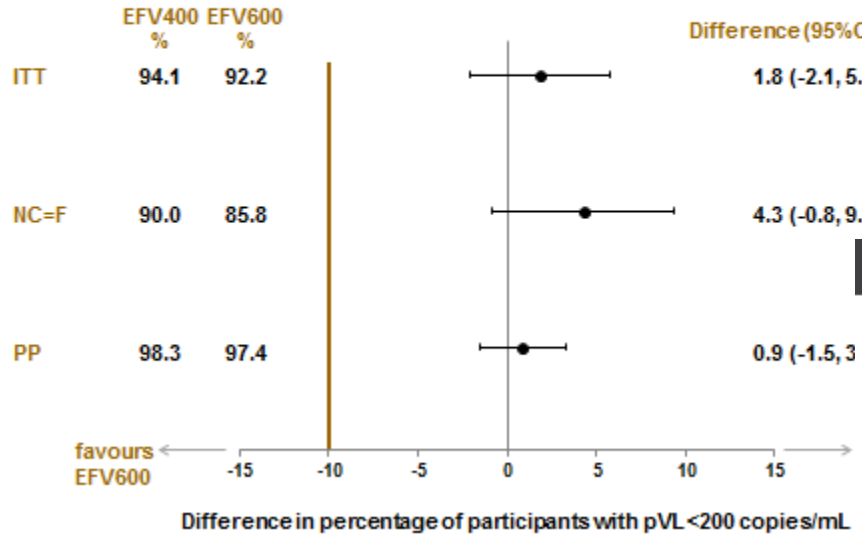
Phase II trial and observational cohort data suggest comparable performance at lower daily doses



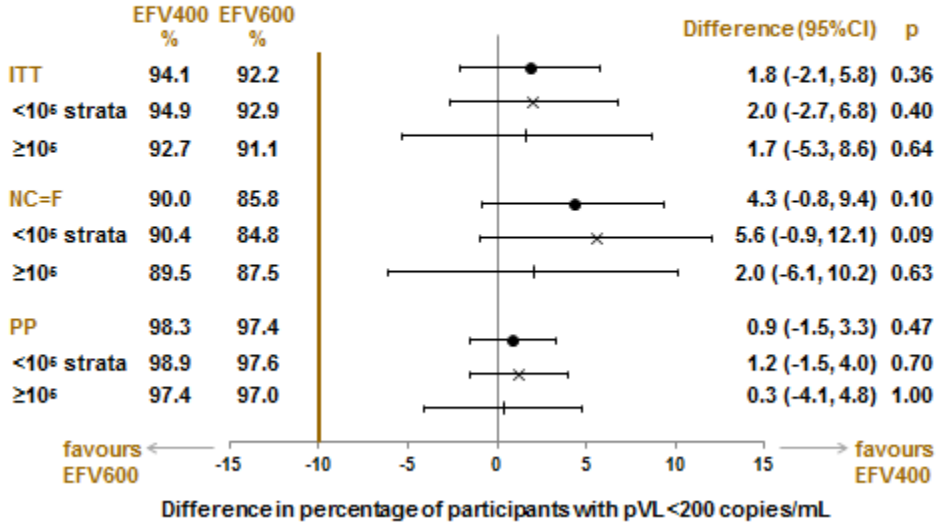
37% Africans
33% Asians
30% Caucasians

VL > 100’000 c/ml: 34%
Mean CD4: 273 c/ul
CD4 between 100 – 350 c/ull: 74%

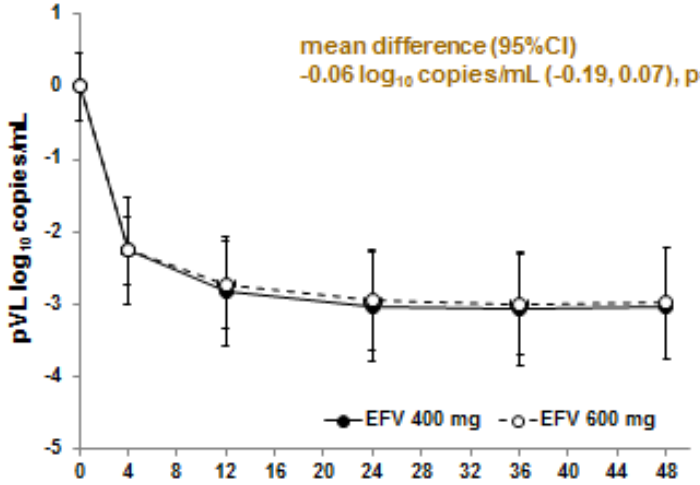
Primary endpoint: non inferiority at week 48



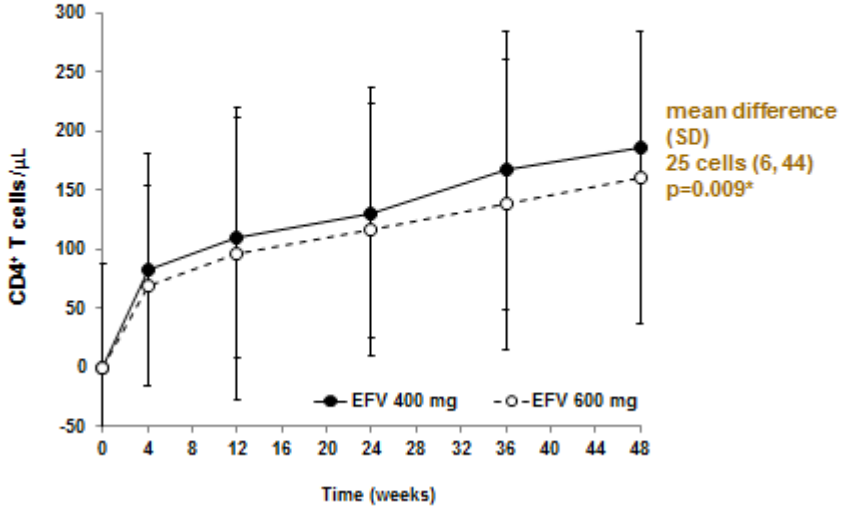
Primary endpoint: non inferiority at week 48



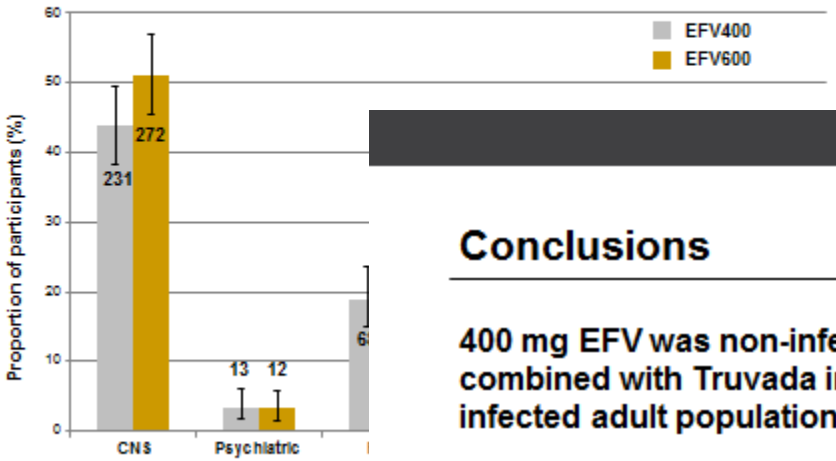
Mean change from baseline to week 48 pVL



Mean change from baseline to week 48 CD4+ T cells



Efavirenz adverse events*



Conclusions

400 mg EFV was non-inferior to 600 mg EFV when combined with Truvada in a treatment-naive, HIV-infected adult population over 48 weeks

Evidence of reduced EFV-related side effects with lower dose

400 mg EFV should be considered for initial ARV treatment.

Methods

Study selection

- **Inclusion criteria**
  - treatment-naïve, HIV-1+ adults
  - prospective design
  - ≥48 weeks duration
  - ITT efficacy analysis
- **Exclusion criteria**
  - retrospective or cross-sectional design
  - ART regimens never recommended and less potent than current therapy (e.g. PI/r monotherapy; 2 NRTIs)
  - directly-observed therapy

Study characteristics

Characteristics		Groups (n=216)	Participants (n=40,124)	Weighted %
Randomised	yes	196	36,534	91.1
Placebo	yes	68	17,630	43.9
Phase	2	50	4,386	10.9
	3	96	26,325	65.6
	4	70	9,413	23.5
Sponsorship	academic	55	10,681	26.6
	industry	123	26,547	66.2
	both	38	2,896	7.2
Year commenced	pre-1996	10	641	1.6
	1997-1999	53	8,108	20.2
	2000-2002	43	9,331	23.3
	2003-2005	61	13,062	32.6
	2006-2008	31	6,597	16.4
	2009-	17	2,346	5.8

Efficacy

By DHHS recommendation

	DHHS recommendation		
	'Preferred'	'Alternative'	'Other'
Groups, n	27	36	153
Participants, n	5,677	8,556	25,891
Follow-up, weeks (SD)	99 (41)	86 (35)	77 (37)
ART efficacy, % (SD)	75 (8)	65 (7)	55 (17)

- Mean difference for 'Preferred' vs. 'Alternative' regimen groups = 10.0% (95%CI 7.6 to 15.4), P<0.001

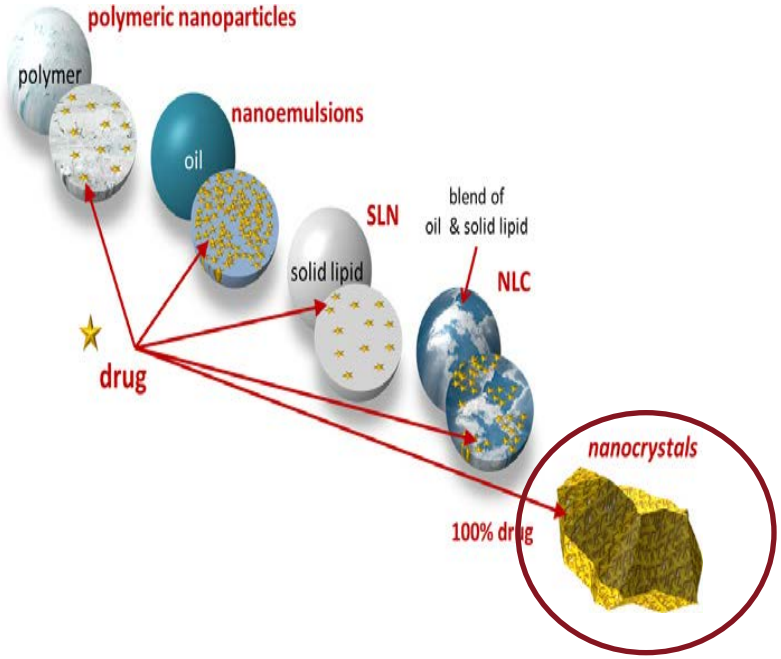
Efficacy

By DHHS recommendation

	DHHS recommendation		
	'Preferred'	'Alternative'	'Other'
Groups, n	27	36	153
Participants, n	5,677	8,556	25,891
Follow-up, weeks (SD)	99 (41)	86 (35)	77 (37)
ART efficacy, % (SD)	75 (8)	65 (7)	55 (17)
ART cessation, % (SD)†	20 (8)	25 (8)	27 (12)
adverse events	5.3	7.3	9.0
patient decision	9.0	11.0	11.0
virological failure	3.6	2.8	3.7
other	3.4	4.5	5.0

GSK744 and TMC278 Nanosuspensions

- Drug nanocrystal suspended in liquid = nanosuspension
- Nanomilled to increase surface area and drug dissolution rate
- Allows ~100% drug loading (vs. matrix approaches) for lower inj. volumes



R H. Müller, et al. European Journal of Pharmaceutics and Biopharmaceutics 78 (2011) 1-9

GSK744 200mg/mL

Component	Function
GSK1265744A (d50 ~200 nm)	Active
Mannitol	Tonicity agent
Surfactant System	Wetting/Stabilizer
Water for Injection	Solvent

TMC278 300mg/mL

Component	Function
TMC278 (d50 ~200 nm)	Active
Glucose	Tonicity agent
Surfactant System	Wetting/Stabilizer
Water for Injection	Solvent