

# The injectables: a new silver bullet?

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**WITS RHI**

**Thanks Clinical Care Options, Helen  
Rees, Joe Eron, Wits RHI sex worker  
team**

# Disclosures...

- Part of optimisation collaborations – grants to improve testing, new drug regimens, linkage to care
- Pharma (including drug donations for studies) and managed care

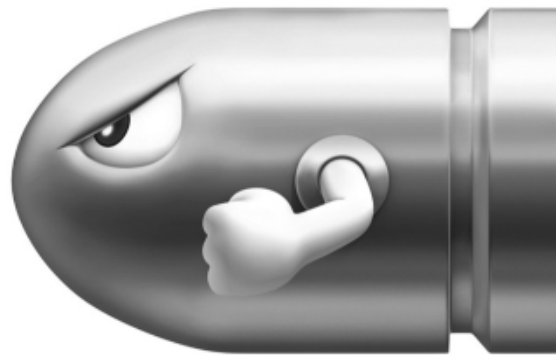


O P T I M I Z E



# The silver bullet...

- For ART treatment and PrEP
- Note: benefits in most of medicine is incremental



# Cabotegravir LA and Rilpivirine LA 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



## GSK744 200mg/mL

Component	Function
GSK1265744 (d50 ~200 nm)	Active
Mannitol	Tonicity agent
Surfactant System	Wetting/Stabilizer
Water for Injection	Solvent

## TMC278 300mg/mL

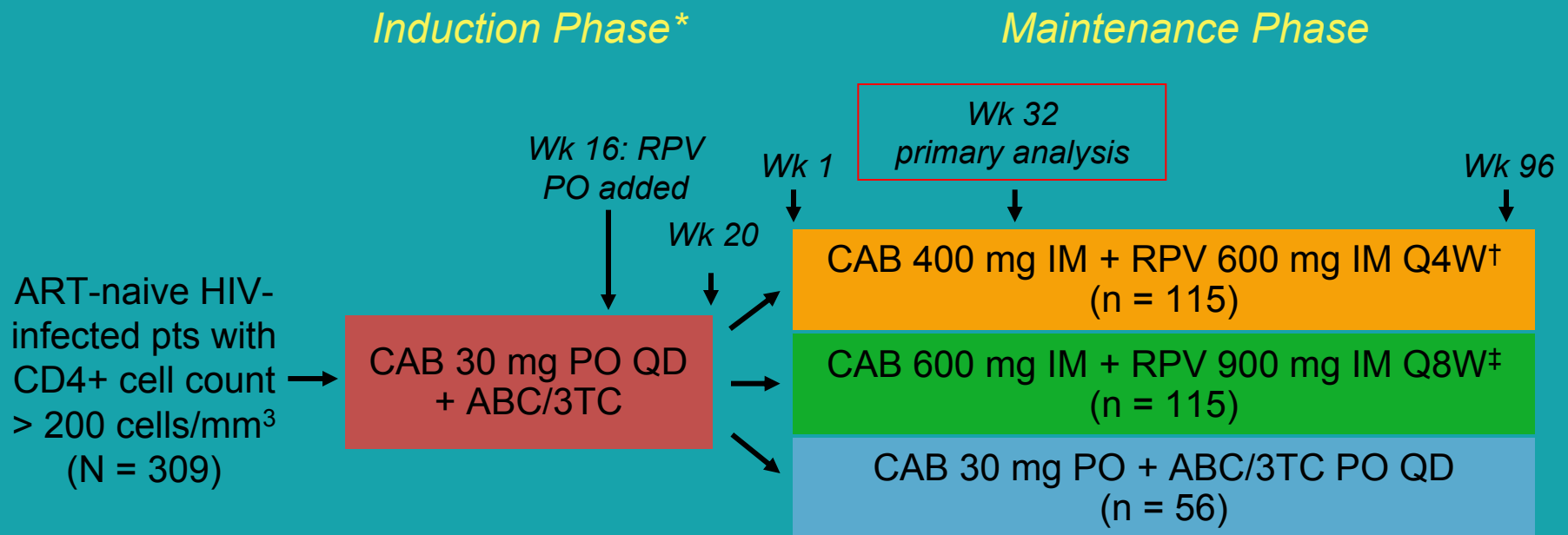
Component	Function
TMC278 (d50 ~200 nm)	Active
Glucose	Tonicity agent
Surfactant System	Wetting/Stabilizer
Water for Injection	Solvent

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



# LATTE-2: Cabotegravir IM + Rilpivirine IM for Long-Acting Maintenance ART

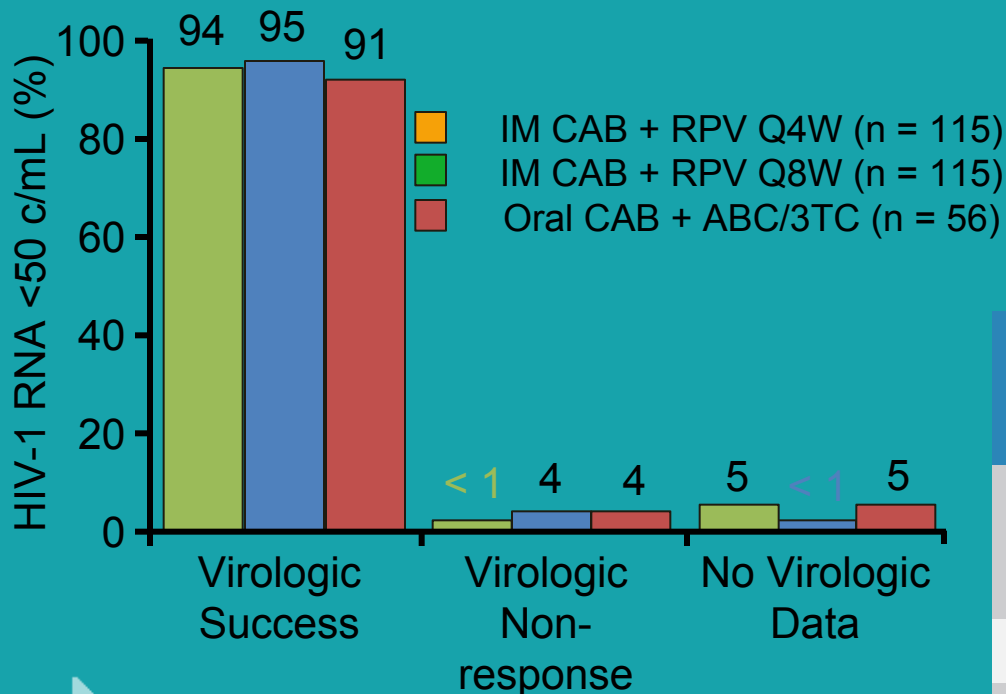
- Multicenter, open-label phase IIb study
  - Cabotegravir: integrase inhibitor



6 pts discontinued for AEs or death in induction analysis. \*Pts with HIV-1 RNA < 50 c/mL from Wk 16 to Wk 20 continued to maintenance phase. <sup>†</sup>Loading dose: Day 1, CAB 800 mg + RPV 600 mg. <sup>‡</sup>Loading dose: Day 1, CAB 800 mg + RPV 900 mg; Wk 4, CAB 600 mg.

# LATTE-2: Wk 32 Efficacy and Safety

Treatment Differences (95% CI):  
 Q4W IM vs Oral: 2.8 (-5.8 to 11.5)  
 Q8W IM vs Oral: 3.7 (-4.8 to 12.2)



- Most frequent ISRs were pain (67%), swelling (7%), and nodules (6%)
  - ISR events/injection: 0.53
  - 99% of ISRs grade 1/2; none grade 4
  - 1% of pts withdrew for ISRs

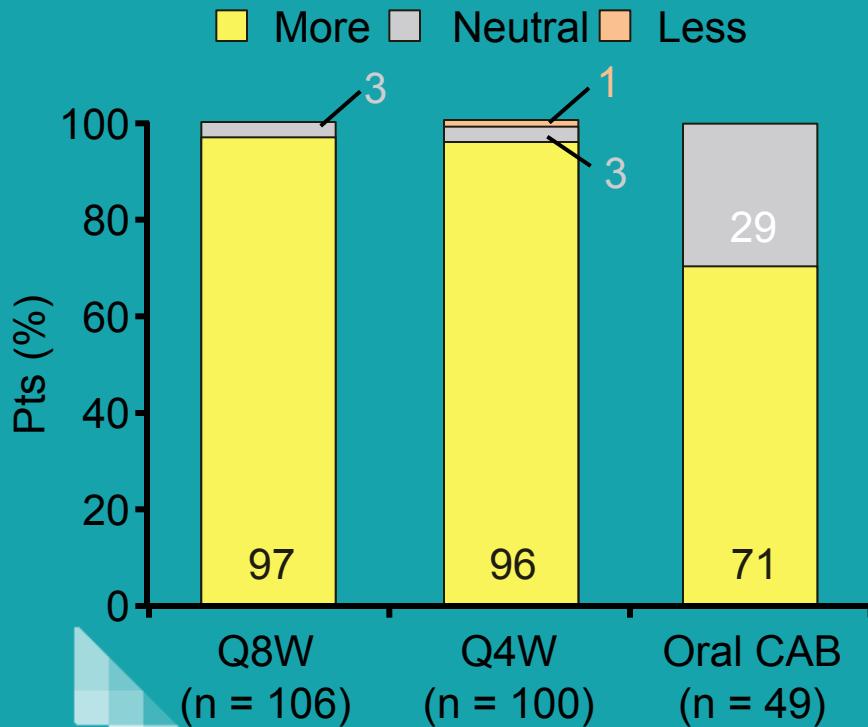
AEs, %	Pooled IM Arms (n = 230)	Oral Arm (n = 56)
Drug-related grade 3/4 AEs (excluding ISRs)	3	0
Serious AEs	6	5
AEs leading to withdrawal	3	2

- No INSTI, NNRTI, or NRTI resistance mutations detected

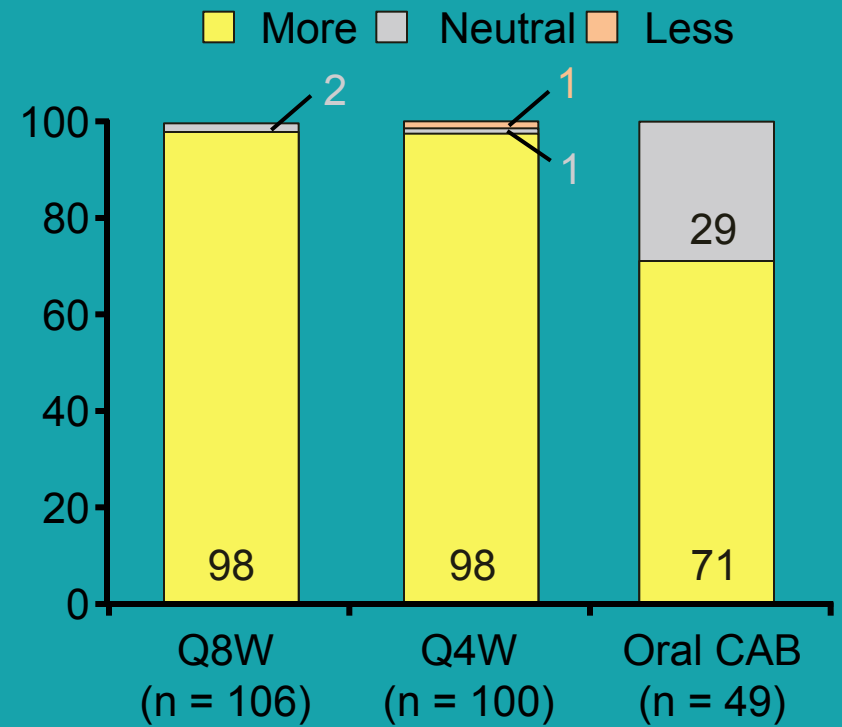


# LATTE-2: Wk 32 Pt Satisfaction With Maintenance Therapy vs Oral Induction

How satisfied are you with your current treatment?  
(vs oral induction treatment)



How satisfied would you be to continue with your present form of treatment?  
(vs oral induction treatment)



# Other Potential Long-Acting ARVs

Agent	MoA	Study results
MK-8591 (EFdA)	NRTI <sup>[1]</sup>	<ul style="list-style-type: none"><li>▪ <b>Phase I study:</b> treatment-naive pts, single 10-mg dose (N = 6)</li><li>▪ Mean <math>t_{1/2}</math>: 108 hrs</li><li>▪ Mean VL reduction at 10 days postdose: 1.78 <math>\log_{10}</math></li></ul>
3BNC117, VRC01	Broadly neutralizing antibodies (bNAbs)	<ul style="list-style-type: none"><li>▪ <b>3BNC117:</b> single infusion reduced VL up to 2.5 <math>\log_{10}</math> (n = 17); mean <math>t_{1/2}</math>: 9 days<sup>[2]</sup></li><li>▪ <b>VRC01:</b> single infusion reduced VL up to 1.8 <math>\log_{10}</math> in treatment-naive pts (n = 8); 2 minimal responders exhibited resistant virus at BL<sup>[3]</sup></li></ul>

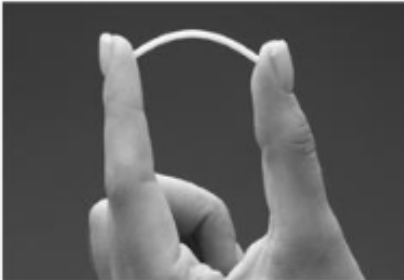
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1. Friedman EJ, et al. CROI 2016. Abstract 437LB.
  2. Caskey M, et al. Nature. 2015;522:487-491.
  3. Lynch RM, et al. Sci Transl Med. 2015;7:319ra206.





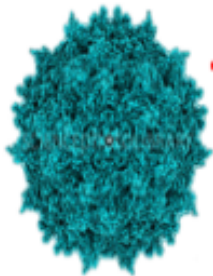
# Antiretroviral Therapy: The Next Generation?

- Implantable (and removable) combination antiretrovirals



- Vectored delivery of combinations of antibody-based therapy or protein based therapy

## Recombinant AAV (rAAV) features



— Transfects both dividing & non-dividing cells

— No host-genome integration & Stable Expression

— Ease to produce at high viral titer (Helper Free)

— Do not elicit significant immune response *in vivo*

— Can be used for *in vivo* gene deliveries



2016

**And  
nanoparticles....**

# Concerns...

- ?breakthrough on PrEP may lead to prolonged exposure to drug, accumulating resistance
- Serious side effects means lead-in dose

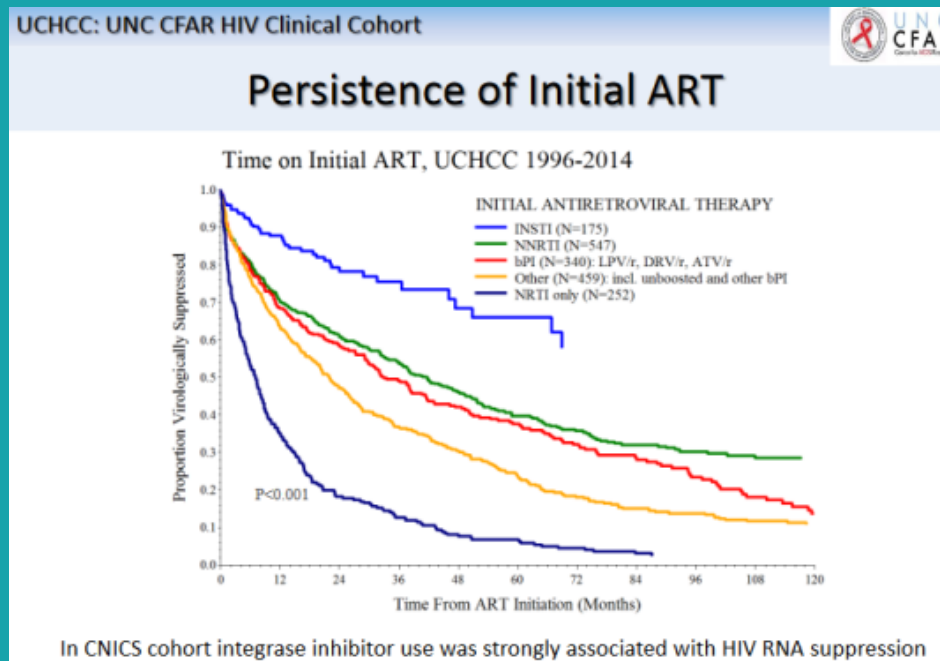


But.... What problem are we  
trying to fix?



# Adherence issues generally?

- But PrEP adherence ins some groups >90%
- And treatment improving



Thanks Joe Eron

# Improved outcomes may be more dependent on social support than new drugs

**Table 1: Severe morbidity in TEMPRANO study at 30 months**

	% events	n	Rate / 100 PY	adj HR	p
WHO ART	11.4%	111	4.9		
Early ART	6.6%	64	2.8	0.56	0.0002
No IPT	10.7%	104	4.7		
IPT	7.2%	71	3.0	0.65	0.005

**Table 1. Primary endpoint and its components in open DSMB report (15 May 2015)**

	Early ART (arm A)		Deferred ART (arm B)		Hazard Ratio Arm A/B (95% CI)
	N	rate/100 PY	N	rate/100 PY	
AIDS, serious non-AIDS, or death (primary)	41	0.60	86	1.25	0.47 (0.32 to 0.68)
AIDS or AIDS death	14	0.20	46	0.66	0.30 (0.17 to 0.55)
Serious non-AIDS or non-AIDS death	28	0.41	41	0.59	0.67 0.42 to 1.09) NS**

\* PY = patient years, \*\* NS = non significant

Thanks: Simon Collins



# And special populations?

- TAPS project – adherence superb to ART and PrEP
- IDUs? Similarly – if support them, they take their treatment and PrEP
- Psychiatric, adolescent, “chaotic patients”



# Clinics in central Johannesburg

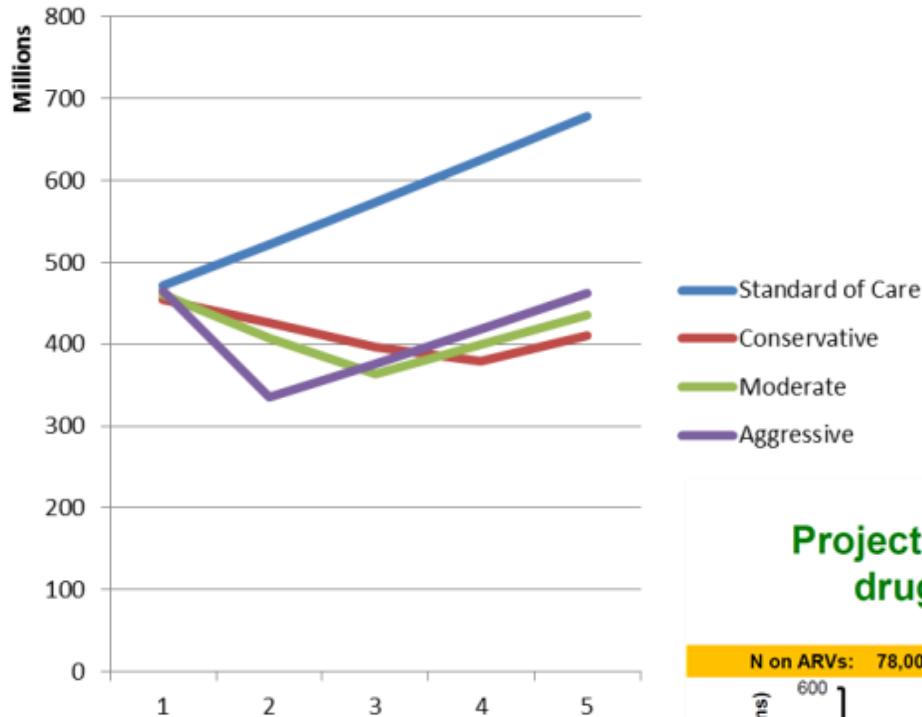
Thanks to Sam Lalla-Edwards and team, M&E Dept, RHI

First and Second line regimens at ART initiation for Jan to Dec 2015														
Facility name		JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	TOTAL INITIATIONS
HCHC	1st Line	166	217	232	175	796	227	235	254	221	268	160	101	3052
	2nd Line	2	0	2	2	0	3	2	1	0	2	1	0	15
Yeoville	1st Line	69	97	144	160	135	104	140	109	106	104	79	30	1277
	2nd Line	0	2	0	1	0	0	0	0	1	0	0	1	5
80 Albert	1st Line	78	91	91	86	110	100	135	91	90	91	101	64	1128
	2nd Line	0	1	0	0	0	1	0	0	1	0	0	0	3
Jeppe Clinic	1st Line	76	95	76	75	113	75	96	83	73	84	116	84	1046
	2nd Line	0	1	2	0	0	0	0	0	0	1	0	0	4
Joubert Park	1st Line	81	81	82	71	92	71	81	79	83	86	73	49	929
	2nd Line	0	0	0	0	0	0	0	0	0	0	0	0	0
Rosettenville	1st Line	57	105	81	77	105	88	68	62	61	84	59	36	883
	2nd Line	0	0	0	0	0	0	0	0	1	0	0	0	1
Malvern	1st Line	78	66	67	77	73	79	75	69	61	70	63	64	842
	2nd Line	0	0	0	0	0	0	0	0	0	0	0	1	1
Jeppe Street	1st Line	36	34	50	28	55	56	47	32	44	51	55	24	512
	2nd Line	1	0	0	0	0	0	0	0	0	0	0	0	1
Bellavista	1st Line	32	40	59	44	40	26	36	36	26	28	37	31	435
	2nd Line	0	0	0	0	0	0	0	0	0	0	0	0	0
Crown Gardens	1st Line	17	31	39	25	27	32	32	30	29	33	27	17	339
	2nd Line	0	0	0	0	0	0	0	0	0	0	1	0	1
Mayfair	1st Line	10	29	38	37	34	18	39	28	37	24	26	17	337
	2nd Line	0	0	0	0	0	0	0	0	0	0	0	0	0
Bezvalley	1st Line	10	11	20	18	22	33	25	30	23	45	19	26	282
	2nd Line	0	0	1	0	0	0	0	0	0	0	0	0	1
Glenanda	1st Line	10	23	28	29	24	30	18	28	21	21	30	18	272
	2nd Line	0	0	0	0	0	0	0	0	0	0	0	0	0
SRH	1st Line	30	45	37	38	20	15	17	6	5	13	17	6	249
	2nd Line	0	1	1	1	0	0	0	0	0	0	0	0	3
South Hills	1st Line	15	32	20	10	19	17	23	23	12	20	20	16	227
	2nd Line	0	0	0	0	0	0	0	0	0	0	0	0	0
Kibler Park	1st Line	12	14	22	15	19	12	11	10	25	15	22	12	189
	2nd Line	0	0	0	0	0	0	0	0	0	0	0	0	0
CMJAH	1st Line	34	27	26	25	16	30	26	27	35	42	28	16	332
	2nd Line	0	0	0	0	0	3	0	0	0	3	0	0	6





## Total Cost of Treatment South Africa



RESEARCH ARTICLE

## Projected Lifetime Healthcare Costs Associated with HIV Infection

Fumiyo Nakagawa<sup>1\*</sup>, Alec Miners<sup>2</sup>, Colette J. Smith<sup>1</sup>, Ruth Simmons<sup>3</sup>, Rebecca K. Lodwick<sup>4</sup>, Valentina Cambiano<sup>1</sup>, Jens D. Lundgren<sup>5</sup>, Valerie Delpech<sup>1</sup>, Andrew N. Phillips<sup>1</sup>

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Abstract

Thanks: Andrew Hill

## Projected UK ARV costs, if branded drugs used (8% growth/year)

N on ARVs: 78,000 84,000 91,000 98,000 106,000



In press, SAMJ



# ART is starting to look increasingly like contraception

- Oral, injectables, implantables, rings....
- Interesting to examine the history – slow and steady move towards more long acting agents
- But: breakthrough pregnancies ESPECIALLY if no reminders/ support



# Injectables are exciting...

- But we must be careful about what problem we are fixing
- Complex if a lead-in oral dose
- Will not cure bad health systems
- Need lots of 'real world' and adherence research
- Lessons from the contraceptive world



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