16th Annual Conference of the
National HIV Nurses Association (NHIVNA)

National HIV Nurses Association

Professor Saye Khoo

University of Liverpool

26-27 June 2014- City Hall, Cardiff

UNIVERSITY OF LIVERPOOL

New Antiretrovirals and New Strategies

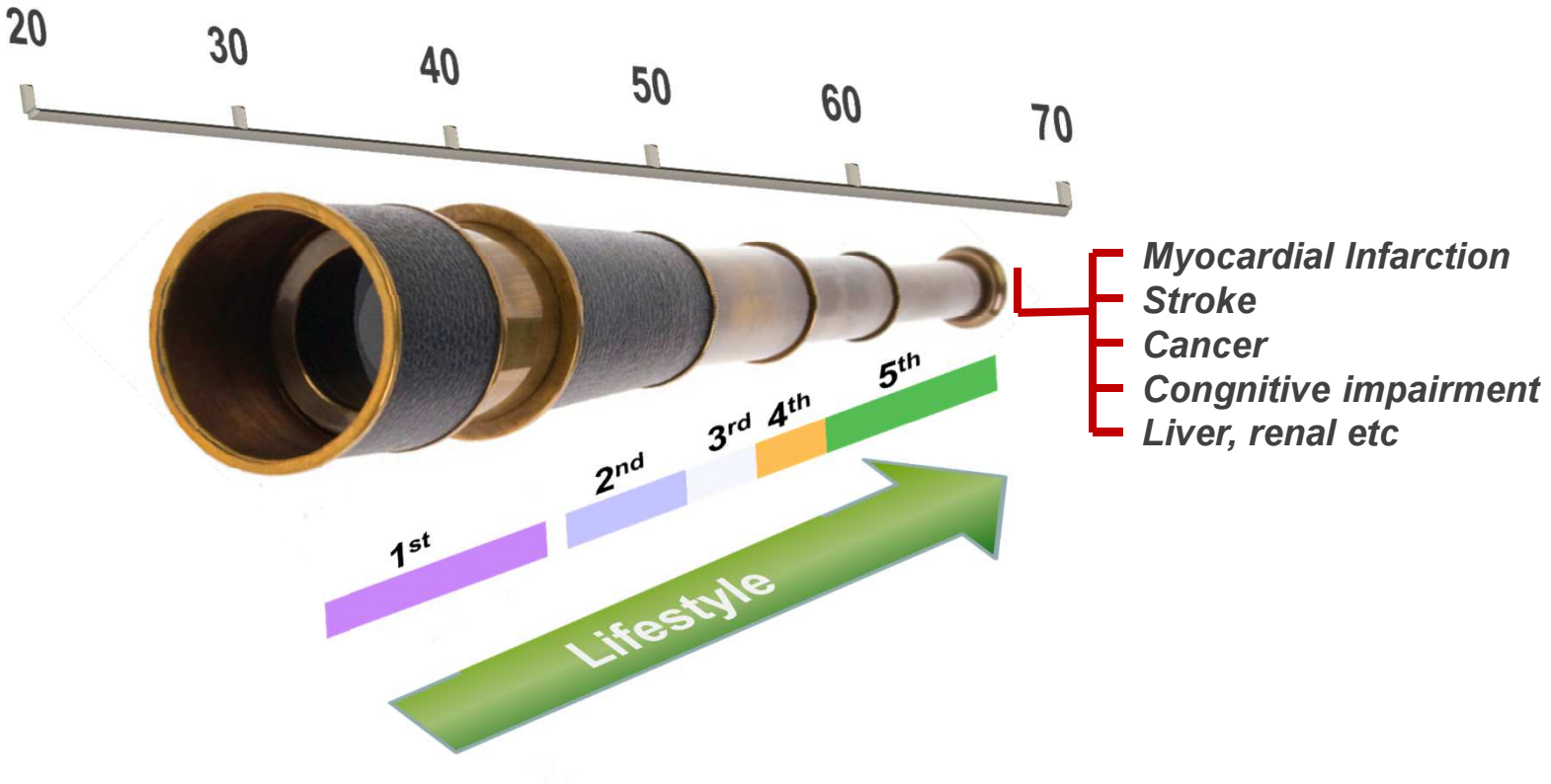
Saye Khoo

HIV Pharmacology Group

Declaration of Interests

- *www.hiv-druginteractions.org* & *www.hep-druginteractions.org* sponsorship from Janssen, ViiV, Abbott, Merck, BMS, Gilead, Boehringer, Vertex. Editorial content remains independent.
- Research Grants: Merck, ViiV
- Speakers bureau: Merck, Janssen, Abbott, Roche
- Travel grants: Gilead, ViiV, BMS, Janssen
- TaiLor trial (NIHR-funded)

Antiretroviral Stewardship



Plan Now

- what to give ?
- when to start ?
- how to manage ?

For Then

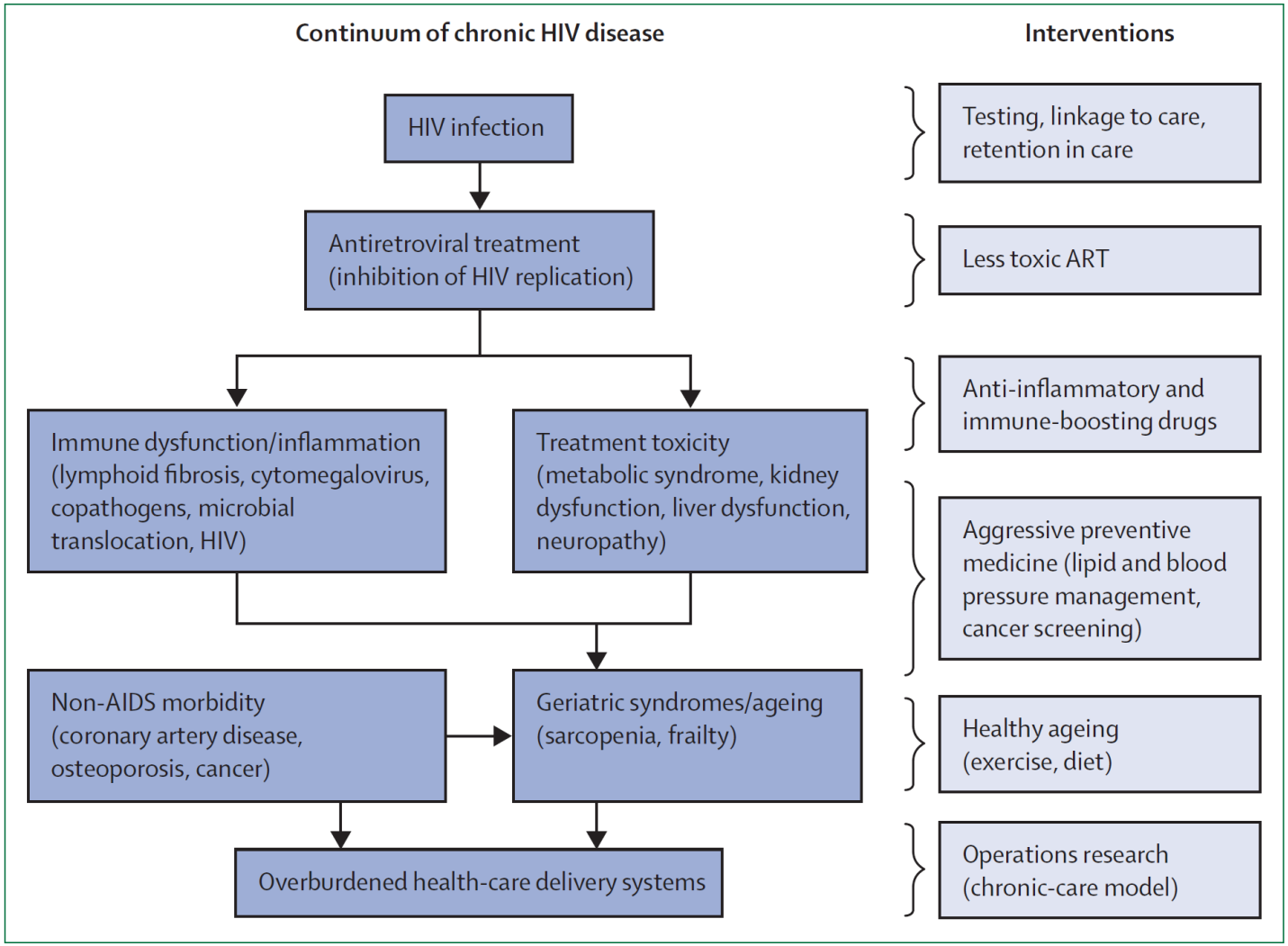
- Minimise resistance
- Minimise toxicity
- Preserve options
- Normalise Immunity
- Equip for future co-morbidity

The end of AIDS: HIV infection as a chronic disease

Steven G Deeks, Sharon R Lewin, Diane V Havlir

The success of antiretroviral therapy has led some people to now ask whether the end of AIDS is possible.

Lancet 2013; 382: 1525–33



Big Treatment Issues 2014

Supporting treatment

- Getting people diagnosed early, and retained
- STRs versus generics
- forgiving regimens
- supporting adherence in special populations
- long term toxicities

Delivering treatment - Models of care

- Integrated care pathways
- patient self-management

Persistent low-level viraemia

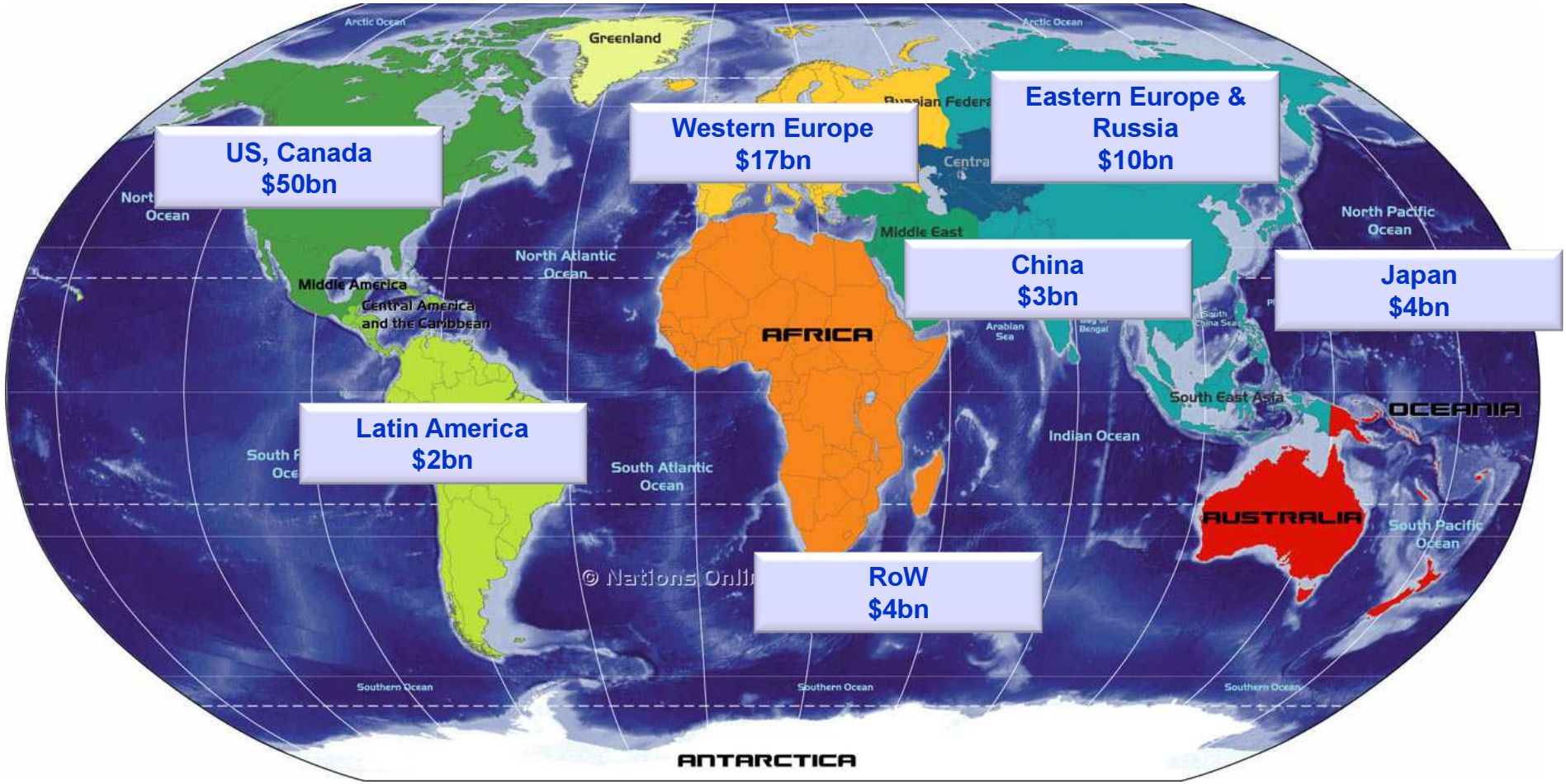
Blunted immune response

Immune activation and non-communicable disease

- increased risk with HIV
- polypharmacy, drug interactions
- developed and developing world
- relationship with low-level viraemia

Generics: A $90 Billion Opportunity

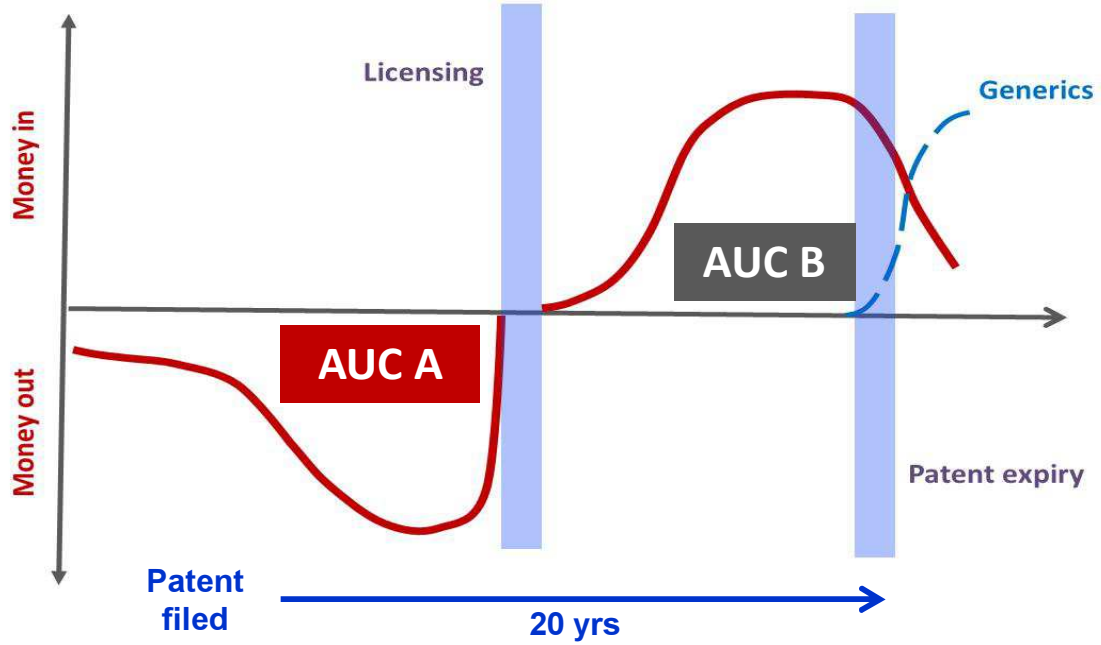
Total world pharmaceutical sales – $600 bn



Source: IMS Health, VOI Pharma Handbook

Generics

– a natural part of the life cycle of any drug



Patent validity

- Depends on territory (US 20 years)
- Hatch Waxman Act (1984)
- Can have extensions eg changes to indications, formulations, dose
- 'Evergreening' strategies – chemical modifications, metabolites
- Differs from 'exclusivity', which may be granted beyond patent

Branded vs 'Approved' Generics

Same	Different
• amount of active compound • dose • route of administration • Indications • Bioequivalence - same absorption (rate and extent) AND same plasma concentrations over time = same safety and efficacy • Similar packaging insert/ product information	• Price • Pill appearance, size, shape, colour or taste • Pill strength • excipients • Reliability of supply chain • (checks over time to monitor 'drift' in quality of some providers)

Bioequivalence = Therapeutic equivalence
Apart from medication error, possible impact on adherence

Potential HIV drug prices: 2014-8

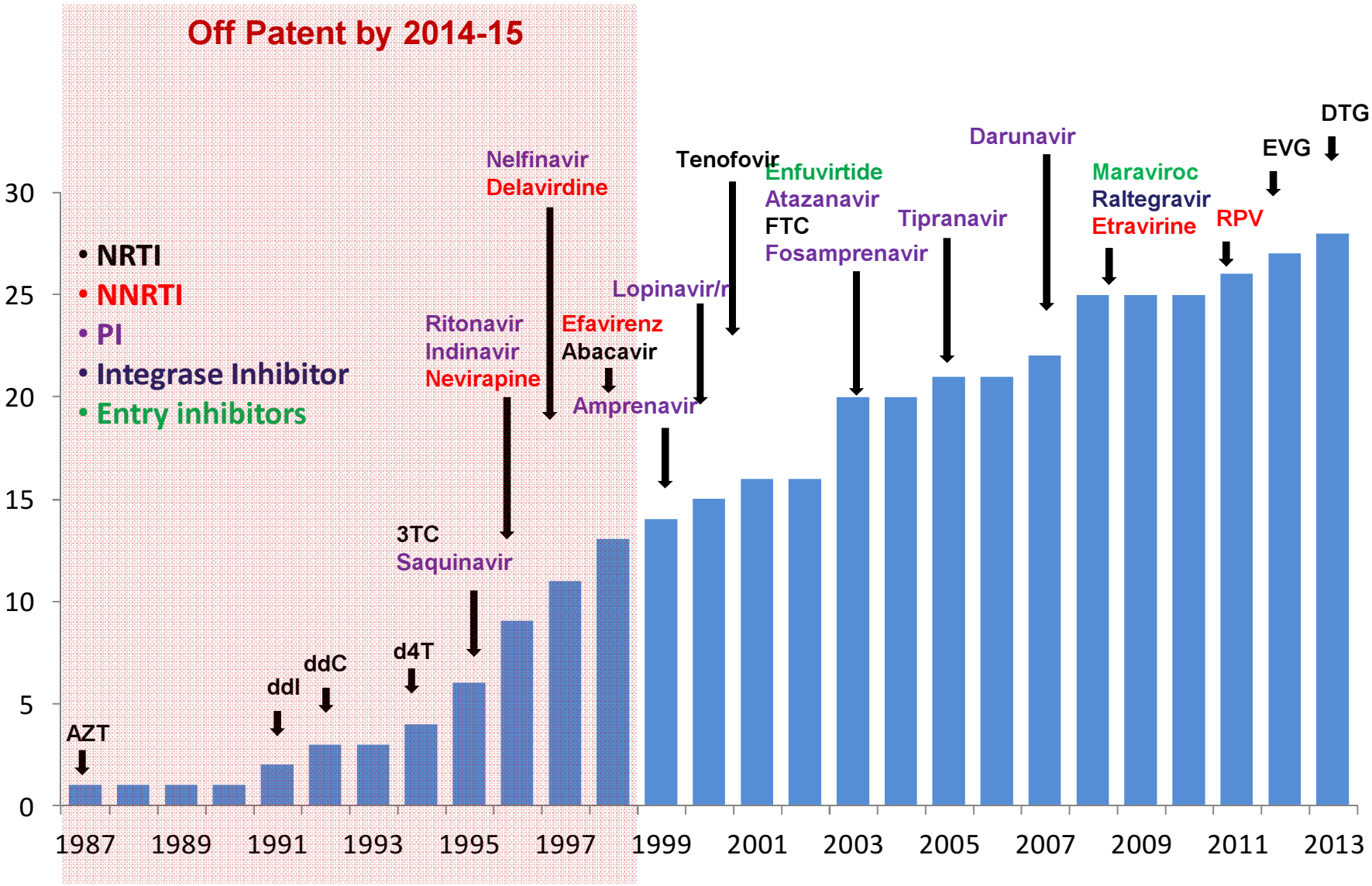
Minimum = cost price (African access programmes)
NHS prices 30% lower than list price
Generic prices 80% lower than NHS price

Drug	Minimum	UK NHS	UK Generic (80% reduction)
3TC	24	1424	284 (now)
Zidovudine	60	1418	709 (now)
Tenofovir	55	2172	434 (2017)
Nevirapine	24	973	389 (now)
Efavirenz	40	1774	355 (now)
Abacavir	140	1889	378 (2014)
Etravirine	600	2724	2723
Lopinavir/r	268	2618	523 (2016)
Atazanavir/r	204	2975	595 (2017)
Darunavir/r	500	2823	565 (2017)
Raltegravir	450	3973	3938

Slide courtesy of A Hill

Sources: CHAI 2011, MSF 2011, BNF 2011

HIV drug development (1987-2013)

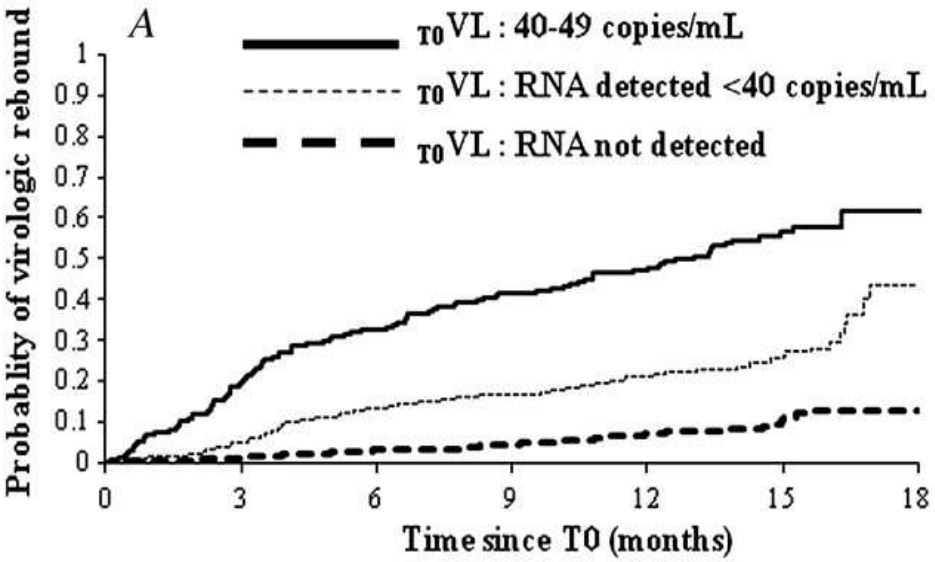


Persistent low-level viraemia

- ***Is it a bad thing ?***
  - May be assay-specific
  - Linked to virological failure, resistance
- ***What is the cause ?***
  - Adherence
  - Latently infected cells
  - anatomical compartment
  - Ceiling to ART efficacy, eg cell-to-cell transmission
- ***Can we do anything about it?***

Low Level Viraemia, Rebound & Resistance

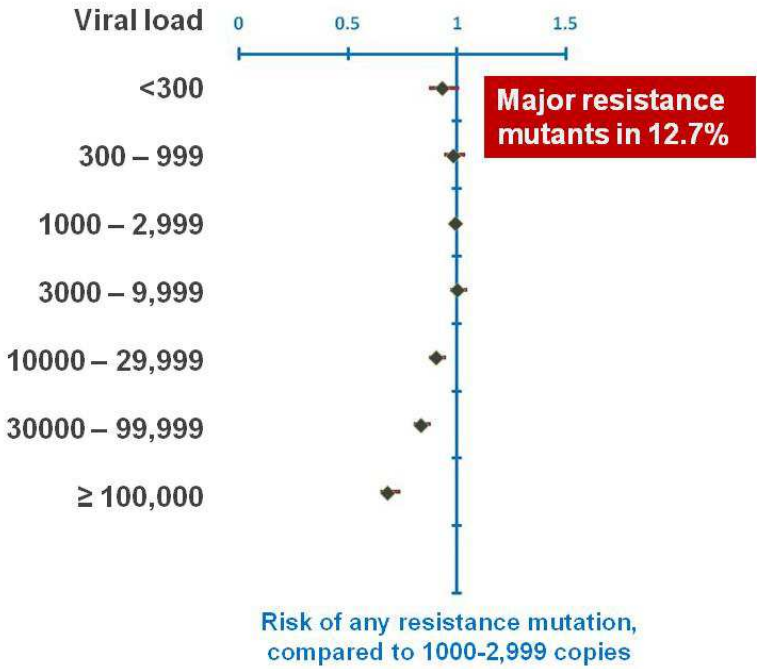
Risk of Rebound
Abbott RealTime



RFH cohort
N = 1247
RNA - (N=500)
RNA <40 (N=507)
RNA 40-49 (N=240) **HR = 10.42**

Doyle et al CID 2012;54:724

Risk of Resistance
UK Resistance Database

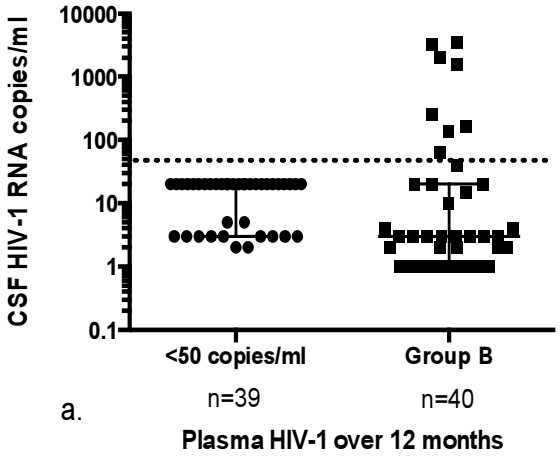


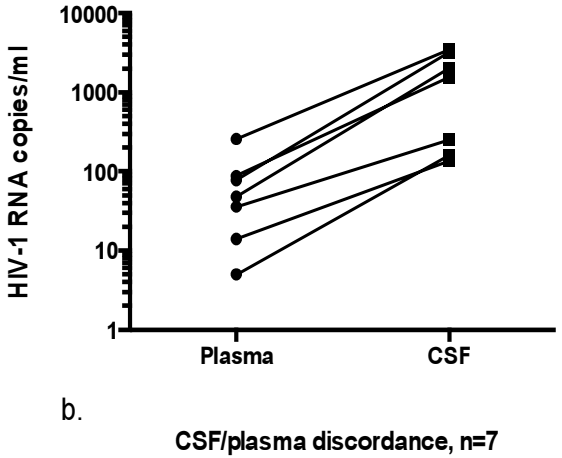
UK resistance database
1999 - 2006

N = 7861 tests

Mackie et al. JID 2010;201:1303

UK PARTITION Study





CSF HIV-1 RNA in 40 subjects with intermittent or persistent HIV-1 RNA ≥50 copies/ml versus 39 subjects with consistent HIV-1 RNA suppression <50 copies/ml. Dashed line is at 50 copies/ml.
b. Plasma and CSF HIV-1 RNA in 7 subjects with CSF/plasma discordance

Nightingale et al. CROI 2014

Persistent low-level viraemia

ERAS Study

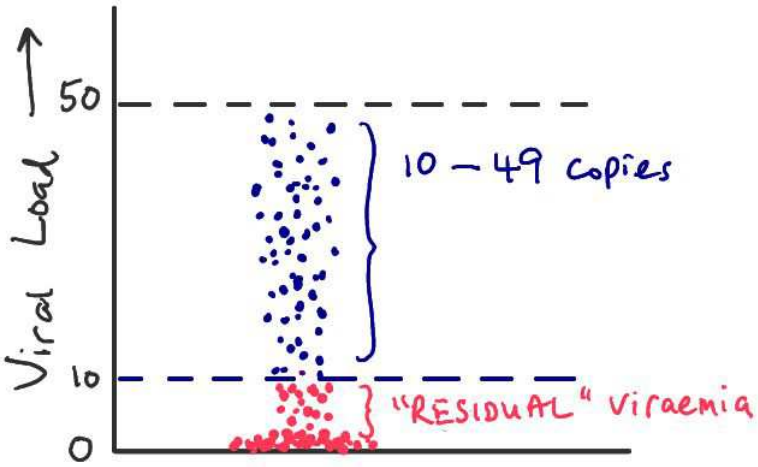
Persistently suppressed - 1st Line NNRTI-ART for up to 15 years
N = 104

HIV RNA detected 52/104 (50%) patients
Median 3 copies

HIV-1 RNA cps/ml	Years VL <50 cps/ml			Total (n=104)	*P*
	0-4 (n=31)	5-7 (n=33)	8-15 (n=40)		
Median (range)	3 (1, 35)	3 (1, 10)	3 (1, 11)	3 (1, 35)	*0.451*
Mean $\log_{10}$ (SD)	0.6 (0.3)	0.5 (0.2)	0.5 (0.2)	0.5 (0.2)	*0.451*

Is there a ceiling of efficacy to ART ?

- Low level viraemia not always indicative of poor adherence
- Not all compartments are sterilised, eg CNS, GALT



- Proviral DNA concentrations only modestly decreased
- Rebound on discontinuation
- Efficacy of ART on cell-to-cell transmission ?
- T cell activation declines, but remains abnormal many years after ART

New Drugs, New Formulations, New Strategies

Improvements on existing classes

- TAF
- dolutegravir and other integrases
- new NNRTIs – MK1439

New Classes

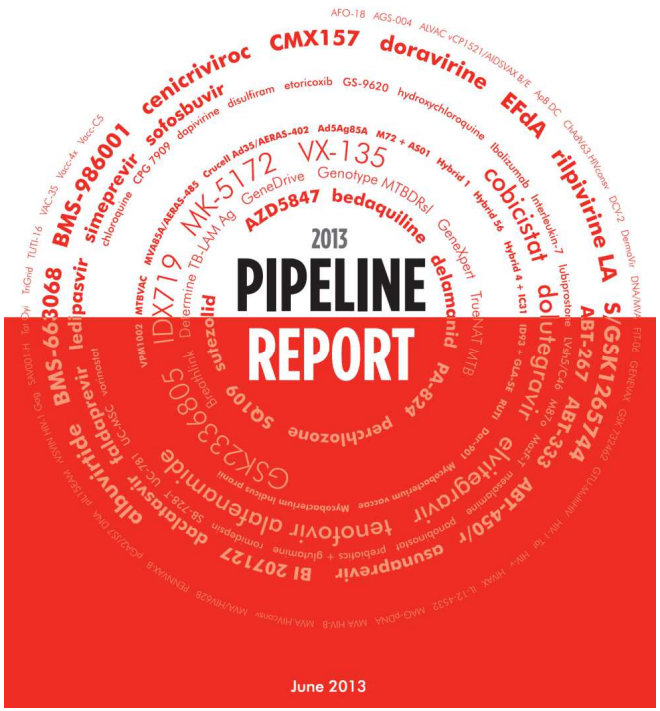
- Maturation inhibitors, LEDGINS, etc

New Formulations

- nanoformulations
- mono- or dual therapy
- LA injections or implants
- targeting latent reservoirs

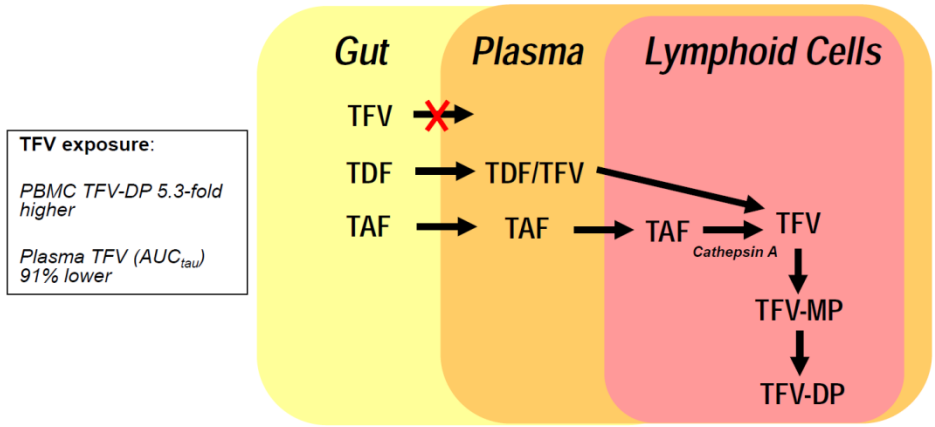
New Strategies

- NRTI-sparing, PI monotherapy
- targeting latent reservoirs
- targeting immune activation, cardiovascular risk
- etc



	INSTIs	NRTIs	PIs	NNRTIs	Other
Approved	Dolutegravir				
Phase 3		TAF	DRVc	Doravirine (MK1349) RPV-LA	TAF/FTC/EVGc Cenicriviroc BMS663068
Phase 2	GSK126744	Racivir Amodoxovir Elvucitabine			ABC/3TC/DTG TAF/FTC/DRVc

Tenofovir Alafenamide (TAF)



- **Tenofovir pro-drug, increased levels in lymphoid cells & hepatocytes**

- **Relative to TDF (300mg), TAF (25mg) has**
  - ↑ anti-HIV activity in Phase I
  - ↑ intracellular TFV-DP (7-fold)
  - ↓ plasma TFV (by 90%)
  - no evidence of increased bone/renal toxicity

- **Coformulations**
  - Elvitegravir/cobi/FTC/TAF (10mg)
  - others ?

Doravirine (MK-1439)

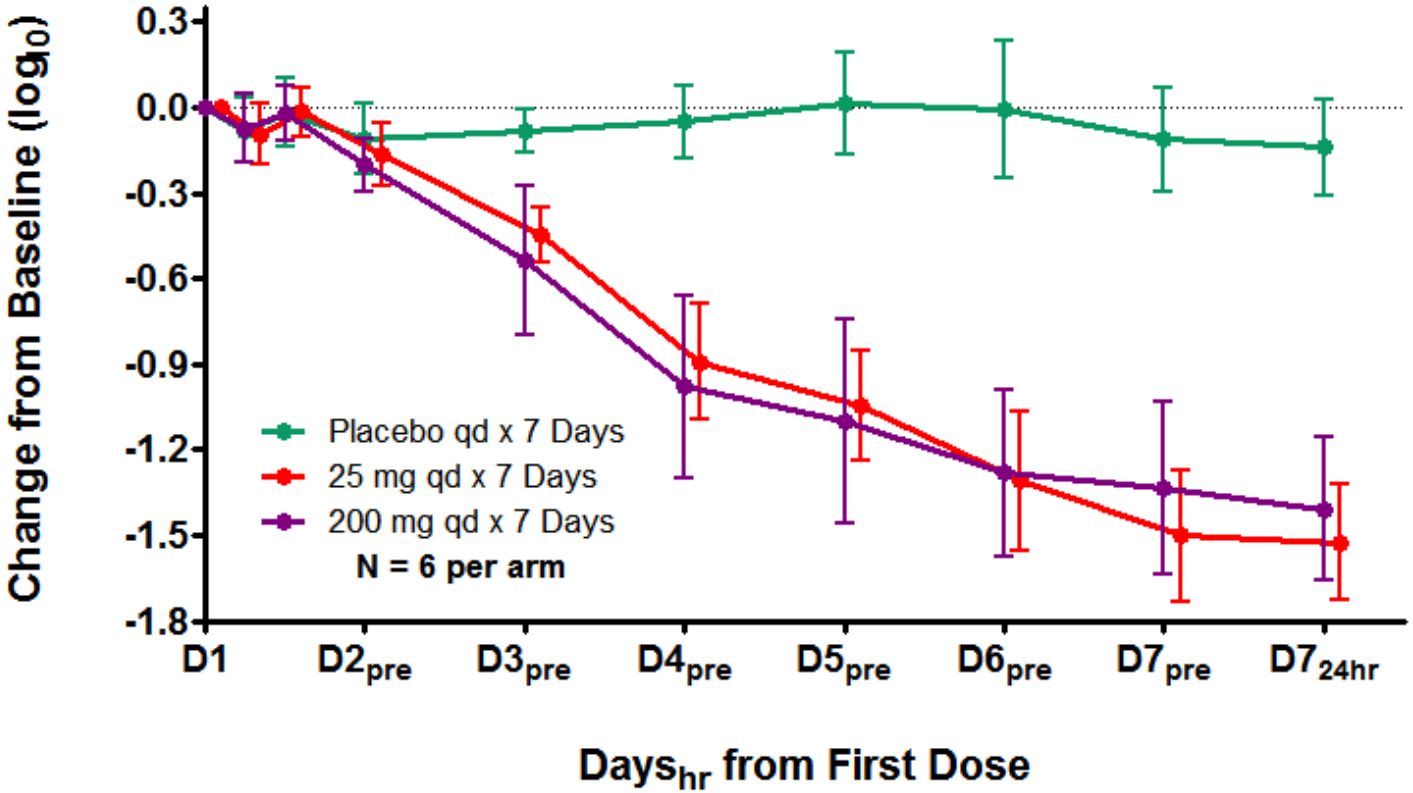
- **Pharmacology**
  - Potent - IC_{95} ~19 nM (50% human serum)
  - Once-daily dosing; T½ 10-16h
  - P450 metabolism (CYP3A4/5)
    - No significant inhibition/induction of CYP P450s
    - No significant interaction with TDF
    - AUC ↑3.54; Cmin↑2.91 fold with RTV (100mg bd)
  - Good Preclinical Safety Profile, no significant ECG changes

- **Potential advantages** :
  - Low rates of CNS toxicity
  - Minimal interactions: enhanced compatibility with concomitant medications
  - Enhanced potency against select NNRTI resistance mutations

    ≤ 3 fold potency shift against the most prevalent transmitted NNRTI mutant viruses (K103N, Y181C, G190A) [Feng M, ICAAC 2012]

Anderson, M., et al., CROI 2013; Paper #100

MK-1439 Phase Ib Pharmacodynamics



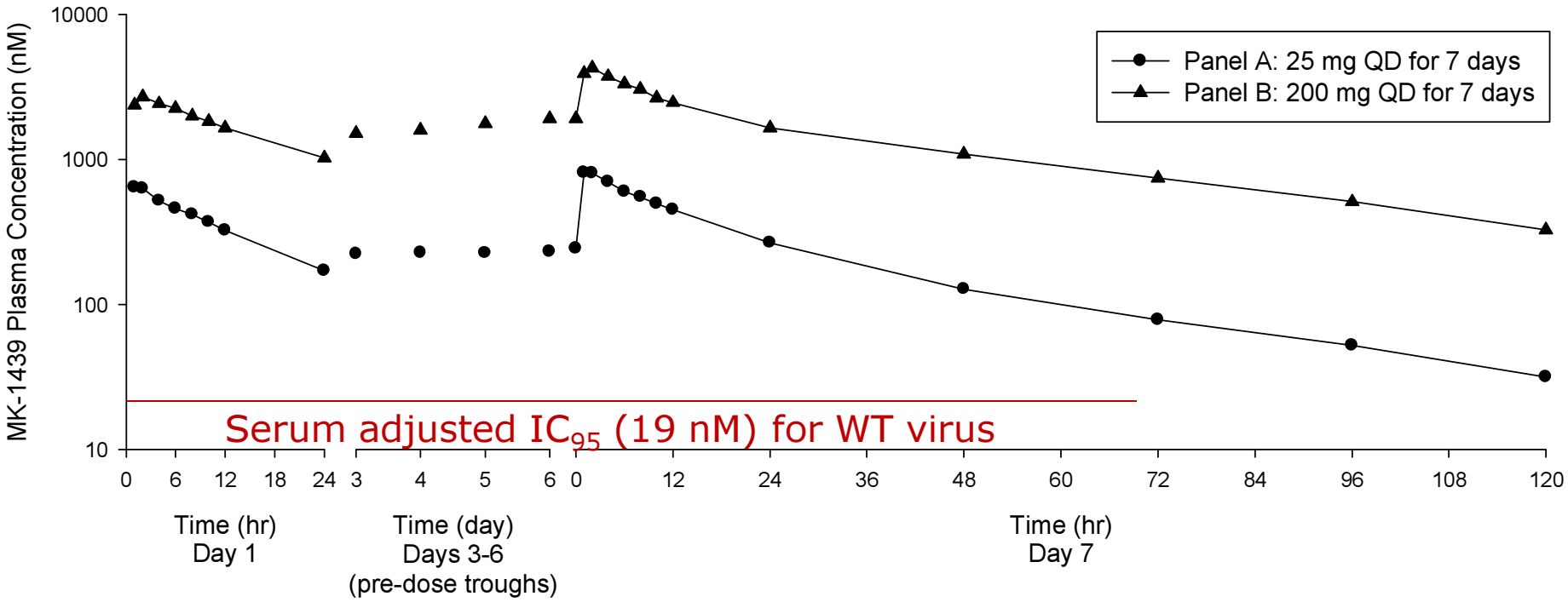
Similar HIV-RNA decline for both doses vs. placebo at 7 days:

- 1.37 $\log_{10}$ copies/mL at 25 mg daily dose
- 1.26 $\log_{10}$ copies/mL at 200 mg daily dose

Anderson, M., et al., CROI 2013; Paper #100

MK-1439 Phase Ib Pharmacokinetics

Mean Plasma Concentration Profiles for MK-1439 Following Administration to HIV-1 Infected Patients

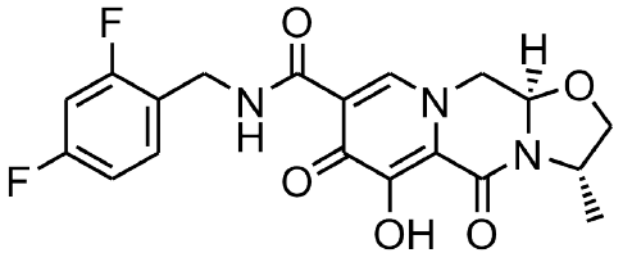


- **N = 6 patients per dose**
- **Pharmacokinetic profiles are comparable to healthy volunteers**
- **Steady state C_{24hr} concentrations exceeded the serum adjusted IC_{95} of wild-type virus by 14-fold (25 mg) and 87-fold (200 mg)**
- **C_{24hr} accumulation ratio of 1.5- to 1.6-fold**

Anderson, M., et al., CROI 2013; Paper #100

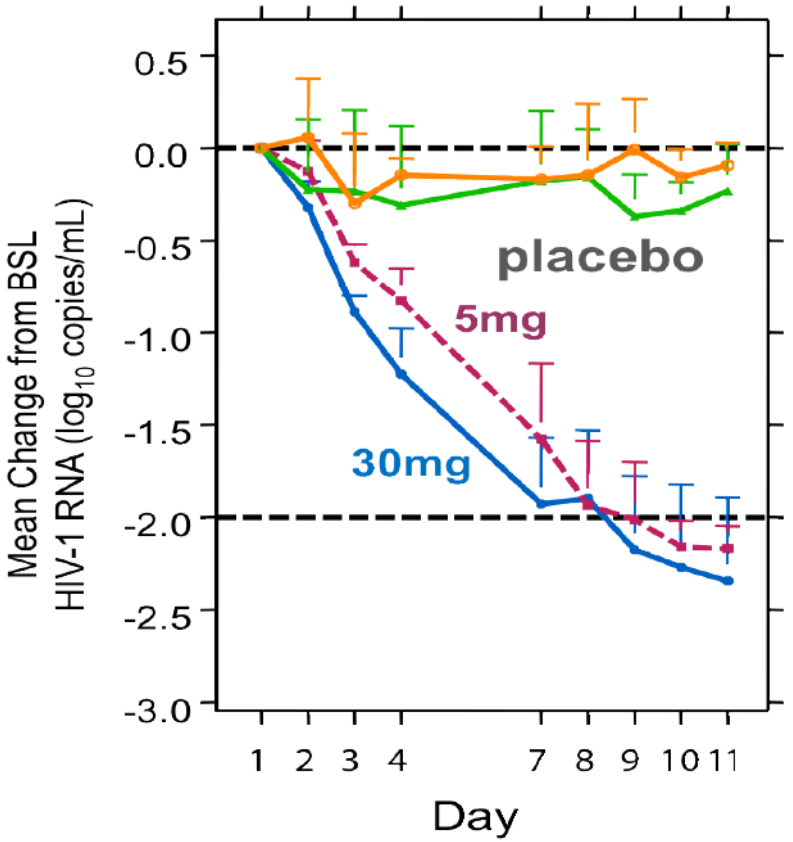
GSK1265744

GSK1265744 (744)

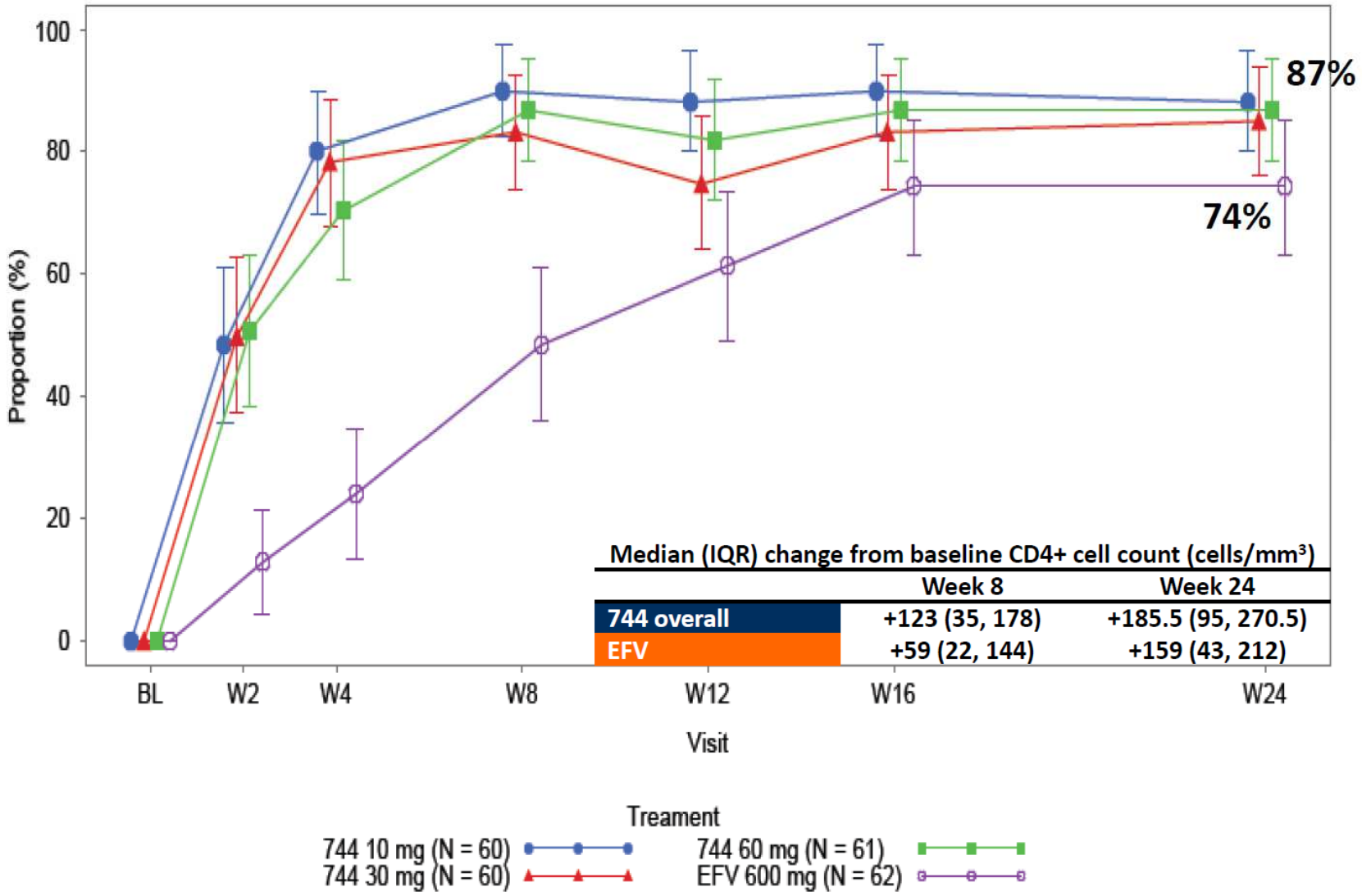


- HIV-1 integrase inhibitor; dolutegravir analogue
- Oral drug ($t_{½}$ = 40 hours)
- Long-acting SC or IM injectable (apparent $t_{½}$ = 21-50 days)

- Demonstrated >2.2 log_{10} c/mL mean reduction in plasma HIV-1 RNA in 10-day monotherapy at 5 and 30 mg PO qd



GSK 126744 – LATTE Study

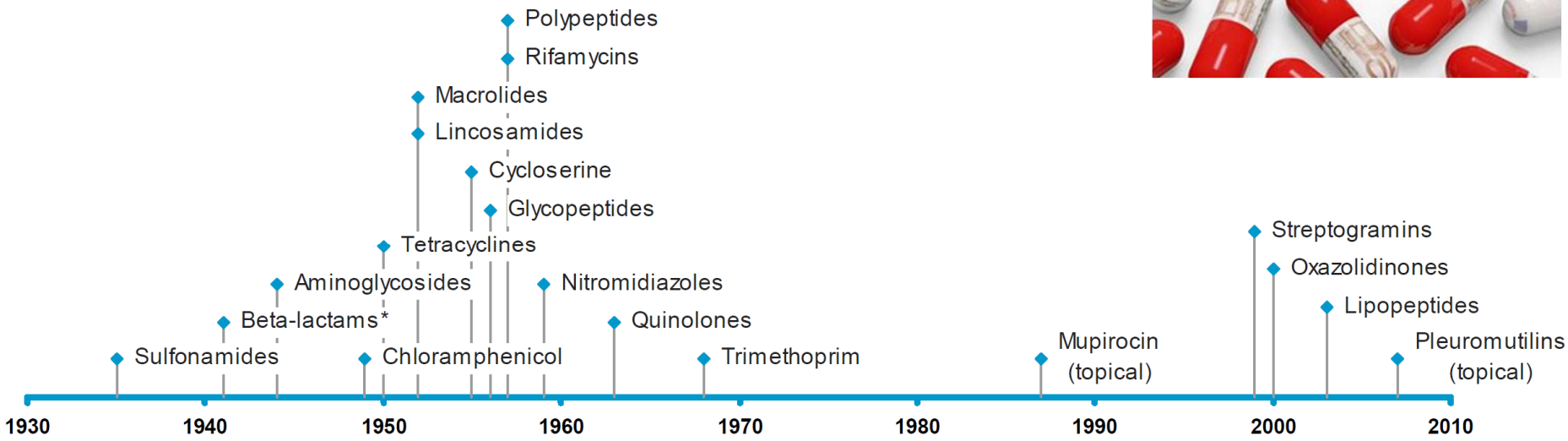


Margolis et al. EACS 2013 Abstr PS7/1

Table 1B. HIV Treatment Pipeline, 2003–2013: Drugs Stopped or Stalled in Phase II/III

Generic Name (Acronym)	Sponsor	Last Active Year	Class
Stopped in Phase III (3)			
capravirine (AG-1549)	Pfizer	2005	NNRTI
vicriviroc (SCH 417690)	Schering	2010	CCR5I
lersivirine (UK-453,061)	Pfizer	2013	NNRTI
Stalled in Phase II (2)			
PRO 140	Progenics/Cytodyn	2010	AI mAb
ibalizumab (TNX-355)	Tanox/Biogen	2011	anti-CD4 mAb
Stopped in Phase II (13)			
DPC-083 (AI-183)	BMS	2004	NNRTI
PRO 542	Progenics	2004	AI mAb
SCH-C	Schering	2004	CCR5RI
calanolide A	Advanced L.S.	2005	NNRTI
reverset (D-D4FC)	Incyte	2006	NRTI
brecanavir	GSK	2007	PI
alovudine (FLT)	Mefuvir Beijing	2008	NRTI
BILR 355/r BS	BI	2008	NNRTI
elvucitabine	Achillion	2008	NRTI
racivir	Pharmasset	2008	NRTI
amdoxivir (DAPD)	Gilead	2010	NRTI
apricitabine	Avexa	2010	NRTI
bevirimat (PA-457)	Panacos/Myriad	2010	AI

The Antibiotic Pipeline



* Beta-lactams include three groups sometimes identified as separate classes: penicillins, cephalosporins, and carbapenems.

- **14 new classes of antibiotics were introduced between 1935 – 1968**
- **Since then, only 5 have been introduced**
- **Since 1980, 75% new drugs in 2 classes- quinolones & ß lactams**

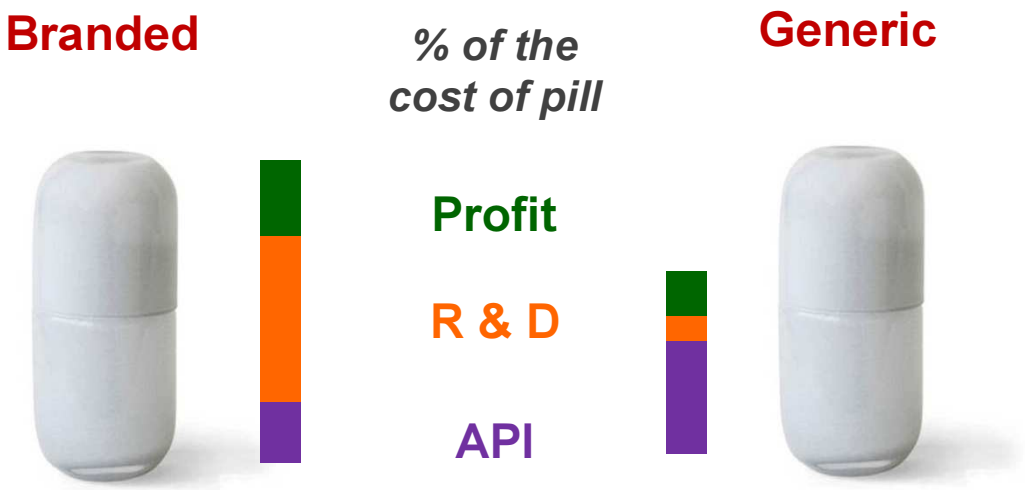
Could this happen with HIV pipeline ?

- **no new PI for past 6 years**
- **better compounds within class**
- **what new targets are being pursued ?**

Nanoformulations

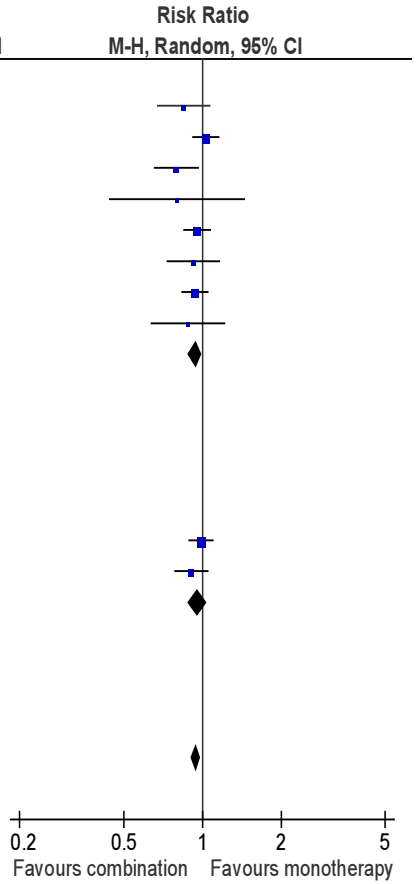
How they are made:

1. Same thing, only smaller (‘solid drug nanoparticle’)
2. oil-in-water nanoemulsions
3. stuck onto something, to get somewhere particular , or release in a particular way *-dendrimers, etc*
4. Tuned by size, charge, & whatever they’re stuck onto



Different Strategies - PI monotherapy

Study or Subgroup	PI monotherapy Events	Total	Combination therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Lopinavir						
Arribas 2005 (OK Pilot)	17	21	20	21	4.3%	0.85 [0.68, 1.07]
Cahn 2011 (wk51.4)	39	41	36	39	17.3%	1.03 [0.92, 1.16]
Gutmann 2010 (MOST)	23	29	31	31	6.0%	0.80 [0.66, 0.97]
Hasson 2011 (KAMON 2)	8	15	10	15	0.6%	0.80 [0.44, 1.45]
Meynard 2010 (KALESOLO)	73	87	87	99	16.3%	0.95 [0.85, 1.07]
Nunes 2009 (KalMo wk 96)	24	30	26	30	4.3%	0.92 [0.74, 1.16]
Pulido 2008 (OK04 wk48)	85	103	90	102	17.4%	0.94 [0.83, 1.05]
Waters 2008 (wk48)	18	26	22	28	2.2%	0.88 [0.64, 1.21]
Subtotal (95% CI)		**352**		**365**	**68.4%**	**0.94 [0.89, 1.00]**
Total events	287		322			
Heterogeneity: Tau² = 0.00; Chi² = 6.99, df = 7 (P = 0.43); I² = 0%						
Test for overall effect: Z = 2.12 (P = 0.03)						
1.1.2 Darunavir						
Arribas 2010 (MONET wk48)	107	127	110	129	20.8%	0.99 [0.89, 1.10]
Katlama 2010 (MONOI)	82	112	91	113	10.8%	0.91 [0.79, 1.05]
Subtotal (95% CI)		**239**		**242**	**31.6%**	**0.96 [0.88, 1.04]**
Total events	189		201			
Heterogeneity: Tau² = 0.00; Chi² = 0.88, df = 1 (P = 0.35); I² = 0%						
Test for overall effect: Z = 0.94 (P = 0.35)						
Total (95% CI)		**591**		**607**	**100.0%**	**0.95 [0.90, 0.99]**
Total events	476		523			
Heterogeneity: Tau² = 0.00; Chi² = 7.91, df = 9 (P = 0.54); I² = 0%						
Test for overall effect: Z = 2.28 (P = 0.02)						
Test for subgroup differences: Not applicable						



Study	Strategy
ACTG 5142 (2008)	bPI+ NNRTI
ANRS 121 (2008)	bPI+ NNRTI
RADAR (2013)	bPI + RAL
ACTG 5262 (2012)	bPI + RAL
NEAT 001 / ANRS 143	bPI + RAL
SPARTAN (2012)	bPI + RAL
PROGRESS (2012)	bPI + RAL
MODERN	bPI + MVC
A4001078	bPI + MVC
ACTG 5116 (2007)	bPI + NNRTI
ROCnRAL ANRS157	MVC+RAL
EARNEST (2013)	bPI + RAL
INROADS (2013)	bPI + NNRTI

Ageing and Inflammation

- Cardiovascular disease
- Cerebrovascular disease
- Diabetes
- Cancer
- Bone disease
- Declining renal function
- Cognition
- Peripheral neuropathy

Natural selection favors gene variants that promote fertility and immunity

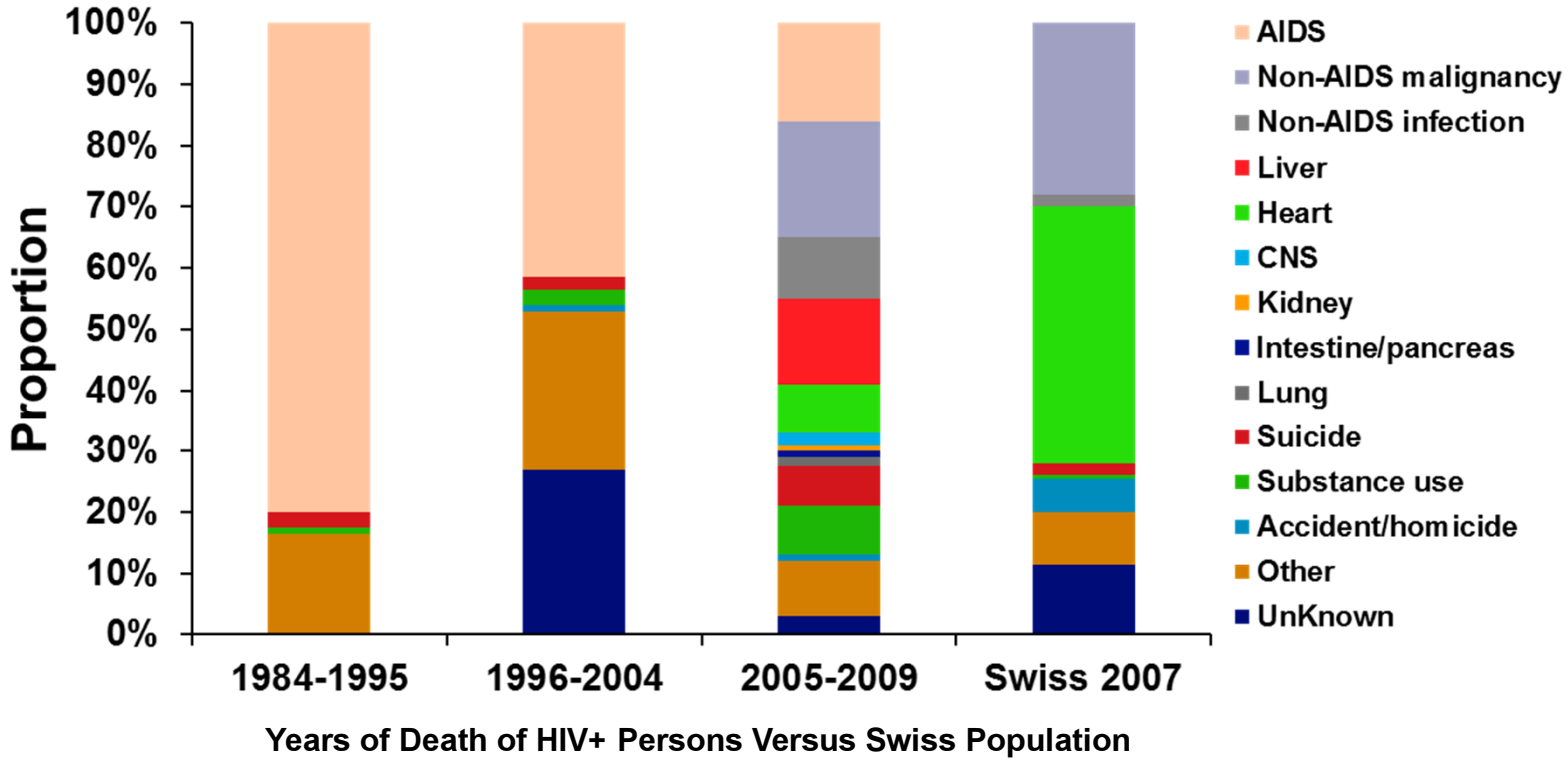
- **i.e. powerful immune response to infection, which later contributes to ageing phenotype and risk for co-morbidities**

ARVs do not currently prevent the cascade of inflammatory responses that are caused by HIV infection

Grund B et al. et al CROI 2013 Abst 60
Vijg and Campisi. Nature 2008; 454: 1065
Hunt et al CROI 2012

AIDS-related deaths have decreased, but non-AIDS-related ones have increased

Causes of death in participants from the Swiss HIV Cohort Study in 3 different time periods, and in the Swiss Population in 2007

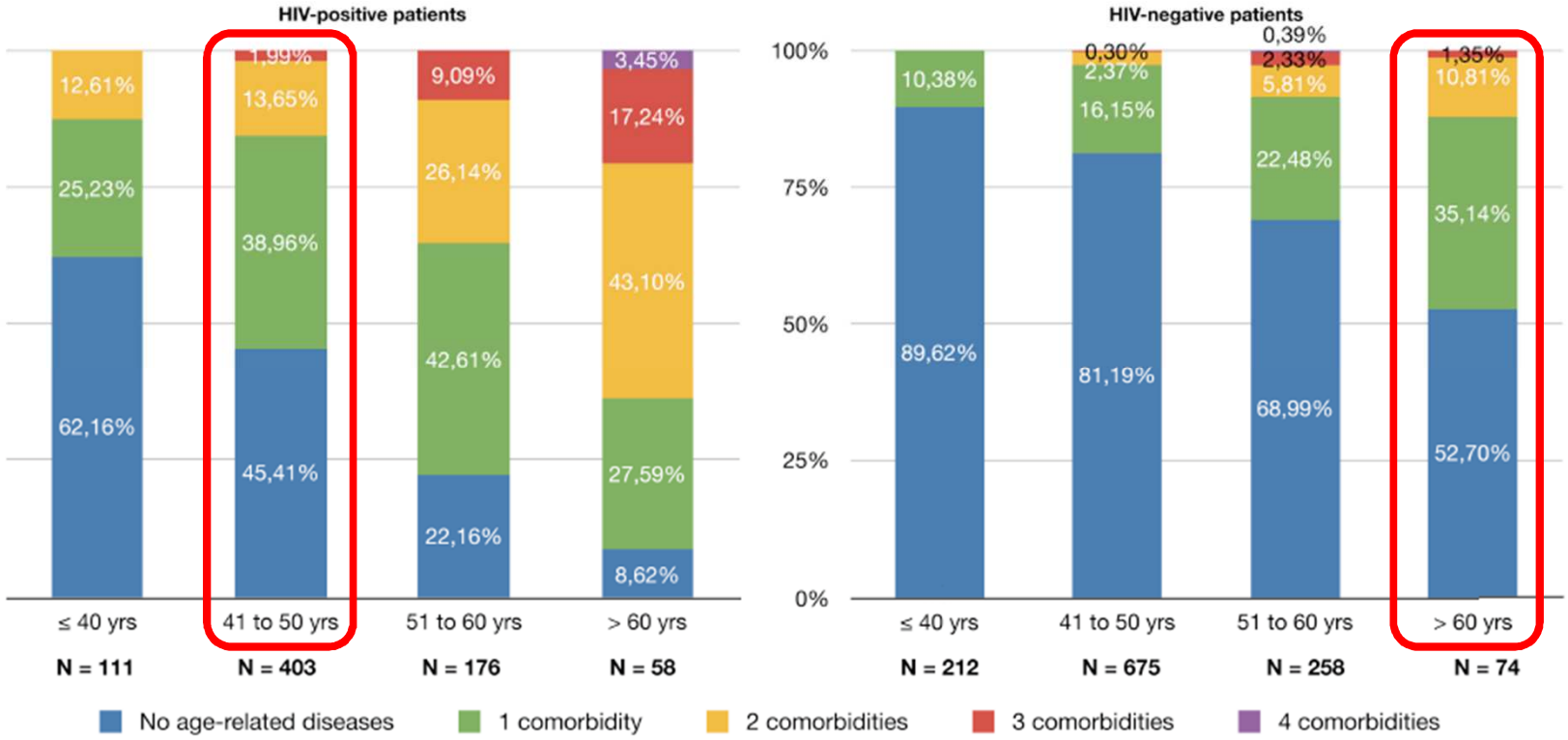


AIDS 2012
TURNING THE TIDE TOGETHER

Ruppik M, et al. 18th CROI; Boston, MA; February 27-March 2, 2011. Abst. 789.

Comorbidities
- more common and occurring earlier in HIV

Co-mobidities prevalence in cases and controls, stratified by age categories.



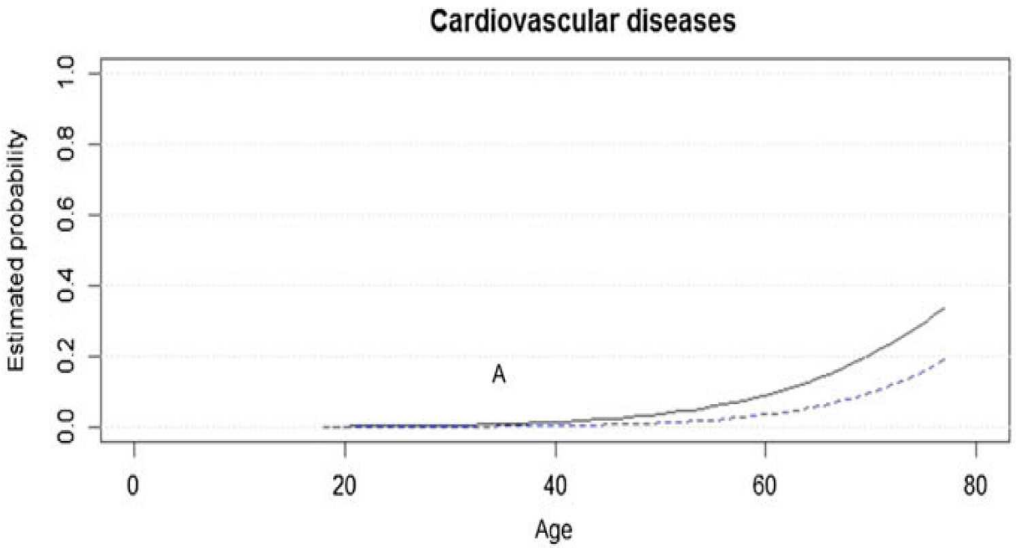
The following co-morbidities were analysed: Hypertension, Type 2 Diabetes, Cardiovascular Disease and Osteoporosis.

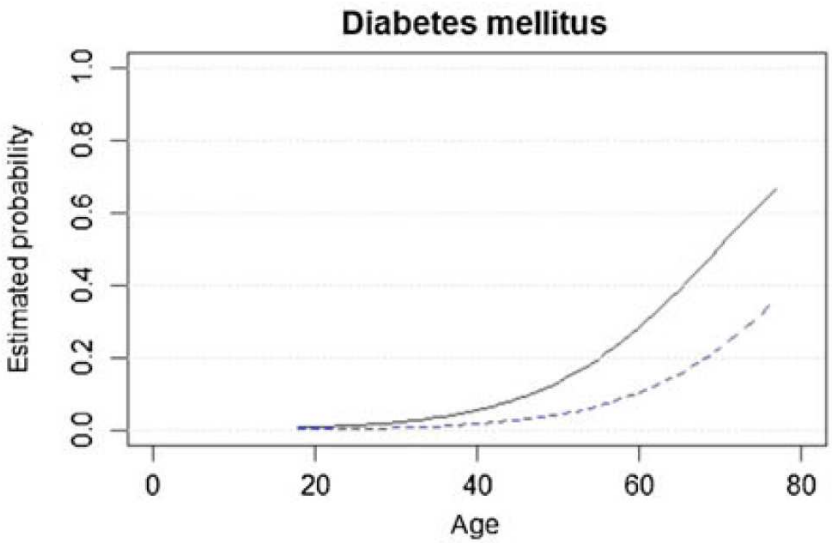
Co-morbidities prevalence was higher in cases than controls in all age strata (all p-values <0.001).

AIDS 2012
TURNING THE TIDE TOGETHER

Guaraldi G et al. Clin Infect Dis 2011; 53: 1120-1126

Cardiovascular Disease and Metabolic Syndrome





- **Pooled MI risk ↑1.5 - 3-fold**
- **HIV patients ≤60y higher CVD & ↑BP than HIV neg controls**

- **Type II DM risk ↑~4-fold**
- **FRAM Study – prevalence 37% (N=926)**

Insulin resistance strong predictor of

- **cardiovascular disease**
  - San Antonio Heart Study (N=2569)
  - Verona Diabetes Complication Study (N>1400)
- **stroke**
  - Northern Manhattan Study (N>1500)

Guaraldi G et al. CID 2011; 53:1120
DAD. Lancet 2008;371:1417
Worm JID 2010;201:318
Islam HIV Med 2012;13:453
Deeks Lancet 2013;382:1525

Grunfield JAIDS 2007;46:283
Worm. AIDS 2010, 24:427–435
Hanley Diabetes Care 2002;25:1177
Verona Diabetes Complications Study. Diabetes Care. 2002 Jul;25(7):1135
Rundek, Arch Neurol 2010;67:1195

Telmisartan

- **Only sartan licensed for cardio-protection**
  - ONTARGET Trial (N=25,620; 120000 patient-years) [NEJM 2008]
    - Equivalent to ramipril, better tolerated
  - TRANSCEND - ↓composite endpoint of CV death, MI, stroke
- **Reverses insulin resistance in T2 DM (non-HIV)**
  - numerous studies
- **Partial PPARγ agonist**
- **Potential effect on adipocytes**

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PLOS ONE

A Pilot Study of Telmisartan for Visceral Adiposity in HIV Infection: The Metabolic Abnormalities, Telmisartan, and HIV Infection (MATH) Trial

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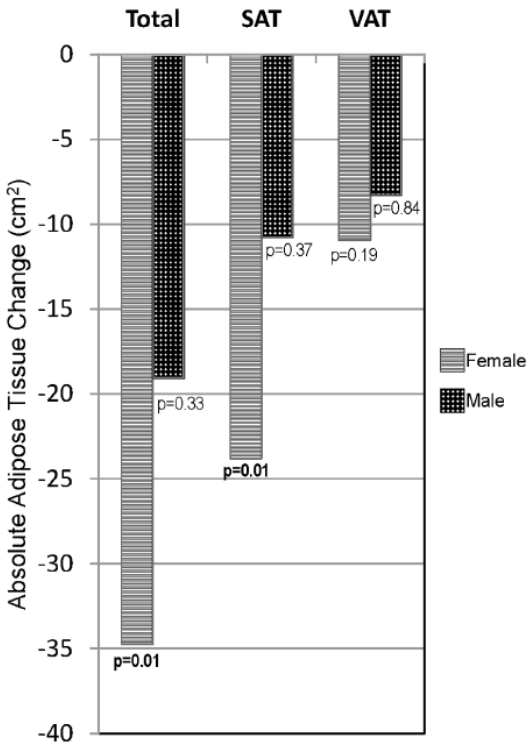
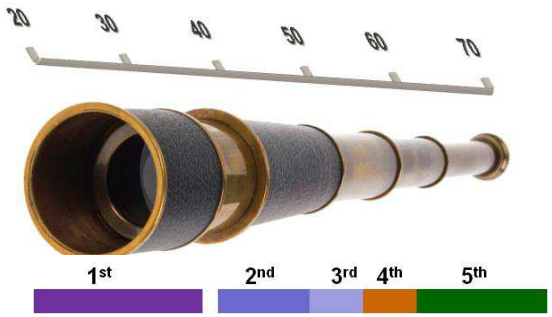
- N= 35
- 40mg q.d.
- Primary endpoint: 24-week change in % computed tomography (CT)-quantified VAT.
- Change in VAT, but not HOMA-IR



Lifetime perspective



- **Virological suppression is largely 'sorted'**
  Impact and management of low-level viraemia needs to be clarified
- **Treatment access, support and delivery has yet to be optimised**
- **HIV testing and prevention challenges remain**
  Innovations in HIV testing in 2014
- **No major advances when it comes to improving adherence**
- **Management of chronic, persistent immune activation**
  Increasingly linked to NCDs
- **Lifestyle adaptation remains a cornerstone**

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