UNIVERSITY OF LIVERPOOL

# *New Antiretrovirals and New Strategies*

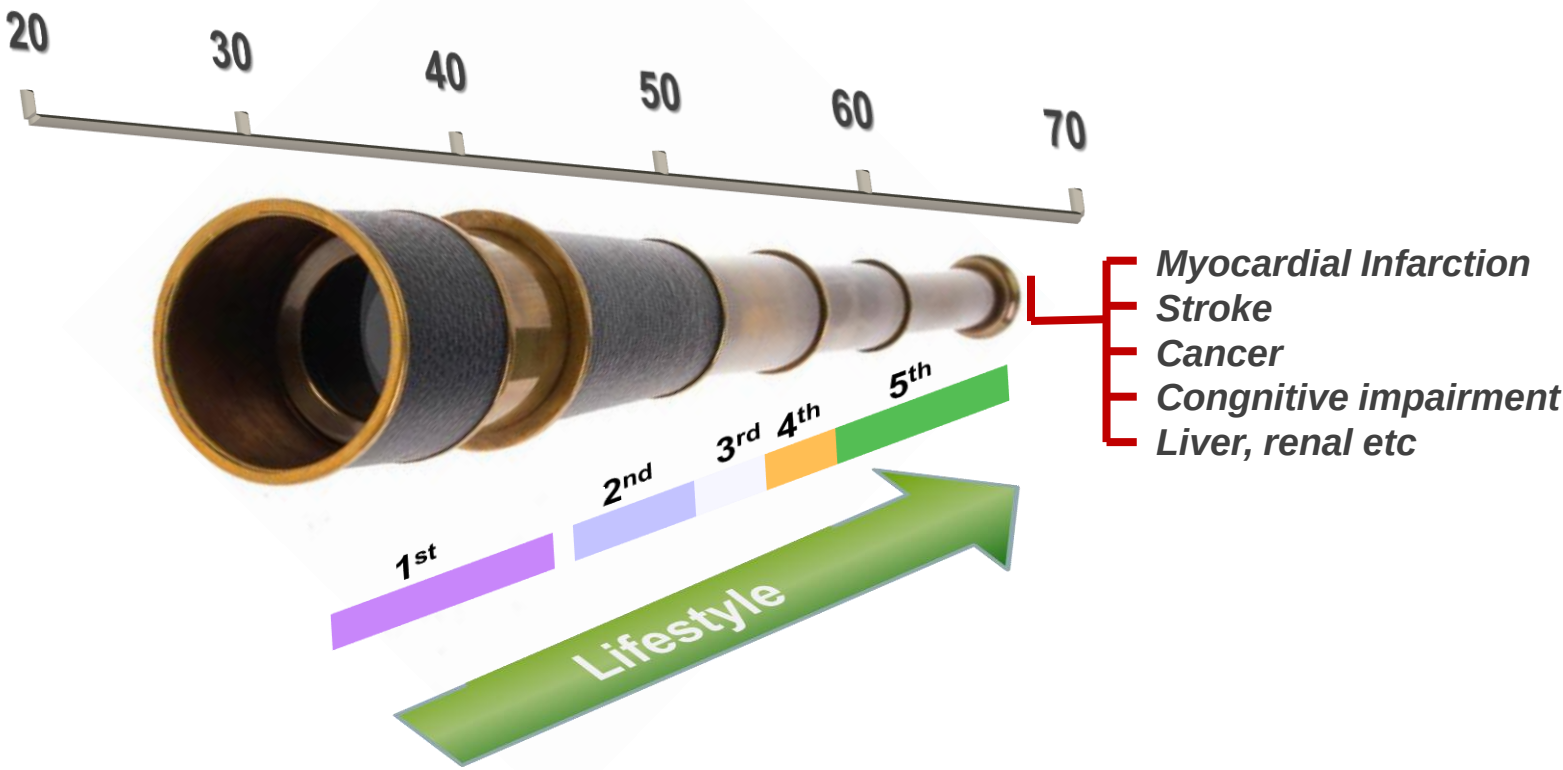
**Saye Khoo**

**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

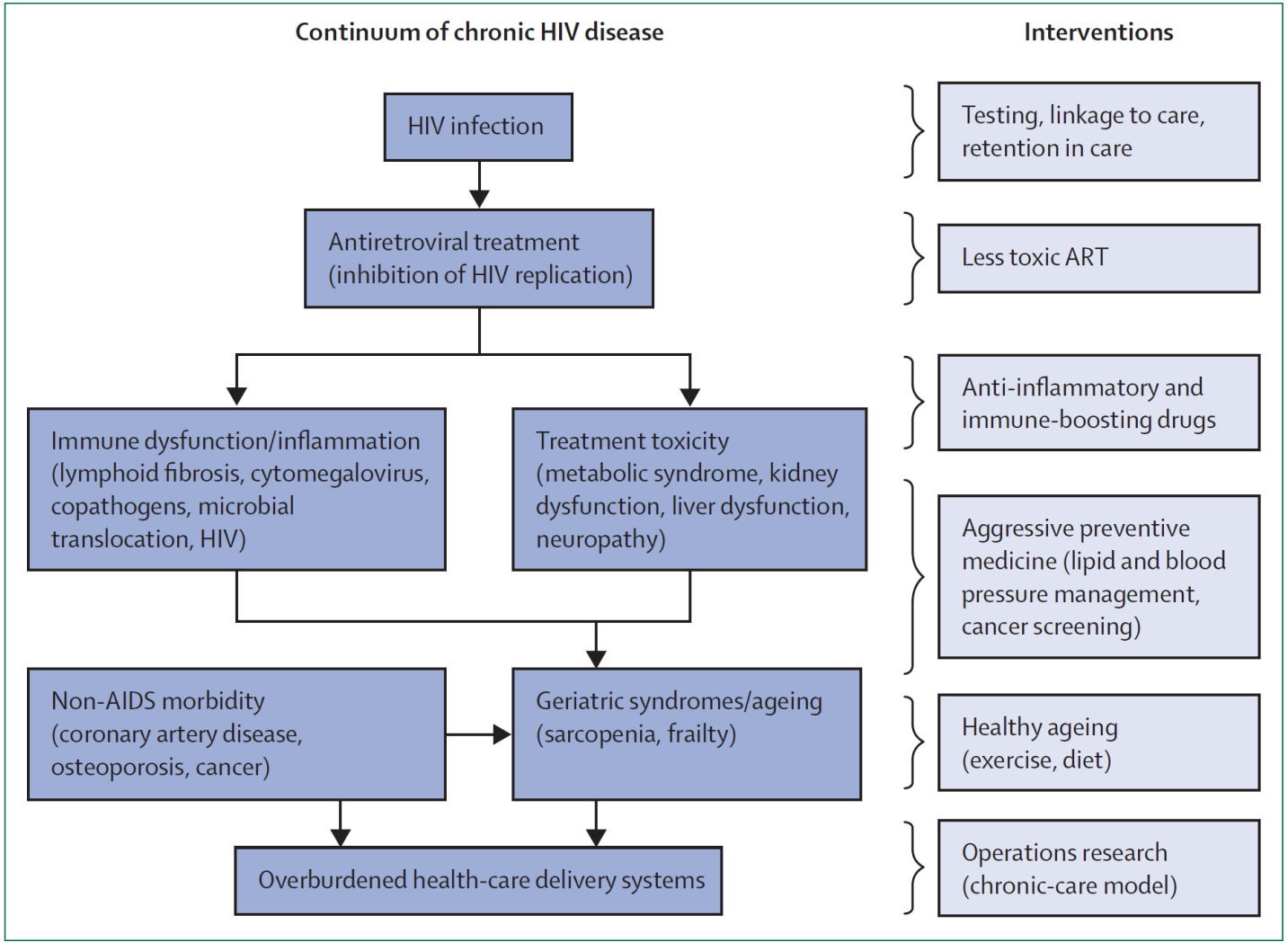
- Minimise resistance
- Minimise toxicity
- Preserve options
- Normalise Immunity
- Equip for future co-morbidity

# 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



# New Drugs, New Formulations, New Strategies

## *Improvements on existing classes*

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

## *New Classes*

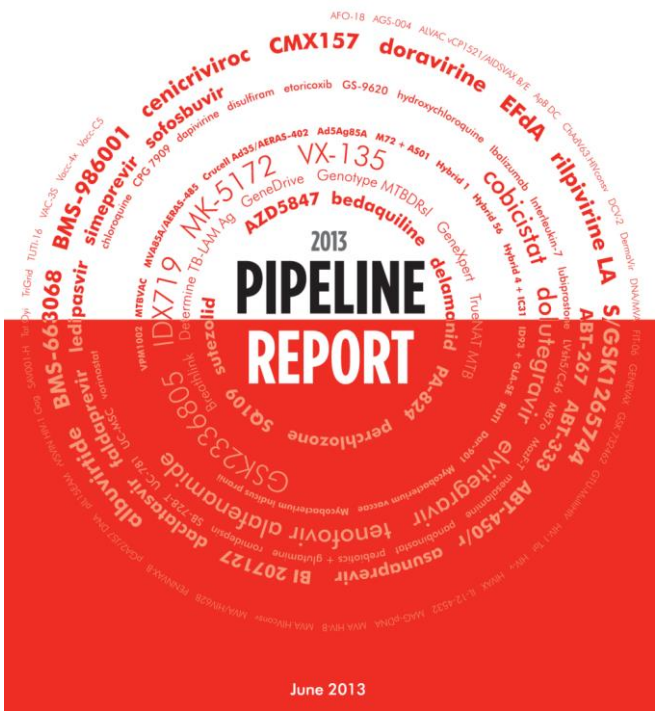
- Maturation inhibitors, LEDGINS, etc

## *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)<br>RPV-LA | TAF/FTC/EVGc<br>Cenicriviroc<br>BMS663068 |
| **Phase 2** | GSK126744 | Racivir<br>Amodoxovir<br>Elvucitabine | | | ABC/3TC/DTG<br>TAF/FTC/DRVc |

# Doravirine (MK-1439)

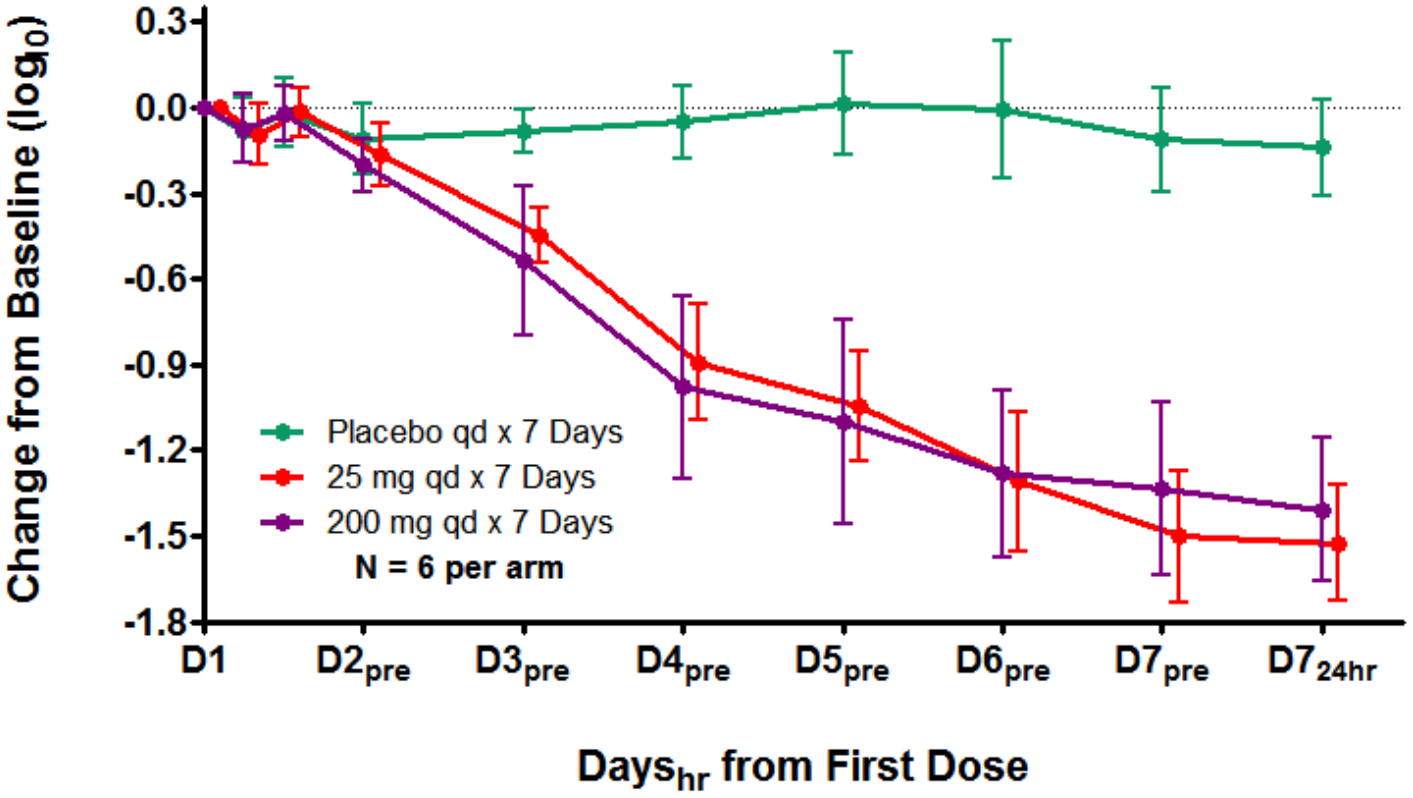
- **Pharmacology**
  - Potent - $IC_{95}$ ~19 nM (50% human serum)
  - Once-daily dosing; T½ 10-16h
  - P450 metabolism (CYP3A4/5)
    - No significant inhibition/induction of CYP P450s
    - No significant interaction with TDF
    - AUC ↑3.54; Cmin↑2.91 fold with RTV (100mg bd)
  - Good Preclinical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



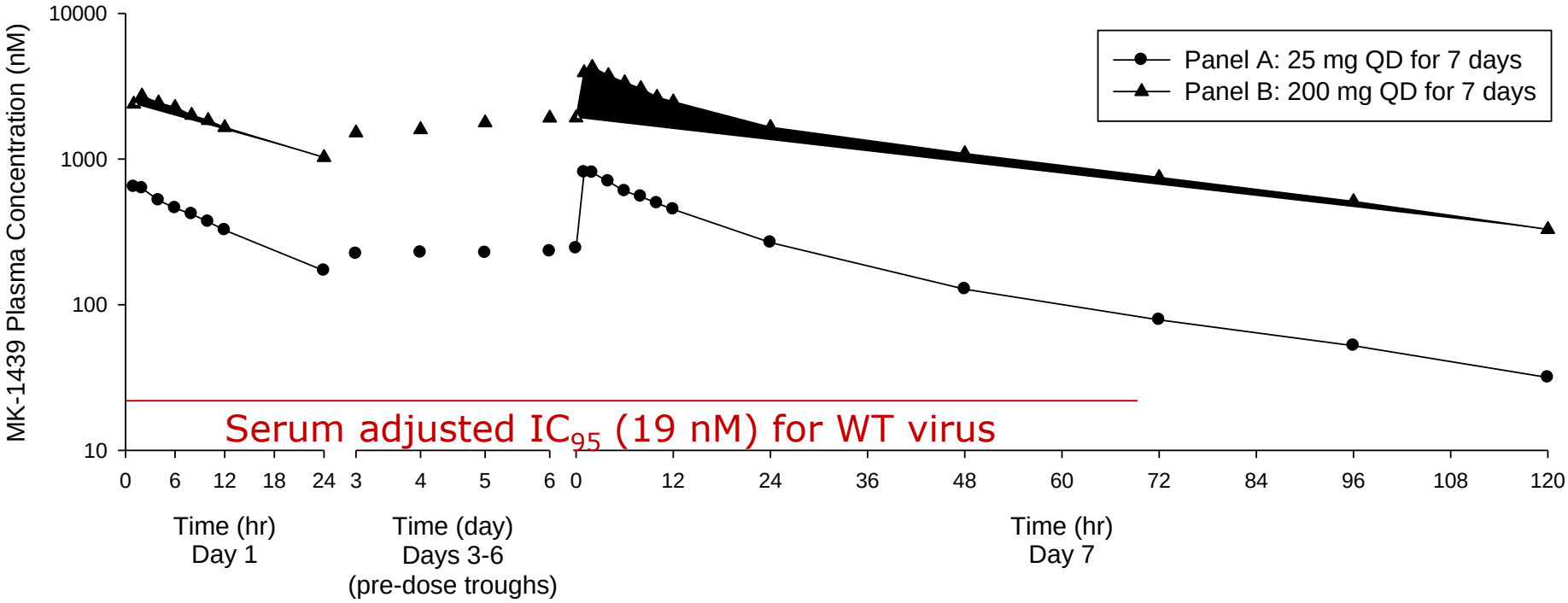

Similar HIV-RNA decline for both doses vs. placebo at 7 days:

- 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

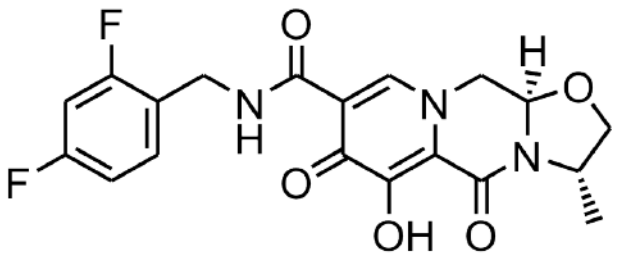



- **N = 6 patients per dose**
- **Pharmacokinetic profiles are comparable to healthy volunteers**
- **Steady state $C_{24hr}$ concentrations exceeded the serum adjusted $IC_{95}$ of wild-type virus by 14-fold (25 mg) and 87-fold (200 mg)**
- **$C_{24hr}$ accumulation ratio of 1.5- to 1.6-fold**

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

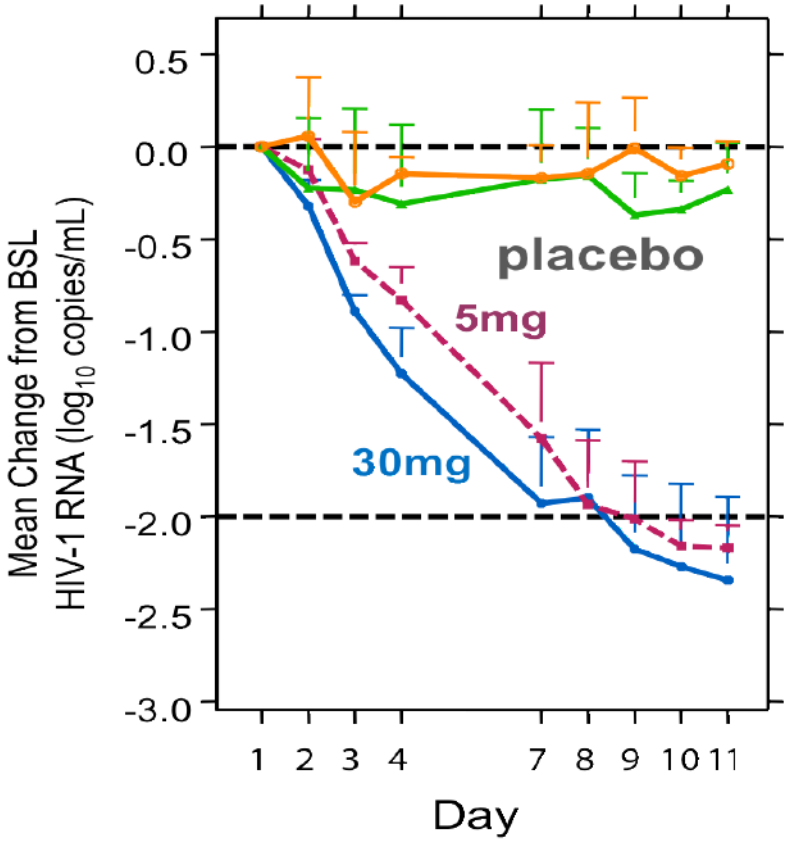
# GSK 126744

## GSK1265744 (744)

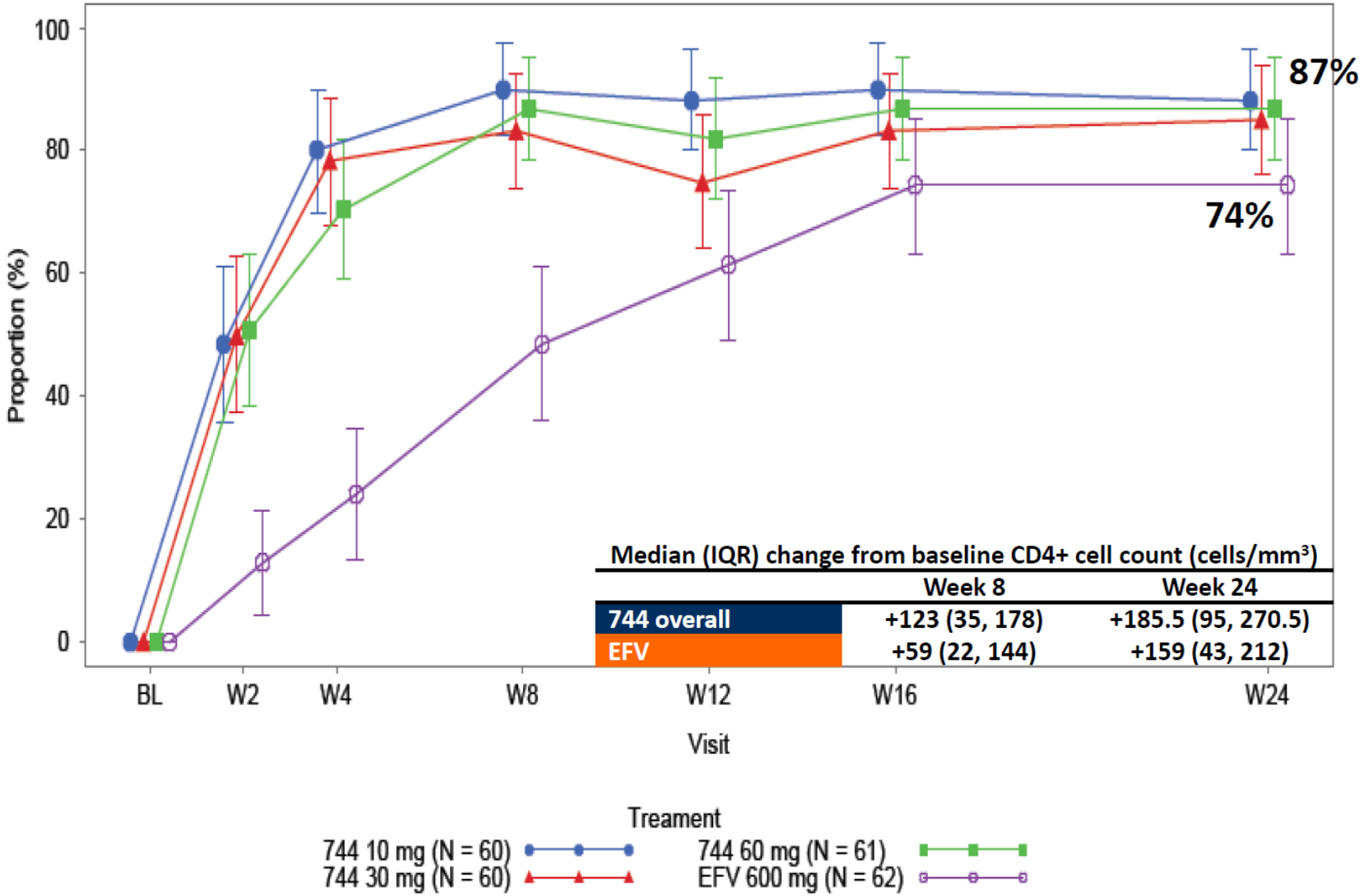



- HIV-1 integrase inhibitor; dolutegravir analogue
- Oral drug ($t_{½}$ = 40 hours)
- Long-acting SC or IM injectable (apparent $t_{½}$ = 21-50 days)

- 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



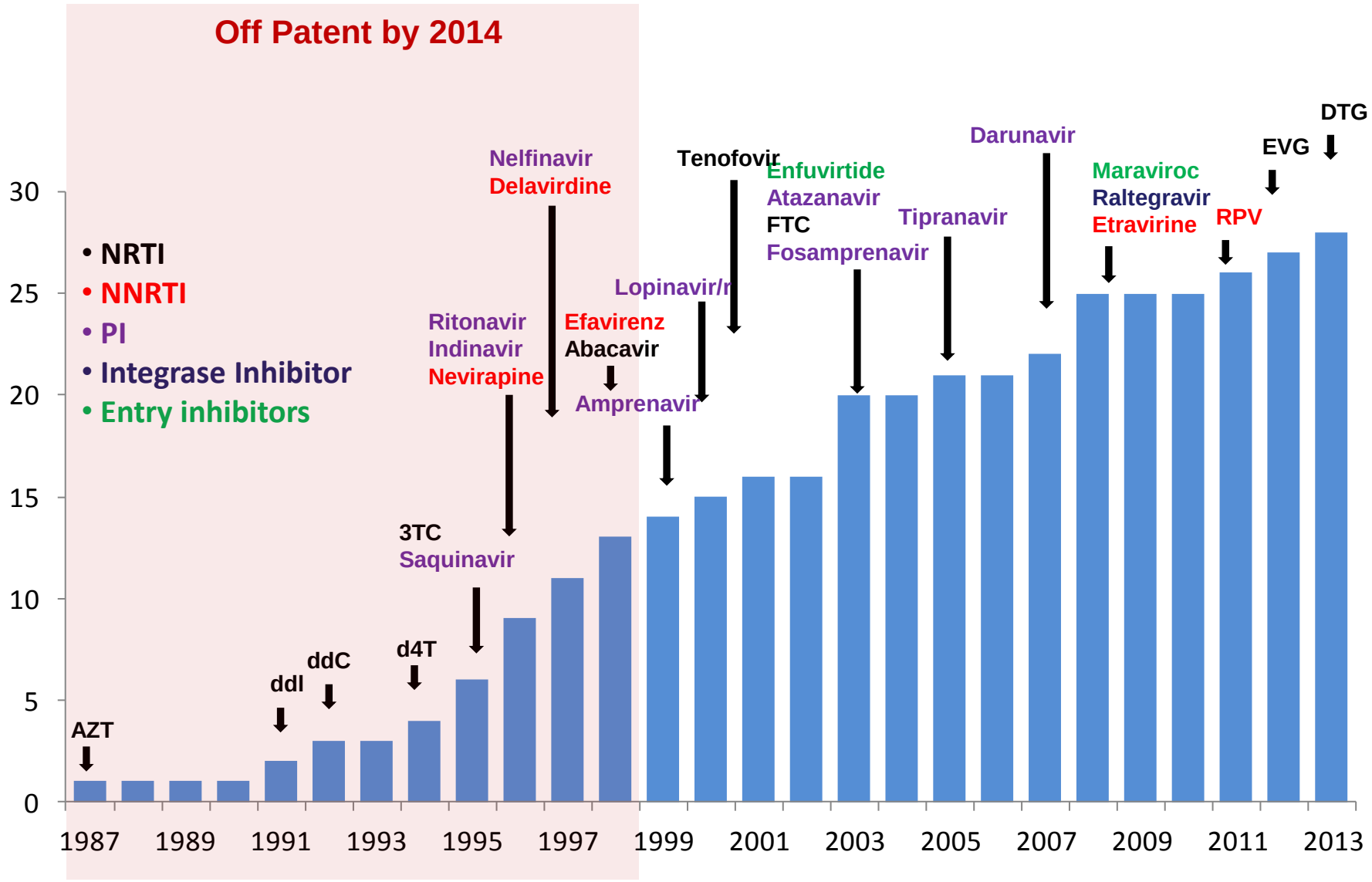

Margolis et al. EACS 2013 Abstr PS7/1


**Should've gone to** Specsavers®

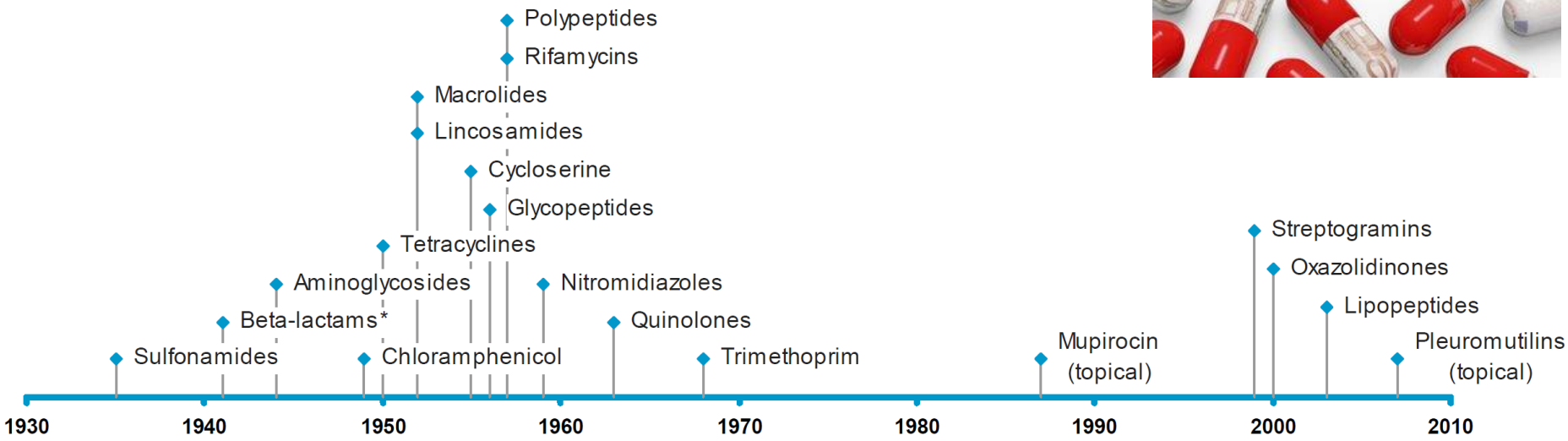
## Table 1B. HIV Treatment Pipeline, 2003–2013: Drugs Stopped or Stalled in Phase II/III

| 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 |

# HIV drug development (1987-2013)



# 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 ?**

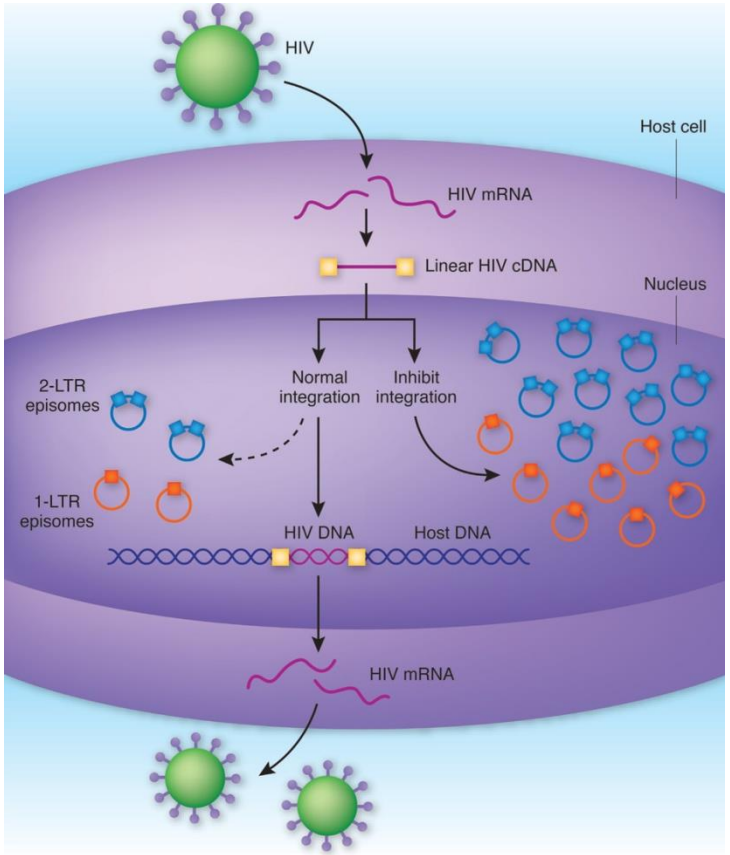
# A neglected pathway of HIV infection ?

Journal of Virology

**An HIV-1 Replication Pathway Utilizing Reverse Transcription Products That Fail To Integrate**

Benjamin Trinité, Eric C. Ohlson, Igor Voznesensky, Shashank P. Rana, Chi N. Chan, Saurabh Mahajan, Jason Alster, Sean A. Burke, Dominik Wodarz and David N. Levy

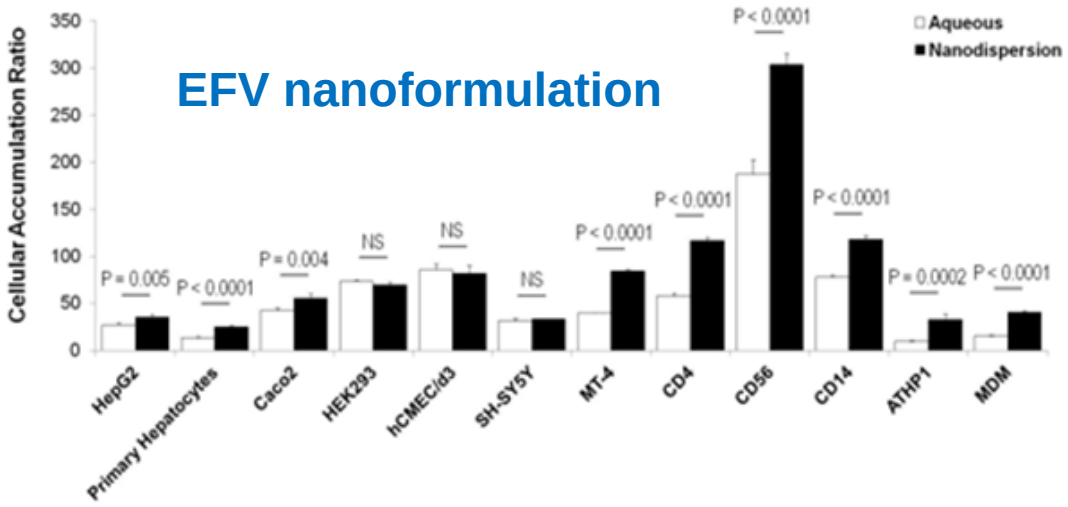
- ≥90% HIV proviral DNA fails to integrate
- 1- and 2LTR circles assumed not to contribute to replicating pool
- Viral rebound following cessation of ART genetically match 2LTR circles
- Alternative, 'salvage' pathway of productive infection from unintegrated viral DNA
- Lasts several weeks, ?? Longer
- Requires *Vpr*
- Levels ~1 order of magnitude less than integrated proviral DNA

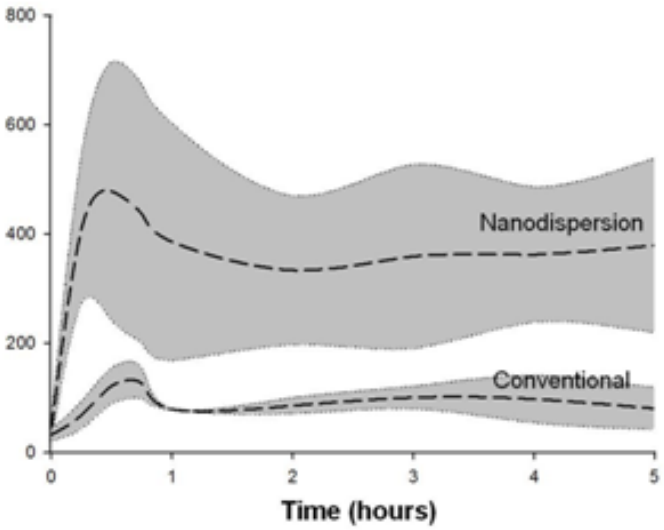



***How important in clinical practice ?***

Trinite et al, J Virol 2013, 87(23):1270

# Nanoformulations



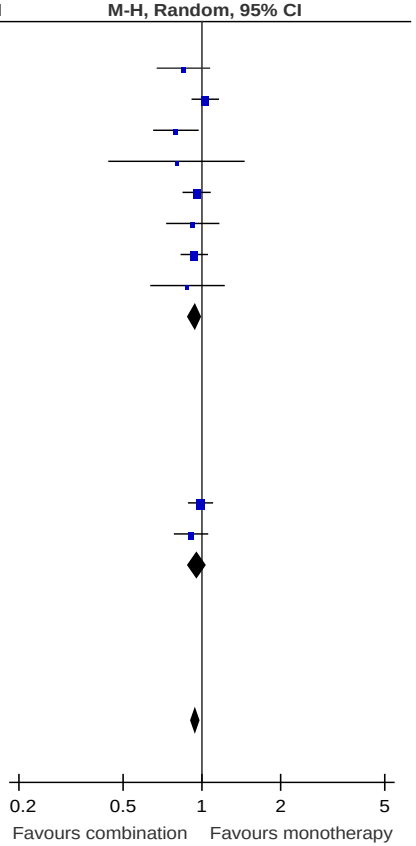




## What they can do:

1. Improve bioavailability of poorly absorbed compounds
2. Increase plasma half life eg through slow release IM injection
   *-rilpivirine LA, GSK1265744*
3. allow co-formulations, potentially tunable to match PK
4. target certain cells and tissues, eg monocyte-macrophages
   - *conjugation to folate, magnetite*
5. allow scale up through cheaper/less drugs, better co-formulations
   *– lower doses, cheap manufacturing costs, high drug loading*

# Different Strategies - PI monotherapy

| Study or Subgroup | PI monotherapy Events | PI monotherapy Total | Combination therapy Events | Combination therapy 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 |

# bPI + Integrases

## Poor performance in NRTI-sparing regimens

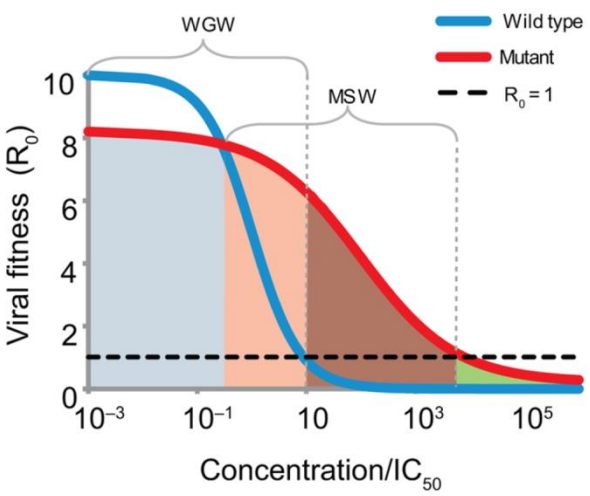
- *Is there a negative interaction between the drugs ?*

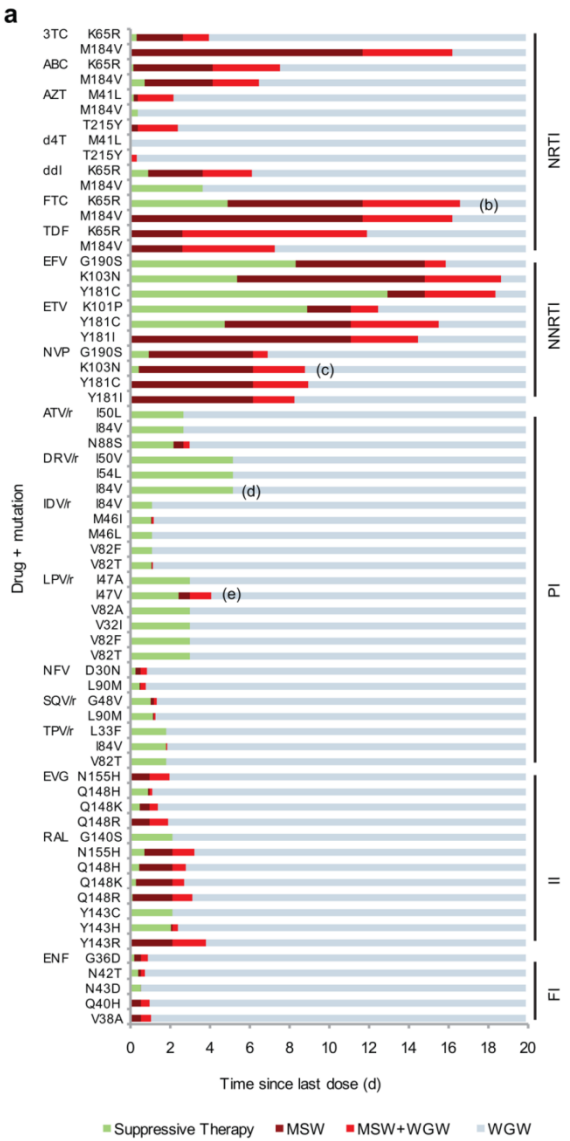
nature medicine

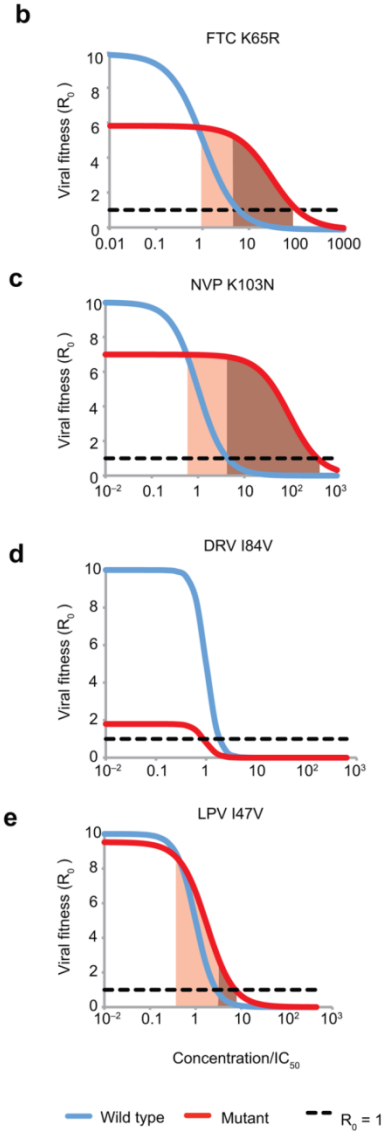
# Antiretroviral dynamics determines HIV evolution and predicts therapy outcome

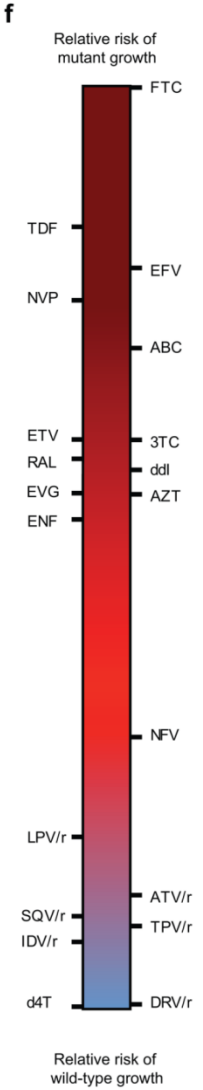
Daniel I. S. Rosenbloom[1,*], Alison L. Hill[1,2,*], S. Alireza Rabi[3,*], Robert F. Siliciano[3,4,†], and Martin A. Nowak[1,†]

*Nat Med.* 2012 September ; 18(9): 1378–1385.



nature medicine

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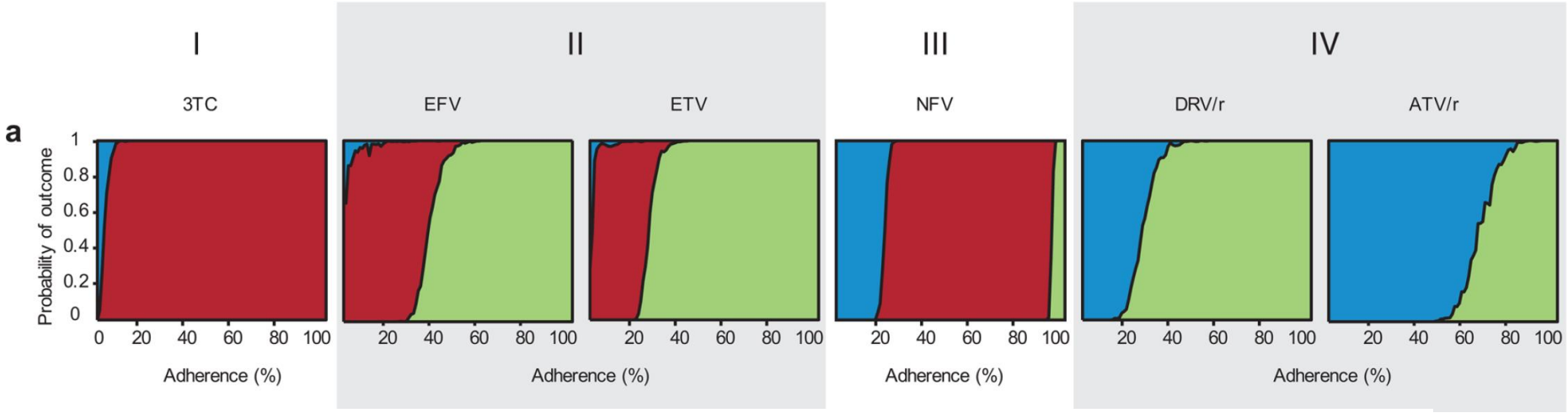


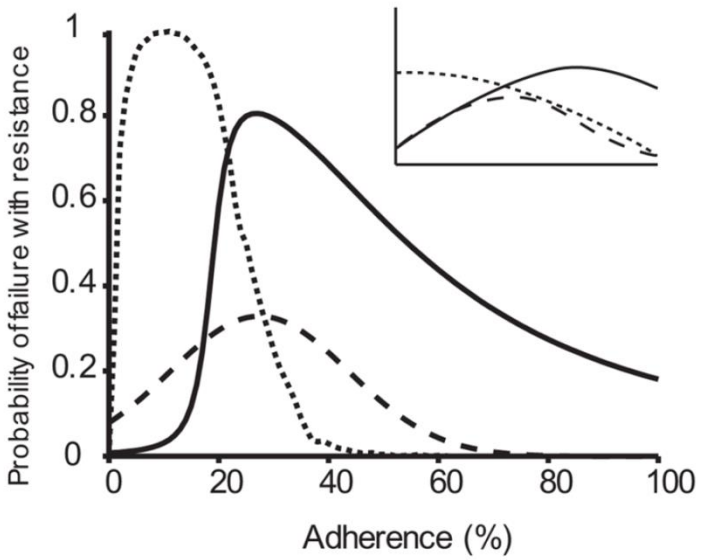


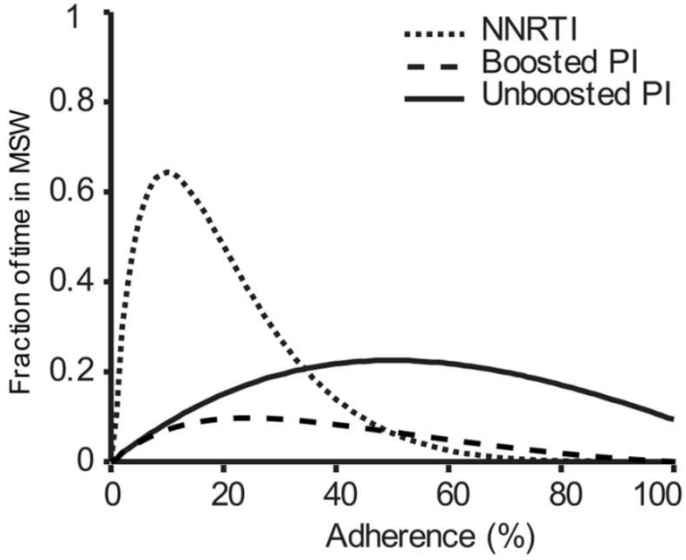

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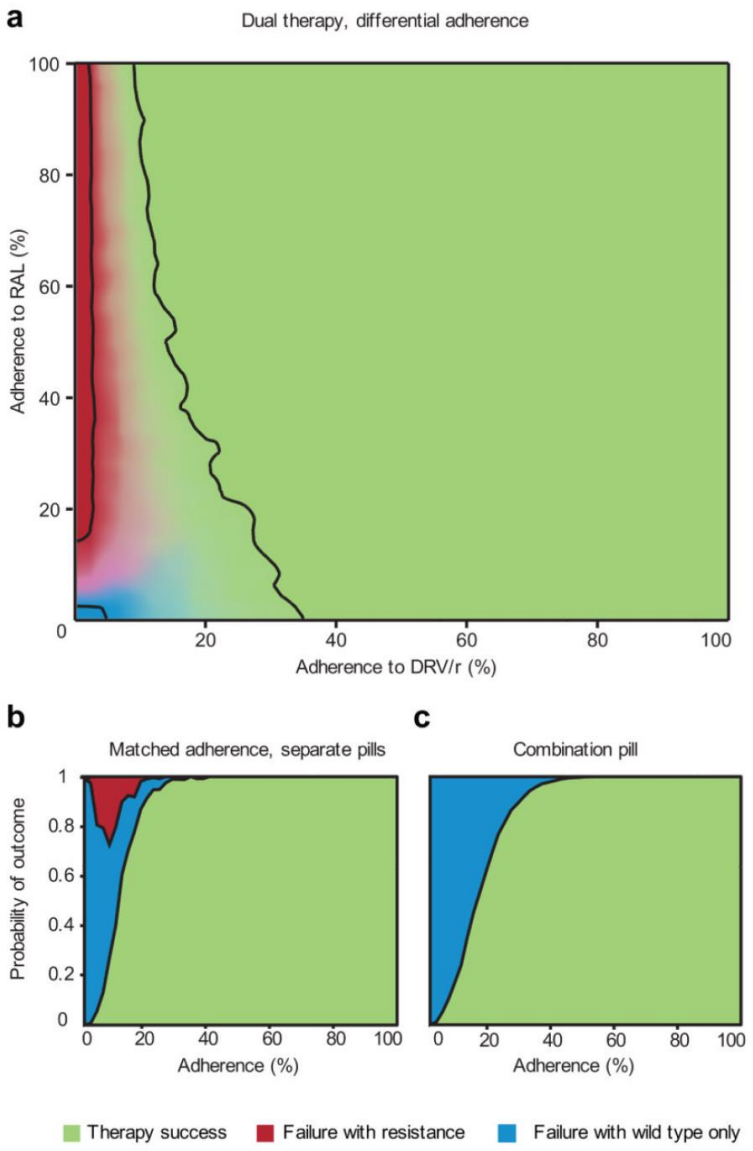
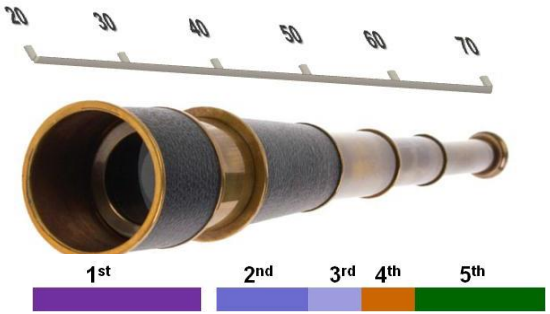
## *Co-formulations*

- Simulated adherence-resistance relationship with DRVr + Raltegravir
- Assumes random missed doses separately
- Raltegravir less forgiving for low adherence than DRVr
- At low levels of adherence (e.g. <40%), co-formulations predicted to be more likely to rebound, but less likely to develop resistance



# Lifetime perspective

## *– how does it influence optimal management in 2013 ?*




## *Optimal CD4 response*

- **Danish Study (N=1758) – magnitude of CD4 rise (but not baseline) associated with mortality.**
- **‘controls’ and lifestyle – risk of MI, lung cancer, head & neck cancer inceased amonst parents of HIV patients**

## *Optimal virological response*

- **should we tolerate blips and low grade viraemia ?**

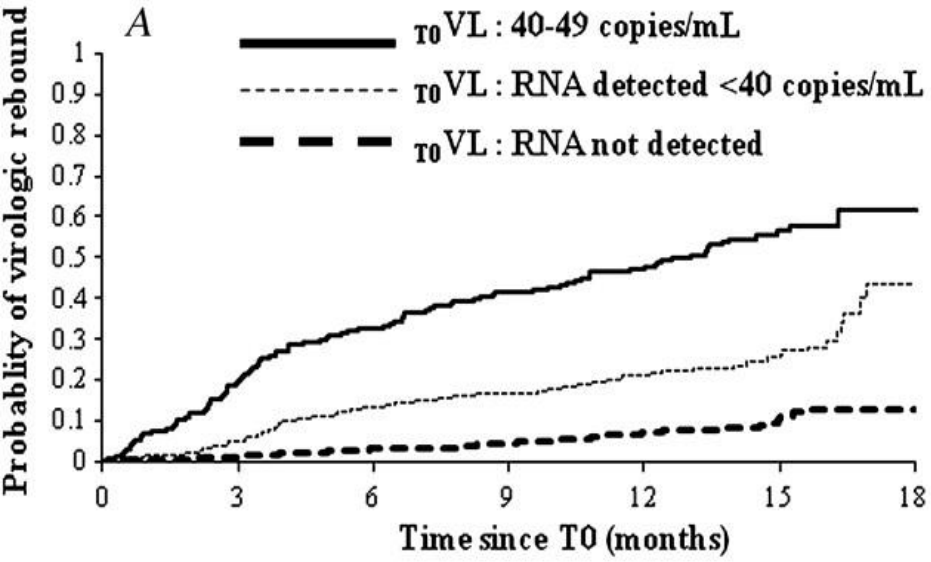
Rasmussen et al. BMC Infect Dis 2010; 10:169
Helleberg et al AIDS 2013, 27*:1021–1026*

# Persistent low-level viraemia

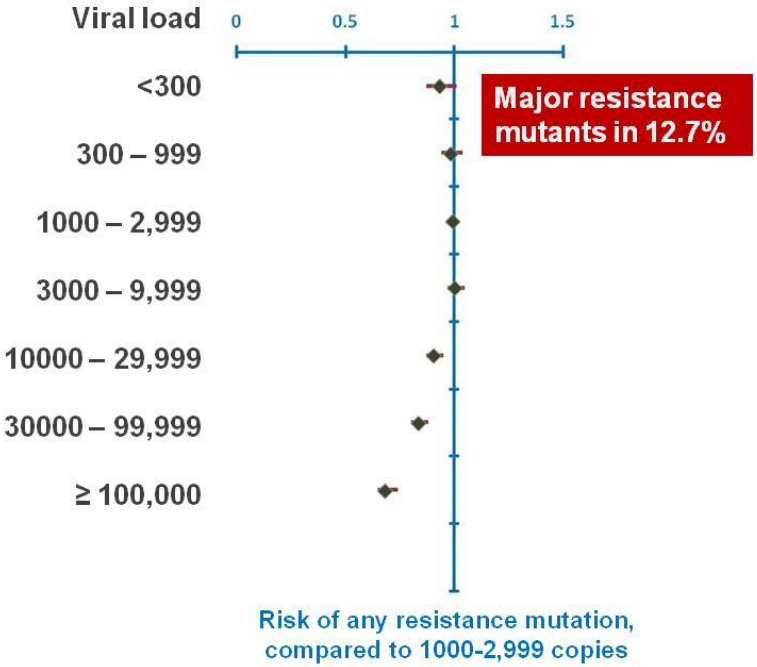
- ***Is it a bad thing ?***
  - **May be assay-specific**
  - **Linked to virological failure, resistance**
- ***What is the cause ?***
  - **Adherence**
  - **Latently infected cells**
  - **anatomical compartment**
  - **Ceiling to ART efficacy, eg cell-to-cell transmission**
- ***Can we do anything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

# Low Level Viraemia, Rebound & Resistance

**Risk of Rebound**
**Abbott RealTime**




**Risk of Resistance**
**UK Resistance Database**




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

**UK resistance database**
**1999 - 2006**

**N = 7861 tests**

Doyle et al CID 2012;54:724

Mackie et al. JID 2010;201:1303

# Persistent low-level viraemia

**ERAS Study**

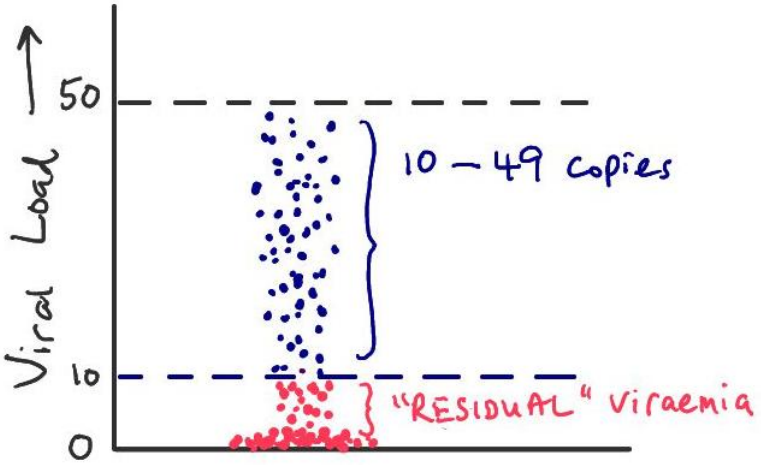
**Persistently suppressed - 1st Line NNRTI-ART for up to 15 years**
**N = 104**

**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 ?

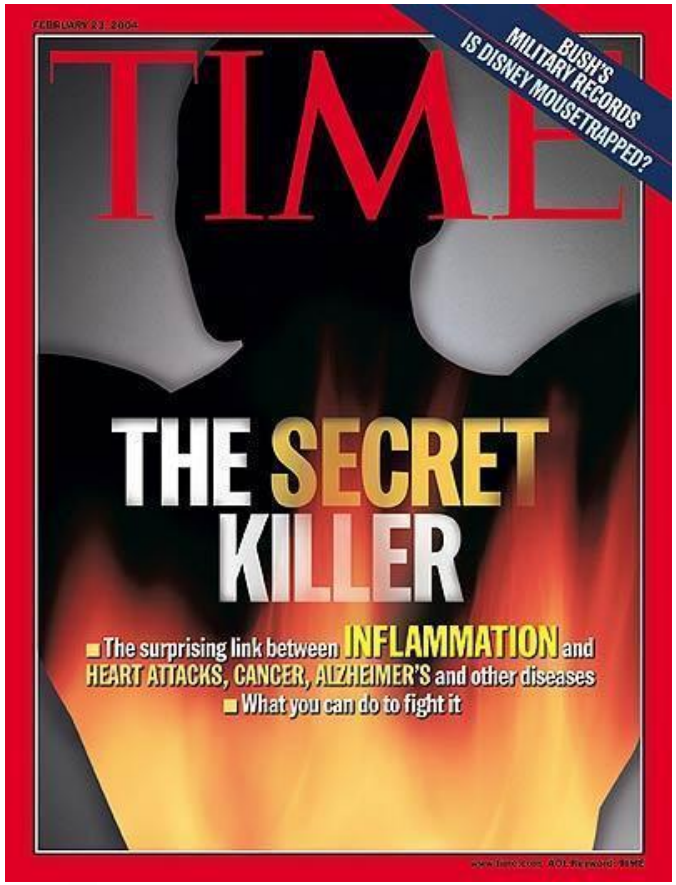
- Low level viraemia not always indicative of poor adherence
- Not all compartments are sterilised, eg CNS, GALT




- 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

# Ageing and Inflammation

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



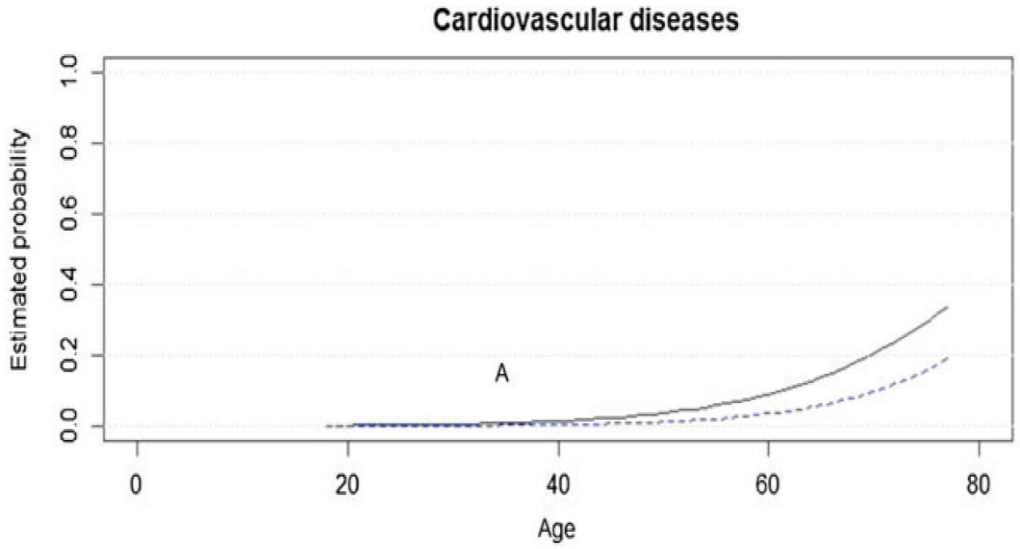

Natural selection favors gene variants that promote fertility and immunity

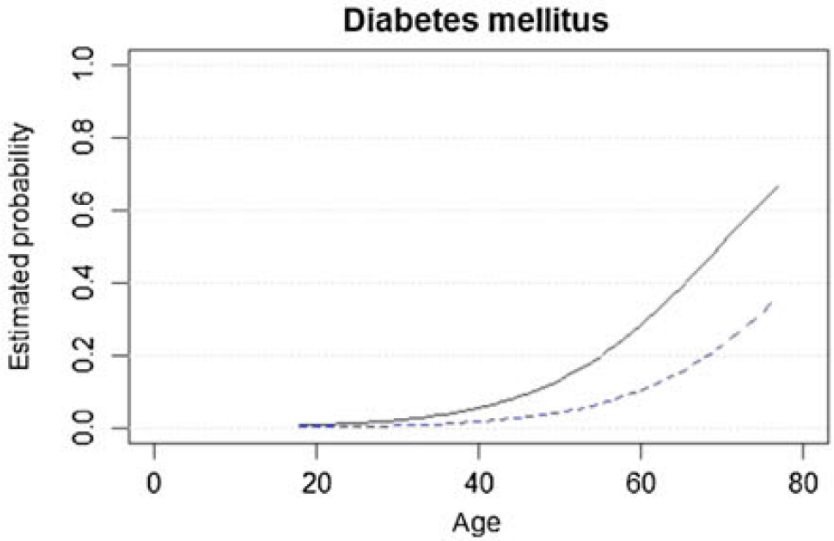
- i.e. powerful immune response to infection, which later contributes to ageing phenotype and risk for co-morbidities

**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

# 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**

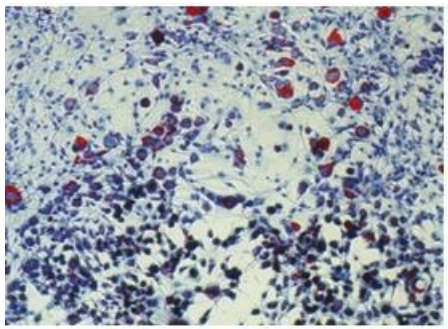
- **cardiovascular disease**
  - San Antonio Heart Study (N=2569)
  - Verona Diabetes Complication Study (N>1400)
- **stroke**
  - Northern Manhattan Study (N>1500)


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

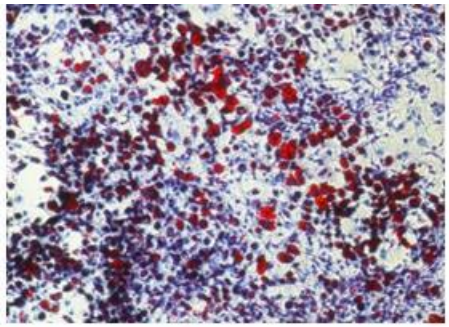
Grunfield JAIDS 2007;46:283
Worm. AIDS 2010, 24:427–435
Hanley Diabetes Care 2002;25:1177
Verona Diabetes Complications Study. Diabetes Care. 2002 Jul;25(7):1135
Rundek, Arch Neurol 2010;67:1195

# Telmisartan

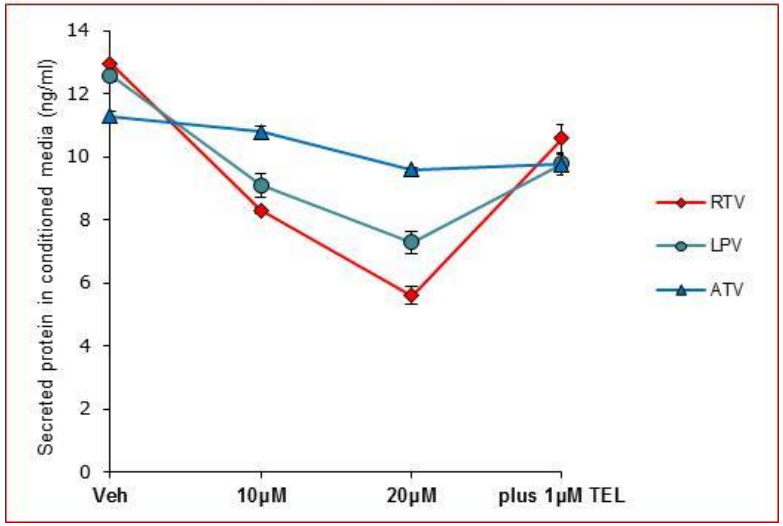
- **Only sartan licensed for cardio-protection**
  - ONTARGET Trial (N=25,620; 120000 patient-years) [NEJM 2008]
    - Equivalent to ramipril, better tolerated
  - TRANSCEND - ↓composite endpoint of CV death, MI, stroke
- **Reverses insulin resistance in T2 DM (non-HIV)**
  - numerous studies
- **Partial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



Lopinavir



Lopinavir + telmisartan



# TEL in HIV context

Original article

Antihypertensive and metabolic effects of telmisartan in hypertensive HIV-positive patients

Jacopo Vecchiet[1]*, Claudio Ucciferri[1], Katia Falasca[1], Paola Mancino[1], Angelo Di Iorio[2], Raffaele De Caterina[3]

Antiviral Therapy 2011; 16:639-645

- N= 18
- 80mg q.d.
- Reduction in HOMA-IR

**Table 2.** Clinical and biochemical characteristics of patients at different time points

| Variable | Time point | | | | *P*-value T0 versus T1 | *P*-value for trend |
|---|---|---|---|---|---|---|
| | Baseline (T0) | 1 Month (T1) | 3 Months (T3) | 6 Months (T6) | | |
| ESR, mm/h | 20.89 ±15.33 | 16.56 ±9.93 | 13.11 ±6.98 | 13.39 ±10.69 | 0.06 | 0.01 |
| Total cholesterol, mg/dl | 229.78 ±36.99 | 232.50 ±36.31 | 214.11 ±35.34 | 207.78 ±39.28 | 0.56 | <0.001 |
| HDL cholesterol, mg/dl | 40.00 ±9.88 | 42.78 ±11.80 | 43.33 ±9.57 | 43.44 ±9.23 | 0.01 | 0.01 |
| LDL cholesterol, mg/dl | 136.42 ±32.54 | 140.11 ±31.57 | 124.34 ±32.62 | 120.99 ±34.42 | 0.04 | <0.001 |
| Triglycerides, mg/dl | 280.44 ±105.57 | 240.11 ±81.77 | 221.67 ±75.38 | 217.67 ±70.44 | <0.001 | <0.001 |
| Systolic blood pressure, mmHg | 151.11 ±6.54 | 137.78 ±5.48 | 133.89 ±9.32 | 131.11 ±7.39 | <0.001 | <0.001 |
| Diastolic blood pressure, mmHg | 96.67 ±7.48 | 86.67 ±6.42 | 83.89 ±7.19 | 83.33 ±4.54 | <0.001 | <0.001 |
| HOMA-IR | 3.87 ±2.64 | 3.15 ±2.14 | 3.15 ±1.83 | 3.23 ±1.93 | 0.01 | 0.01 |
| 10-Year cardiovascular risk, % | 16.83 ±8.04 | 18.11 ±8.17 | 15.50 ±8.40 | 14.22 ±7.68 | 0.20 | 0.01 |
| Cystatin C, mg/l | 1.04 ±0.30 | 0.97 ±0.27 | 0.95 ±0.29 | 0.89 ±0.25 | 0.21 | <0.001 |
| Microalbuminuria, mg/l | 5.82 ±5.44 | 3.33 ±2.85 | 2.54 ±2.27 | 2.12 ±1.78 | 0.05 | <0.001 |
| Interleukin-18, pg/ml | 420.25 ±138.03 | 392.61 ±153.67 | 361.48 ±158.33 | 340.68 ±155.28 | <0.001 | 0.01 |
| Endothelin-1, pg/ml | 16.49 ±2.93 | 15.60 ±2.40 | 15.17 ±2.51 | 14.71 ±2.47 | 0.05 | <0.001 |

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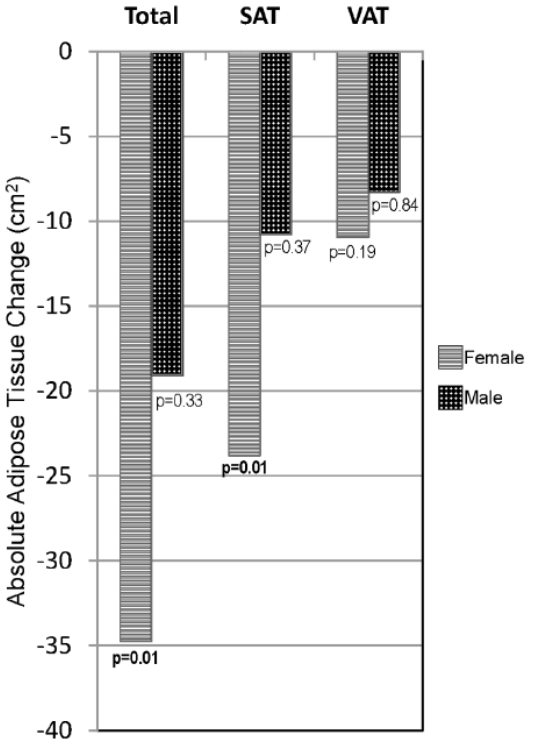
PLOS ONE

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

Jordan E. Lake[1]*, Chi-Hong Tseng[2], Judith S. Currier[1]

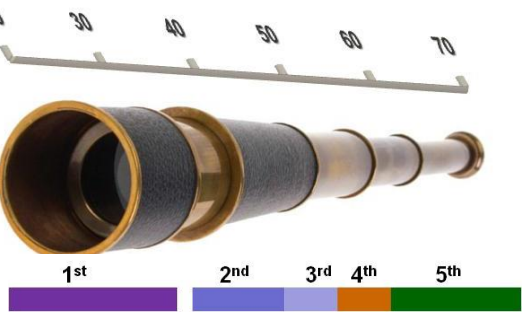
PLoS One. 2013; 8(3): e58135

- 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

## *– how does it influence optimal management in 2013 ?*




### *Role of ongoing immune activation*

- optimal timing of ARV initiation – seeding of latent reservoir, and maximal reduction of immune activation

### *Adjunctive therapy ?*

- Treat blunted CD4 responses
- Treat immune activation
- Modulation of metabolic syndrome
- Prevent other toxicities
- HDAC Inhibitors
- etc, etc

### *Lifestyle Adaptation*

Rasmussen et al. BMC Infect Dis 2010; 10:169
Helleberg et al AIDS 2013, 27*:1021–1026*

# Acknowledgements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***.. and many others ....***