New Antiretrovirals and New Strategies

Saye Khoo
HIV Pharmacology Group

Declaration of Interests

• 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

Myocardial Infarction
Stroke
Cancer
Cognitive impairment
Liver, renal etc

Lifestyle

20 30 40 50 60 70
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.

Continuum of chronic HIV disease

- HIV infection
- Antiretroviral treatment (inhibition of HIV replication)
  - Immune dysfunction/inflammation (lymphoid fibrosis, cytomegalovirus, copathogens, microbial translocation, HIV)
  - Treatment toxicity (metabolic syndrome, kidney dysfunction, liver dysfunction, neuropathy)
- Non-AIDS morbidity (coronary artery disease, osteoporosis, cancer)
- Geriatric syndromes/ageing (sarcopenia, frailty)
- Overburdened health-care delivery systems

Interventions

- Testing, linkage to care, retention in care
- Less toxic ART
- Anti-inflammatory and immune-boosting drugs
- Aggressive preventive medicine (lipid and blood pressure management, cancer screening)
- Healthy ageing (exercise, diet)
- Operations research (chronic-care model)
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
<table>
<thead>
<tr>
<th>INSTIs</th>
<th>NRTIs</th>
<th>PIs</th>
<th>NNRTIs</th>
<th>Other</th>
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<tr>
<td>Approved</td>
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<tr>
<td>Dolutegravir</td>
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<td>Phase 3</td>
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<tr>
<td>TAF</td>
<td>DRVc</td>
<td>Doravirine (MK1349) RPV-LA</td>
<td>TAF/FTC/EVGc Cenicriviroc BMS663068</td>
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<td>Phase 2</td>
<td></td>
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<tr>
<td>GSK126744</td>
<td>Racivir</td>
<td>Amodoxovir Elvucitabine</td>
<td>ABC/3TC/DTG TAF/FTC/DRVc</td>
<td></td>
</tr>
</tbody>
</table>
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]
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 ($t_{1/2} = 40$ hours)
- Long-acting SC or IM injectable (apparent $t_{1/2} = 21-50$ 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

### Median (IQR) change from baseline CD4+ cell count (cells/mm³)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Week 8</th>
<th>Week 24</th>
</tr>
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<tbody>
<tr>
<td>744 overall</td>
<td>+123 (35, 178)</td>
<td>+185.5 (95, 270.5)</td>
</tr>
<tr>
<td>EFV</td>
<td>+59 (22, 144)</td>
<td>+159 (43, 212)</td>
</tr>
</tbody>
</table>

Visit Scale:
- BL
- W2
- W4
- W8
- W12
- W16
- W24

Proportion (%):
- 0
- 20
- 40
- 60
- 80
- 100

Margolis et al. EACS 2013 Abstr PS7/1
How can we tell if these will lead to successful new drugs?

“There are clear signs of a recovery”

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

- 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 & β 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?

- ≥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

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

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

EFV nanoformulation
Different Strategies - PI monotherapy

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PI monotherapy</th>
<th>Combination therapy</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
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<tr>
<td>1.1.1 Lopinavir</td>
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<td>Arribas 2005 (OK Pilot)</td>
<td>17</td>
<td>21</td>
<td>20</td>
<td>21</td>
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<tr>
<td>Cahn 2011 (wk51.4)</td>
<td>39</td>
<td>41</td>
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<td>Gutmann 2010 (MOST)</td>
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<td>Hasson 2011 (KAMON 2)</td>
<td>8</td>
<td>15</td>
<td>10</td>
<td>15</td>
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<td>Meynard 2010 (KALESOLO)</td>
<td>73</td>
<td>87</td>
<td>87</td>
<td>99</td>
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<td>Nunes 2009 (KalMo wk 96)</td>
<td>24</td>
<td>30</td>
<td>26</td>
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<td>Pulido 2008 (OK04 wk48)</td>
<td>85</td>
<td>103</td>
<td>90</td>
<td>102</td>
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<td>Waters 2008 (wk48)</td>
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<td>26</td>
<td>22</td>
<td>28</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>352</td>
<td>365</td>
<td>68.4%</td>
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<tr>
<td>Total events</td>
<td>287</td>
<td>322</td>
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</tbody>
</table>

Heterogeneity: $\tau^2 = 0.00$; $I^2 = 6.99$, df = 7 (P = 0.43); $I^2 = 0$
Test for overall effect: Z = 2.12 (P = 0.03)

1.1.2 Darunavir

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PI monotherapy</th>
<th>Combination therapy</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Arribas 2010 (MONET wk48)</td>
<td>107</td>
<td>127</td>
<td>110</td>
<td>129</td>
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<tr>
<td>Katlama 2010 (MONOI)</td>
<td>82</td>
<td>112</td>
<td>91</td>
<td>113</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>239</td>
<td>242</td>
<td>31.6%</td>
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<tr>
<td>Total events</td>
<td>189</td>
<td>201</td>
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</table>

Heterogeneity: $\tau^2 = 0.00$; $I^2 = 88.8$, df = 1 (P = 0.35); $I^2 = 0$
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: $\tau^2 = 0.00$; $I^2 = 7.91$, df = 9 (P = 0.54); $I^2 = 0$
Test for overall effect: Z = 2.28 (P = 0.02)
Test for subgroup differences: Not applicable
<table>
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<th>Study</th>
<th>Strategy</th>
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<td>ACTG 5142</td>
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<td>(2008)</td>
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<td>ANRS 121</td>
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<td>(2008)</td>
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<td>RADAR</td>
<td>bPI + RAL</td>
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<td>(2013)</td>
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<td>ACTG 5262</td>
<td>bPI + RAL</td>
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<tr>
<td>(2012)</td>
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<td>NEAT 001 /</td>
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<td>ANRS 143</td>
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<td>SPARTAN</td>
<td>bPI + RAL</td>
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<td>(2012)</td>
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<td>PROGRESS</td>
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<td>(2012)</td>
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<td>MODERN</td>
<td>bPI + MVC</td>
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<td>A4001078</td>
<td>bPI + MVC</td>
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<tr>
<td>ACTG 5116</td>
<td>bPI + NNRTI</td>
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<td>(2007)</td>
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<tr>
<td>ROCnRAL</td>
<td>MVC+RAL</td>
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<td>ANRS157</td>
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<td>EARNEST</td>
<td>bPI + RAL</td>
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<tr>
<td>(2013)</td>
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<tr>
<td>INROADS</td>
<td>bPI + NNRTI</td>
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<tr>
<td>(2013)</td>
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</tbody>
</table>
Poor performance in NRTI-sparing regimens

• *Is there a negative interaction between the drugs?*
Antiretroviral dynamics determines HIV evolution and predicts therapy outcome

Daniel I. S. Rosenbloom¹,*, Alison L. Hill¹,2,*, S. Alireza Rabi³,*, Robert F. Siliciano³,4,†, and Martin A. Nowak¹,†

Antiretroviral dynamics determines HIV evolution and predicts therapy outcome

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

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 increased amongst 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, e.g., cell-to-cell transmission

- **Can we do anything about it?**
Low Level Viraemia, Rebound & Resistance

Risk of Rebound
Abbott RealTime

- $T_0$ VL: 40-49 copies/mL
- $T_0$ VL: RNA detected <40 copies/mL
- $T_0$ VL: RNA not detected

Time since $T_0$ (months)

Probability of virologic rebound

Risk of Resistance
UK Resistance Database

Viral load
- <300
- 300 - 999
- 1000 - 2,999
- 3000 - 9,999
- 10,000 - 29,999
- 30,000 - 99,999
- $\geq$ 100,000

Major resistance mutants in 12.7%

Risk of any resistance mutation, compared to 1000-2,999 copies

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

<table>
<thead>
<tr>
<th>HIV-1 RNA cps/ml</th>
<th>Years VL &lt;50 cps/ml</th>
<th>Total (n=104)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-4 (n=31)</td>
<td>5-7 (n=33)</td>
<td>8-15 (n=40)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>3 (1, 35)</td>
<td>3 (1, 10)</td>
<td>3 (1, 11)</td>
</tr>
<tr>
<td>Mean log_{10} (SD)</td>
<td>0.6 (0.3)</td>
<td>0.5 (0.2)</td>
<td>0.5 (0.2)</td>
</tr>
</tbody>
</table>
Is there a ceiling of efficacy to ART?

- Low level viraemia not always indicative of poor adherence
- Not all compartments are sterilised, e.g. 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
Hunt et al CROI 2012
Cardiovascular Disease and Metabolic Syndrome

- Pooled MI risk \( \uparrow 1.5 - 3 \)-fold
- HIV patients \( \leq 60 \)y higher CVD & \( \uparrow \)BP than HIV neg controls

- Type II DM risk \( \uparrow \)~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)

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

Grunfield JAIDS 2007;46:283
Worm. AIDS 2010, 24:427–435
Hanley Diabetes Care 2002;25:1177
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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**Adiponectin**

- Lopinavir
- Lopinavir + telmisartan

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**Graph:**

- X-axis: Concentration (μM)
- Y-axis: Secreted protein in conditioned media (ng/ml)
- RTV, LPV, ATV curves indicate different concentrations.
TEL in HIV context

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

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

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
Acknowledgements

David Back
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Sara Gibbons
Catia Marzolini
Kay Seden
Andrew Owen
Marco Siccardi
Marta Boffito
Andrew Hill

.. and many others ....