Dr Iain Reeves
Homerton University Hospital, London

<table>
<thead>
<tr>
<th>Speaker Name</th>
<th>Statement</th>
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<tbody>
<tr>
<td>Dr Iain Reeves</td>
<td>Honoraria and sponsorship to attend conferences from Gilead</td>
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<tr>
<td>Date</td>
<td>April 2016</td>
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Translating recent research into clinical practice

Iain Reeves
Patient Journey

HIV Positive

Success

Failure

Celebration
HIV testing
RHIVA 2 RCT – universal offer of POCT in primary care

- “…thoroughly evaluated for acceptability and feasibility … better inform the ongoing implementation of these guidelines”

- Intervention practices diagnosed more HIV and trend to earlier diagnosis

BHIVA National HIV Testing Guidelines 2008
Diffusion of innovations model

- Structural issues and resources
  - 10 vs 30 mins per patient; staff member; room
  - Management relations and leadership
- “Relative advantage”
  - Seeing test as beneficial to patients

- “Re-invention”
  - Adapting test technology to practice
- Compatibility
  - Emotionally prepared to administer test

McMullen et al, Trials 2015; 16:242
The fear factor

“What if it’s positive?”

Involve PLWH?
CHER – reversion of child antibody tests – Payne et al

- CHER – RCT of ART in infants < 12 weeks and CD4% >25% vs deferred ART

- 46% by conventional serology in early ART arm were **seronegative** at 2 years

- → Confirmation of diagnosis in migrant or other children who started ART in early life

Treatment initiation
Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group*

ABSTRACT

BACKGROUND
Data from randomized trials are lacking on the benefits and risks of initiating antiretroviral therapy in patients with asymptomatic human immunodeficiency virus (HIV) infection who have a CD4 count of more than 350 cells per cubic millimeter.
START Study Design

HIV-infected individuals who are ART-naïve with CD4+ count > 500 cells/mm$^3$

N = 4685

Immediate ART Group
Initiate ART immediately following randomization; N=2,326

Deferred ART Group
Defer ART until CD4+ count declines to < 350 cells/mm$^3$ or AIDS develops; N=2,359

Primary composite endpoint, target = 213
- Serious AIDS or death from AIDS
- Serious Non-AIDS Events and death not attributable to AIDS
  - CVD, ESRD, decompensated liver disease, & non-AIDS defining cancers
Overall risk reduction = 57%

AIDS risk ↓ = 72%

Serious non-AIDS ↓ = 39%
Primary Endpoint Counts and Rates in Participants with Latest CD4+ Count >500 or <350 cells/mm³

Latest CD4+ count >500 cells/mm³:

<table>
<thead>
<tr>
<th></th>
<th>Imm. ART</th>
<th>Defer. ART</th>
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</thead>
<tbody>
<tr>
<td>% of primary events</td>
<td>88% (37/42)</td>
<td>59% (57/96)</td>
</tr>
<tr>
<td>Rate (/100 PY)</td>
<td>0.6</td>
<td>1.1</td>
</tr>
</tbody>
</table>

**Immediate ART**

<table>
<thead>
<tr>
<th>Latest CD4+ Count (cells/mm³)</th>
<th>No. of Participants with Events (Rates per 100 PY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;350</td>
<td>2 (4.7)</td>
</tr>
<tr>
<td>350 - 499</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>500 - 649</td>
<td>6 (0.4)</td>
</tr>
<tr>
<td>650 - 799</td>
<td>11 (0.6)</td>
</tr>
<tr>
<td>&gt;800</td>
<td>20 (0.6)</td>
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**Deferred ART**

<table>
<thead>
<tr>
<th>Latest CD4+ Count (cells/mm³)</th>
<th>No. of Participants with Events (Rates per 100 PY)</th>
</tr>
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<tbody>
<tr>
<td>&lt;350</td>
<td>5 (1.8)</td>
</tr>
<tr>
<td>350 - 499</td>
<td>34 (2.0)</td>
</tr>
<tr>
<td>500 - 649</td>
<td>34 (1.5)</td>
</tr>
<tr>
<td>650 - 799</td>
<td>9 (0.6)</td>
</tr>
<tr>
<td>&gt;800</td>
<td>14 (1.1)</td>
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</table>
Talking with PLWH

What is a “good” CD4 count?
START and cancer risk

- Reduction in risk of infection driven cancers > not infection related
- Adjustment for latest HIV VL but not CD4 attenuated risk for any cancer / not infection-cancer
- Risk reduction for infection driven cancer not changed by adjusting for VL

Borges et al, CROI 2016
Will the deferred arm participants get the same benefit from treatment?
Rapid initiation studies
Rap_IT: ART Initiation ≤ 90 Days

377 ART eligible patients enrolled

190 standard patients
54 did not initiate ≤ 90 days (28%)
2 initiated ≤ 180 days
52 did not initiate

136 initiated ≤ 90 days (72%)

187 rapid patients
5 did not initiate ≤ 90 days (3%)
1 initiated ≤ 180 days
4 did not initiate (all lost during TB workup)

182 initiated ≤ 90 days (97%)

Risk difference 25% (95% CI 19 to 33%)
Crude relative risk 1.36 (95% CI 1.24 to 1.49)

Rosen S et al CROI 2016 abstract 1091
Primary Protocol Outcome: Initiated, Retained, and Suppressed ≤ 10 Months

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Standard arm (n, %) n=190</th>
<th>Rapid arm (n, %) n=187</th>
<th>Crude risk difference [95% CI]</th>
<th>Crude relative risk* [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiated ≤ 90 days</td>
<td>136 (72%)</td>
<td>182 (97%)</td>
<td>25% (19-33%)</td>
<td>1.36 (1.24-1.49)</td>
</tr>
<tr>
<td>Initiated ≤ 90 days and retained and suppressed by 10 months</td>
<td>96 (51%)</td>
<td>119 (64%)</td>
<td>13% (3-23%)</td>
<td>1.26 (1.05-1.50)</td>
</tr>
</tbody>
</table>

Of those not initiated ≤ 90 days and suppressed by 10 months:

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<thead>
<tr>
<th></th>
<th>Standard arm (n, %) n=190</th>
<th>Rapid arm (n, %) n=187</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not initiated</td>
<td>54 (28%)</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Initiated but not suppressed or with no viral load reported</td>
<td>40 (21%)</td>
<td>63 (34%)</td>
</tr>
<tr>
<td>Initiated ≤ 90 days and retained at 10 months</td>
<td>121 (64%)</td>
<td>151 (81%)</td>
</tr>
</tbody>
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Of those not initiated ≤ 90 days and retained at 10 months:

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<th>Rapid arm (n, %) n=187</th>
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<tr>
<td>Not initiated</td>
<td>54 (28%)</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Initiated but not retained</td>
<td>15 (8%)</td>
<td>31 (17%)</td>
</tr>
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Possible futures
New drugs
LATTE-2 Week 32 Results: HIV-1 RNA <50 c/mL by Snapshot (ITT-ME)

Induction period

Maintenance period

Proportion of patients with virological suppression, %

0 20 40 60 80 100

BL W-16 W-12 W-8 W-4 D1 W4 W8 W12 W16 W20 W24 W28 W32

Snapshot success: D1

Q4W 99%

Q8W 95%

Oral CAB 98%

Oral CAB induction (ME population) Q8W IM (n=115) Q4W IM (n=115) Oral CAB (n=56)

Margolis et al. CROI 2016; Boston, MA. Abstract 31LB.
Long-acting agents

• Sound good
• People will want them
• Offer options as in other areas of health

• Cost vs generic tablets?
• Trials
HIV-1 mAb Potency and Breadth

Panel of 208 diverse isolates

New antibodies up to 500-fold more potent than first generation mAbs

CAVD, VRC collaboration: Montefiori, Seaman, Bailler, Louder et al. From Mascola, CROI 2016
ACTG 5340: Time to Rebound in Viral Load After Infusions with VRC01

- 38% vs. 13% suppression at 4 weeks, p=0.04
- 8% vs. 3% suppression at 8 weeks, p=0.44
  - compared to historical controls on non-NNRTI regimens
  - ATI in ACTG studies

Bar K, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 32LB.
Combined Antibodies: Improved Potency and Breadth

Fractions of HIV-1 strains neutralized

IC₅₀ cut-off (µg/ml)

2 mAbs > 98% coverage

- VRC07
- PG9
- PGT128 10E8
- 2 mAb Combinations
- 3 mAb Combinations
- 4 mAb Combination


From Mascola, CROI 2016
Bi-functional antibodies (e.g. bind HIV and CD3/CD8)

- Potential to mediate cell killing
- Antibody platforms exist and entered clinical trials (Cancer Rx)
- For HIV-1: *In vitro* proof-of-concept of cell killing

From Mascola, CROI 2016
Decrease in Latent Reservoir Following Therapeutic Vaccination and Romidepsin

Vacc-4x/rhuGM-CSF  Romidepsin  ATI

Infectious units per million

Day -21  Day 91  Day 161

Leth S, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 26LB.
Early ART results in a restricted reservoir in all memory subsets.
Potential for the future

- **If** improved potency allowing sub-cut admin every few months and (perhaps) given in combinations
  - PrEP
  - PMTCT
  - Add on to ART or maintenance of viral suppression
  - Facilitate killing of infected cells
  - Limiting viral diversity and size of reservoir in acute HIV
Problems
Management of 1st line treatment failure
ACTG 5273 Randomized Trial of Second-line ART Supports WHO Guidance

Phase III, open-label, randomized, non-inferiority study
15 sites in 9 low-middle income countries
3 continents

Planned N=600
Failing on NRTIs + NNRTI as initial regimen with VF: confirmed >1,000 cps/mL

48 weeks Primary endpoint
96 weeks f/u for each participant

LPV/r + RAL (n = 300)
LPV/r + best available NRTIs (n = 300)

• **Primary objective**: To determine whether the efficacy of RAL arm is non-inferior to that of NRTI arm by 48 weeks
• **Primary endpoint**: Time to VF= confirmed VL>400 cps/mL at > 24 wks
• **N adjusted** to 480 after results of SECOND LINE, EARNEST and A5234:
  - Power >90% and 10% non-inferiority margin maintained
  - Follow up shortened to 52 weeks after the last enrollment

La Rosa A et al CROI 2016 abstract 30
Associations of other NRTI Resistance Characteristics at Entry with the risk of Virologic Failure (VF) – Both arms included

K65R, ≥3 TAMs, Q151M or 69 ins/del
- No
- Yes

IAS NRTI mutations
- <3
- ≥3

K65R and/or M184V/I
- no M184V/I
- no K65R but M184V/I
- K65R and M184V/I

Hazard Ratio (95% CI) and p-value

No difference by arm
Results consistent when adjusted for entry HIV-1 RNA, week 4 self-report adherence, prior exposure to TDF, and country

La Rosa A et al CROI 2016 abstract 30
Is Dolutegravir really like a boosted PI?

- 33 of VL<40 patients switched to open label DTG mono remained suppressed at 24 weeks

- PADDLE study: n = 20 patients starting DTG = 3TC dual therapy had similar viral decay to 24 weeks as seen in other DTG based triple therapy studies

Rojas et al, EACS 2015; Sued et al, CROI 2016
Impact of socioeconomic factors and gender
REACH Study: Objectives

• examine HIV OPA patterns among PLWH
• identify predictive factors of disengagement
• calculate health & financial costs of disengaging from care
• develop retention-risk assessment tool
• understand situational, environmental, behavioural & social factors which influence OPA
• develop intervention models to improve engagement in care, to be tested in future studies
Survey participants

983 survey responses

**Attendance:** 56.0% regular; 27.4% irregular; 16.7% non-attender

(550: 269: 164)

**Age:** mean = 44.5 years (s.d. = 10.4 years)

**Women:** 27.6%

**Ethnicity:** 53.6% white; 28.1% Black African; 18.3% other

**Born outside UK:** 59.3%

**Post-18 education:** 70.2%

**Sexuality:** 62.1% gay or bisexual; 37.9% heterosexual
The COM-B model: Behaviour occurs as an interaction between three necessary conditions

- **Capability**: Psychological or physical ability to enact the behaviour
- **Motivation**: Reflective and automatic mechanisms that activate or inhibit behaviour
- **Opportunity**: Physical and social environment that enables the behaviour

Michie et al (2011) *Implementation Science*
Background factors by attendance

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<th>RA</th>
<th>IA</th>
<th>NA</th>
<th>p</th>
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<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>24.2</td>
<td>30.5</td>
<td>34.1</td>
<td>.020</td>
</tr>
<tr>
<td><strong>Age group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30 years</td>
<td>6.0</td>
<td>13.0</td>
<td>11.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>30 - 45 years</td>
<td>40.7</td>
<td>46.1</td>
<td>51.2</td>
<td></td>
</tr>
<tr>
<td>&gt; 45 years</td>
<td>53.3</td>
<td>40.9</td>
<td>37.8</td>
<td></td>
</tr>
<tr>
<td><strong>18+ education</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>72.9</td>
<td>70.1</td>
<td>61.2</td>
<td>.021</td>
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No significant association (p<.05) with ethnic group, place of birth, sexual orientation
### Capability

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<tr>
<td><strong>Health (past 4 weeks)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent/v good</td>
<td>50.6</td>
<td>35.2</td>
<td>42.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Good</td>
<td>24.9</td>
<td>26.4</td>
<td>33.5</td>
<td></td>
</tr>
<tr>
<td>Fair/poor</td>
<td>24.5</td>
<td>38.3</td>
<td>24.2</td>
<td></td>
</tr>
<tr>
<td><strong>Neurocognitive impairment</strong></td>
<td>37.3</td>
<td>52.5</td>
<td>36.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Recreational drug use (past 5 yrs)</strong></td>
<td>33.1</td>
<td>41.7</td>
<td>46.2</td>
<td>.003</td>
</tr>
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Psychological or physical ability to enact the behaviour

- Health: Excellent/very good, Good, Fair/poor
- Neurocognitive impairment
- Recreational drug use (past 5 years)
### Motivation

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<tbody>
<tr>
<td><strong>2 / 7 items from internalised stigma scale</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low self-esteem</td>
<td>32.6</td>
<td>40.0</td>
<td>29.4</td>
<td>.046</td>
</tr>
<tr>
<td><em>Feel suicidal</em></td>
<td>9.4</td>
<td>16.5</td>
<td>11.9</td>
<td>.013</td>
</tr>
<tr>
<td>Overall (ticked 1+ item)</td>
<td>54.7</td>
<td>58.5</td>
<td>57.5</td>
<td>.563</td>
</tr>
<tr>
<td>Ever diagnosed depression</td>
<td>29.1</td>
<td>38.2</td>
<td>31.4</td>
<td>.043</td>
</tr>
<tr>
<td>In charge of life</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Disagree</em></td>
<td>17.8</td>
<td>17.6</td>
<td>21.7</td>
<td>.044</td>
</tr>
<tr>
<td><em>Uncertain</em></td>
<td>15.5</td>
<td>23.8</td>
<td>16.6</td>
<td></td>
</tr>
<tr>
<td><em>Agree</em></td>
<td>66.7</td>
<td>58.6</td>
<td>61.8</td>
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Reflective and automatic mechanisms that activate or inhibit behaviour
## Opportunity - barriers

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<tbody>
<tr>
<td>Has children</td>
<td>27.2</td>
<td>34.3</td>
<td>40.7</td>
<td>.002</td>
</tr>
<tr>
<td>Not always money - basic needs</td>
<td>50.5</td>
<td>64.7</td>
<td>65.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Moderate or severe hunger</td>
<td>13.6</td>
<td>28.5</td>
<td>23.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Get to clinic</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Public transport</td>
<td>75.2</td>
<td>82.0</td>
<td>86.0</td>
<td>.037</td>
</tr>
<tr>
<td>Car / motorbike</td>
<td>11.1</td>
<td>11.5</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td>On foot / bicycle</td>
<td>12.6</td>
<td>5.7</td>
<td>6.7</td>
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</table>

Physical and social environment that enables the behaviour
Gender/sexuality and VL rebound (>200c/mL) N=1586 with VL<50c/mL on ART, started ≥6m ago

Unadjusted:
- Women
- MSW
- MSM

Adjusted for age:
- Women
- MSW
- MSM

Adjusted for age, ethnicity socio-economic factors,* depression symptoms
- Women
- MSW
- MSM

Comparison across gender/sexuality groups

- Women: p<0.001
- MSW: p<0.001
- MSM: p=0.010

Hazard ratios by Cox proportional hazards regression

*UK birth/English fluency; financial status; housing; employment; education; supportive network

O’Connell et al, EACS 2015
What next?

- Risk tool
- Interventions
Sexual health
Chemsex in HIV+ MSM

- Positive Voices survey (CASI)
  - Recruited from representative sample of HIV clinics in England/Wales
  - 532 of 777 respondents were MSM
  - Nationally weighted population prevalence estimates calculated for responses from 392 sexually active MSM (past year)
Positive Voices and Chemsex: Results

- 29% chemsex; 10% injection use
- Significant associations between Chemsex and “Slamsex” with condomless sex, STIs and Hepatitis C
- Chemsex also associated with sdUAI with detectable VL
- More likely to live in London (37% vs 17%)
- Diagnosed with depression or anxiety (38% vs 24%)

Prufall et al, CROI 2016
Clinical practice and chemsex

- Ask
- Recognise problems
  - Intrinsic harms, e.g. G overdose
  - Mental health difficulties
  - Dependence
- Manage sexual health
  - 3 monthly SHS
  - More frequent Hep C testing?
- Information is usually not enough to change behaviour
- Know how to refer to or get help with psychological problems and drug use support
Finally...
Acknowledgements

- Chloe Orkin
- Sarah Fidler
- Rebecca O’Connell
- Fiona Burns
- Alison Howarth
- Adrian Palfreeman
- Heather McMullen
- BHIVA CROI feedback team