BHIVA BASHH Feedback

Professor Clifford Leen
University of Edinburgh
Regional Infectious Diseases Unit
Western General Hospital
OUTLINE

• Cure strategies
• ART
  • New drugs
  • Switch studies
  • Generics
• Co-morbidities
• PREP
• Others
A short history of HIV cure research: a shift from cure to remission but a long way to go

1997
HIV latency identified

2009
The Berlin patient

2010
Post treatment control

2014-now
Case reports of remission

2018
Latency far more complex
Single interventions haven’t worked
Have cured a few monkeys
This is not going to be easy!

VISCONTI
SPARTAC
CHAMP
Clinical strategies to achieve remission off ART

**Virus elimination**
- Very early ART
- Latency reversal or “shock and kill”
- Permanent silencing or “block and lock”
- Immunotoxins
- Gene editing
- Transplantation

**Boosting immunity**
- Broadly neutralising antibodies
- T-cell vaccines
- T-cell immunotherapy
- Reduce inflammation
- Alter T-cell trafficking
Shock and Kill Strategy to Eliminate HIV Latently Infected Cells

Latency Reversing Agents (LRAs) activate HIV DNA in the host genome of resting CD4+ T cells, leading to the production of HIV RNA. ART (Antiretroviral Therapy) treatment may induce cell death through immune-mediated clearance or virus-mediated cytotoxicity.
Advances in HIV Care for 2018

Professor Chloe Orkin
Barts Health NHS Trust
Treatment and management strategies

Reducing ART exposure
- Drug dose
- Dosing frequency
- Number of drugs

New agents
- Investigational ARTs
- Monoclonal antibodies

Different ART formulations
- Long-acting oral
- Implantable
- Long-acting injectable
HIV drug pipeline under clinical evaluation (Phase I–III)

**Entry inhibitors**
- Fostemsavir (GSK-934; FTR)
- Cenicriviroc (TBR-652; CVC)
- Sifuvirtide (FS-0101)
- Albuviride (FB006M; ABT)

**Monoclonal antibodies (mAb)**
- UB-421 (CD4 receptor)
- PRO-140 (CCR5 receptor)
- Ibalizumab (TMB-355)
- VRC01
- VRC01-LS

**NRTIs/NtRTIs (‘nukes’)**
- EFdA (MK-8591)
- Doravirine (MK-1439)
- Elsulfavirine (VM1500)
- Rilpivirine-LAI (TMC278; RPV)
- Dapivirine (TMC120; DPV)
- PC-1005 (MIV-150/zinc acetate)

**NNRTIs (‘non-nukes’)**
- Bictegravir (GS-9883)
- Cabotegravir-LAI (GSK-744; CAB)
- MK-2048

**Integrase inhibitors**
- GS-PI1
- GS-CA1
- GSK2838232
- MK-8507
- ABX464
- LEDGIIs

**Protease inhibitors**
- Doravirine (MK-1439)
- Elsulfavirine (VM1500)
- Rilpivirine-LAI (TMC278; RPV)
- Dapivirine (TMC120; DPV)

**Capsid inhibitors**

**Maturation inhibitors**

**Unique/unknown MoA**

**Chemokine co-receptor**
- CD4

**Viral DNA**

**Attachment**
- Chemokine co-receptor

**Fusion**

**Reverse transcription**

**Integration**

**Transcription**

**Translation**

**Assembly/cleavage**

**Maturation**

**HIV LIFE CYCLE**
Ways to avoid the safety concerns of the NRTI ‘backbone’

Options:
- TAF backbone in triple ART
- Two-drug regimens (2DR)
First-line ART

TAF vs TDF or ABC

- EVG/c + TAF/FTC vs TDF/FTC
- TAF: favorable renal biomarkers and BMD
- No renal or bone discontinuations to Week 144

GS-104/111\(^1,2\)

GS-1489\(^3\)

- TAF/FTC/BIC vs ABC/3TC/DTG
- No differences in renal or bone biomarkers at Week 48

3TC, lamivudine; ABC, abacavir; BIC, bictegravir; BMD, bone mineral density; c, cobicistat; DTG, dolutegravir; EVG, elvitegravir; FTC, emtricitabine; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate.
2DR-naïve studies: Efficacy

**WK 48 ANDES** \((N=145)\)
- FDC DRV/r + 3TC vs DRV/r + TDF/3TC
- Non-inferior 93% DT, 94% TT
- >100,000 c/mL 91% DT vs 92% TT
- Safety: TC better in DT arm

**ACTG 5353** \((N=120)\)
- Single-arm study DTG + 3TC
- > 100,000 c/mL vs < 100,000 c/mL randomisation
- 3 PDVF
- n=1 [emergent M184V, R263R/K]

Adapted from clinicaloptions.com

2. Taiwo BO, et al. IAS 2017, Paris, France; abstract #MOAB0107LB.
3. Figueroa M CROI 2018 Poster 489
Current challenges of the INSTI as third agent

### CNS AEs
- **Phase III FDA trials DTG**
  - Only SINGLE reported >5% events (especially insomnia)
- **Six cohorts**
  - More DTG discontinuations than other INSTIs
- **Opera cohort**
  - Similar CNS incident events for third agents
- **Wohl series**
  - Depression and sleep disturbances were significantly higher in DTG vs EVG, and DRV/r, but not RAL

### Resistance
- **First-generation INSTI**
  - RAL and EVG more resistance than PI
- **Second-generation INSTI**
  - Genetic barrier closer to PI/r

### DDIs
- **INSTI drug–drug interactions**
  - RAL/DTDG chelation
  - EVG/c booster, so DDIs
  - BIC: UGT1A1 and Cyp3 A4 metabolism

AE, adverse event; ART, antiretroviral therapy; BIC, bictegravir; CNS, central nervous system; DDI, dideoxyinosine; DRV, darunavir; DTG, dolutegravir; EVG, elvitegravir; FDA, The Food and Drug Administration; INI, integrase inhibitor; PI, protease inhibitor; r, ritonavir; RAL, raltegravir.

Renal, Inflammatory and Bone Biomarkers Following Switch to the DTG + RPV 2-Drug Regimen: The SWORD-1 & SWORD-2 Studies

C Orkin,1 JM Llibre,2 L Kahl,3 E Blair,4 B Wynne,5 L Curtis,6 K Angelis,6 R Shah,3,* M Aboud,3 M Gartland4

1Barts Health NHS Trust, London, UK; 2Hospital Germans Trias i Pujol, Badalona, Spain; 3ViiV Healthcare, Brentford, UK; 4ViiV Healthcare, Research Triangle Park, NC, USA; 5ViiV Healthcare, Collegeville, PA, USA; 6GlaxoSmithKline, London, UK

*Submitted on behalf of the authors.
Introduction

• Two-drug regimens (2DRs) are being evaluated for their ability to minimize cumulative drug exposure

• We evaluated the effect of switching from 3- or 4-drug current antiretroviral therapy (CAR) to the NRTI–sparing 2DR DTG + RPV in 2 randomized phase III studies (SWORD-1 and SWORD-2)

• DTG/RPV 2DR was non-inferior to triple therapy as demonstrated for the pooled primary efficacy endpoint
  • Patients with HIV RNA <50 c/mL at Week 48: DTG + RPV, 95%; CAR, 95%
  • Adjusted treatment difference: −0.2%; 95% CI, −3.0, 2.5 (non-inferiority margin, −8%)

• We present the pre-specified secondary endpoint analysis on biomarkers of renal, atherogenesis, inflammation, and bone turnover
**SWORD-1 and SWORD-2 Phase III Study Design**

*Identically designed, randomized, multicenter, open-label, parallel-group, non-inferiority studies*

**Inclusion criteria**
- On stable CAR ≥6 months before screening
- First or second ART with no change in prior regimen due to VF
- Confirmed HIV-1 RNA <50 c/mL during the 12 months before screening
- HBV negative

**Primary endpoint at 48 weeks:** subjects with VL <50 c/mL (ITT-E snapshot)

- Non-inferiority margins
  - Pooled data, −8%
  - Individual studies, −10%

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**Timeline**

- **Screening**
  - VL <50 c/mL on INI, NNRTI, or PI + 2 NRTIs
  - 1:1

- **Early switch phase**
  - DTG + RPV (N=513)
  - CAR (N=511)

- **Late switch phase**
  - DTG + RPV

- **Continuation phase**
  - DTG + RPV

- **Day 1**
  - Screening

- **Week 52**
  - Early switch phase
  - Late switch phase

- **Week 148**
  - Continuation phase
In addition, a subgroup analysis by baseline third-agent class showed consistent virologic efficacy results regardless of baseline third agent.\(^2\)

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Conclusions

• DTG + RPV is associated with a numerically favorable trend on renal tubular biomarkers, with no difference in the ratios and a neutral effect on surrogate biomarkers of atherogenesis and inflammation

• DTG + RPV treatment resulted in a significant improvement in biomarkers of bone health compared with a standard 3- or 4-drug regimen
  • Viral suppression was preserved during treatment

Data included in this presentation have been previously presented at the 16th European AIDS Conference; October 25-27, 2017; Milan, Italy; Poster O37.
New drugs
• OD Raltegravir
• TAF/FTC/darunavir/Cobi
• TAF/FTC/Bictegravir
• Dolutegravir/Rilpivirine
Investigational agents for treatment-experienced patients

FOSTEMSAVIR¹

- Fostemsavir is an attachment inhibitor to gp120
- BRIGHTE: FTR in treatment experienced, ≤2 active ARV classes (N=371)
- FTR mean HIV RNA decline of 0.79 log$_{10}$ in 8 days functional monotherapy

IBALIZUMAB²,³ & PRO-140 ⁴

- Ibalizumab is a humanised monoclonal antibody to CD4 receptor
- PRO-140: is a humanised monoclonal antibody to CCR5 receptor-subcutaneous weekly

ATV/r, atazanavir/ritonavir; RAL, raltegravir; TDF, tenofovir disoproxil fumarate; VL, viral load.

Phase 3 study of fostemsavir in heavily treatment experienced HIV-1 infected subjects: day 8 and week 24 primary efficacy and safety results (Study 205888, formerly AI438-047) P 18

<table>
<thead>
<tr>
<th>Antiviral efficacy Day 8 – Randomized cohort</th>
</tr>
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<tbody>
<tr>
<td></td>
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<tr>
<td>HIV-1 RNA log_{10} c/ml, least squares mean change (95% CI)</td>
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</table>

<table>
<thead>
<tr>
<th>Antiviral efficacy week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized cohort (N=272)</td>
</tr>
<tr>
<td>HIV-1 RNA &lt;40 c/ml</td>
</tr>
<tr>
<td>FDA Snapshot[n (%)] (95% CI)</td>
</tr>
</tbody>
</table>

• 2 subjects in the FTR arm, who had missing Day 1 HIV-1 RNA values, were not included in the primary analysis
Investigational agents for treatment-experienced patients

Fostemsavir is an attachment inhibitor to gp120
BRIGHTE: FTR in treatment experienced ≤2 active ARV classes (N=371)
FTR mean HIV RNA decline of 0.79 log₁₀ in 8 days functional monotherapy

Ibalizumab is a humanised monoclonal antibody to CD4 receptor
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ATV/r, atazanavir/ritonavir; RAL, raltegravir; TDF, tenofovir disoproxil fumarate; VL, viral load.
Trogarzo™ (ibalizumab-uiyk) injection in resistant HIV isolates

TMB-301 is a single arm, 24-week study of **IBA plus optimized OBR** in treatment-experienced patients with at least 3-class resistance, failing ART

One active class to form OBR

**Study Design**

**Day 0:** Control Period

**Day 7:** 2000 mg IV Loading Dose

**Day 14:** Add OBR

**Day 21:** 800 mg IV Maintenance Dose

800 mg IV Every 2 wks until Week 24

**Between Day 0-7,** patients taking current failing therapy

**Primary Endpoint**

% of patients achieving $\geq 0.5 \log_{10}$ VL decrease

**Secondary Endpoints**

Safety/Tolerability

VL CD4+ count

Lalezari et al CROI 2017, Seattle
Efficacy at Day 14 and Week 24

### Day 14

<table>
<thead>
<tr>
<th></th>
<th>Day 7</th>
<th>Day 14</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent with ≥0.5 log₁₀ reduction</td>
<td>3%</td>
<td>83%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Percent with ≥1.0 log₁₀ reduction</td>
<td>0%</td>
<td>60%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean VL decrease</td>
<td></td>
<td>1.1 log₁₀</td>
<td>&lt;0.0001</td>
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</tbody>
</table>

### Week 24

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Percent with VL &lt; 50 copies/mL</td>
<td>43%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent with VL &lt; 200 copies/mL</td>
<td>50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean VL decrease</td>
<td></td>
<td>1.6 log₁₀</td>
<td></td>
</tr>
<tr>
<td>Percent with ≥1.0 log₁₀ reduction</td>
<td>55%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent with ≥2.0 log₁₀ reduction</td>
<td>48%</td>
<td></td>
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</tbody>
</table>

Lalezari et al CROI 2017, Seattle
## Results: savings by switch - L Waters

<table>
<thead>
<tr>
<th>Switch</th>
<th>2016/17 saving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Branded to generic abacavir/lamivudine</td>
<td>£6,946,811</td>
</tr>
<tr>
<td>Branded to generic nevirapine-PR</td>
<td>£722,022</td>
</tr>
<tr>
<td>Branded tenofovir-DF/emtricitabine/efavirenz FDC to branded tenofovir-DF/emtricitabine FDC + generic efavirenz (1 to 2 pills)</td>
<td>£1,131,212</td>
</tr>
<tr>
<td>Darunavir + ritonavir to darunavir/cobicistat FDC</td>
<td>£752,172</td>
</tr>
<tr>
<td>Atazanavir + ritonavir to atazanavir/cobicistat FDC</td>
<td>£240,404</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>£9,792,621</strong></td>
</tr>
</tbody>
</table>
Switching to gEfavirenz, S Tyler P 02

- 2547 patients on Atripla 1556/2547 (61%) switched to Truvada & gEFV and 48/2547 (2%) to different NRTIs & gEFV.

- 1507/1604 (94%) remained on gEFV and 97/1604 (6%) subsequently switched off gEFV

- CNS toxicity was the most common reason for discontinuation from gEFV with 63/97 (65%) patients stopping gEFV for this reason, of which 34/63 (54%) patients felt these had developed since switch to gEFV
Switching drugs for savings

• 78% patients agreed/strongly agreed that switching makes best use of limited NHS resources.

• 38% 25% and 15% patients indicate their overall satisfaction with the switch process as excellent, very good and good respectively. Castellino P 17

• Switching to B/F/TAF was noninferior to continuing DTG/ABC/3TC with low rates of W48 virologic failure, and no resistance. B/F/TAF was well tolerated, with a similar bone and urine protein safety profile to DTG/ABC/3TC. A Ustianowski P 25

• Switching generally safe to gEFV or RTV to Cobi but need to monitor symptoms

• 10% of Cobi patients switched back to RTV or another third agent; Byrne P 34
others
Post transition outcomes in young adults living with HIV: (90):99:80

C Foster, S Ayers, S McDonald, G Frize, S Fidler

- 90% of all living with HIV will know their HIV status
- 90% of all living with HIV will receive antiretroviral therapy
- 90% of all receiving antiretroviral therapy will have viral suppression
Current cohort

• median age 22.9 years (range 18.1-33.6)
• 56% female
• 85% Black African

99.4% (157/158) received ART
80.4% (127/158) latest VL <200 c/ml

• median CD4 count 626 cells/ul (IQR 441-820)

[Naomi Lin P151 – predictors of viral suppression]
ART Regimen (%)

Yara Abo [P149]
Clare Peterson [O20]
Mental Health and Disability (%)

- Depression/anxiety: T Pasvol [P285]
- Disability
- Psychosis
- Drug/alcohol
Conclusion

90+% Diagnosed

4% LTFU/death

99% ART

11% CD4 <200

80% VL <200

Of those registered 74% retained in care on suppressive ART

Imperial College Healthcare NHS Trust
Met and unmet health, welfare and social needs of people accessing HIV services

Findings from Positive Voices survey 2017

Meaghan Kall
Public Health England
on behalf of the Positive Voices study group
Methods (P317)

- February – September 2017
- Nationally representative
  - Random sample from HARS
  - ~20% patients/clinic
- Clinic-based recruitment
  - Face to face, post or email
  - Self-completion
  - Paper (87%) or online (13%)
- Incentive
  - £5 high street voucher
Results:
- 73 clinics
- 4,418 responses
- 51% response rate
HIV RELATED SERVICES
- Peer support
- Disclosure support
- Support managing LTC
- Information - living with HIV
- HIV treatment advice
- Adherence support

HEALTH SERVICES
- Drug detox or maintenance
- Chemsex support
- Stress management
- Smoking cessation
- Alcohol counselling/treatment
- Weight management
- Drug counselling
- Advice regarding sex life
- Psychologist or counsellor
- Home health services
- Family planning

SOCIAL & WELFARE SERVICES
- Loneliness or isolation
- Career skills and training
- Childcare services
- Financial advice
- Employment advice
- Legal advice
- Relationship advice
- Meal or food services
- Immigration support
- Domestic violence services
- Housing support
- Benefit claim support
HIV treatment advice and information

HIV treatment advice
- Need 61%
- Met 93%
- Not Needed 39%

Information about living with HIV (including websites)
- Need 47%
- Met 87%
- Not Needed 53%

Average HIV Clinic Rating: 9.3

- Supported to self-manage 94%
- Involved in decisions 95%
- Enough information 98%
- Enough time at appts 96%
- Staff listen 97%
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**SOCIAL & WELFARE SERVICES**
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Peer support/social contact with other people living with HIV

- Not needed: 68%
- Need: 32%

- Met: 57%
- Unmet: 43%

28,000 needed peer support
12,000 with unmet need
Drug treatment and Chemsex

Drug detox or maintenance treatment
- Not Needed: 95%
  - Need: 5%
  - Met: 40%
  - Unmet: 60%
- Needed: 5%

Chemsex support
- Not Needed: 94%
  - Need: 6%
  - Met: 45%
  - Unmet: 55%
- Needed: 6%

Any drugs in past 3 months
- Met: 27%
- Unmet: 73%

MSM reported chemsex in past 3 months
- Met: 15%
- Unmet: 85%
Help dealing with loneliness and isolation

- Not needed: 80%
- Need: 20%
- Met need: 25%
- Unmet need: 75%

No difference by:
- Age
- Sex
- Exposure
- Ethnicity

<table>
<thead>
<tr>
<th>Category</th>
<th>No need</th>
<th>Need</th>
<th>Unmet Need</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main partner</td>
<td>65%</td>
<td>39%</td>
<td>37%</td>
</tr>
<tr>
<td>London resident</td>
<td>47%</td>
<td>53%</td>
<td>54%</td>
</tr>
<tr>
<td>Life Satisfaction (median 10)</td>
<td>8</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Depression (ever diagnosed)</td>
<td>27%</td>
<td>61%</td>
<td>60%</td>
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The greatest area of need was HIV-related services: particularly treatment advice, information on living with HIV and adherence support (61%, 47% and 40% needed the services, respectively); for each >90% had their needs met.

A third (32%) needed peer support/social contact with people with HIV, and just over half (56%) received this.

Long-term condition management support (42% needed the service), help to manage stress (33%), counselling (31%), weight management (29%) and sexual advice (27%) were the most needed health-related services: around half of these needs had been met (67%, 45%, 59%, 46% and 59% respectively).

Generally the greatest area of unmet need was for social and welfare services, - 62%

Housing support (22%), help dealing with loneliness and isolation (20%) and help claiming benefits (19%) were each needed by a fifth of respondents, 50% met, but only 24% received help with loneliness and isolation.
For those with irregular status (refused asylum seeker, visa overstayer, unlawfully entered etc)

- Free: testing and treatment for HIV, all other STIs/BBVs;
- primary care;
- A&E – and PrEP!
- Chargeable: most other secondary care;
CHARGING FOR NHS CARE
2017 REGS

- Up-front assessment of eligibility for free NHS care; recovery in advance of full cost of care
  - eligibility assessment **NOT** required of HIV/sexual health clinics
- Immediately necessary treatment must always be provided at once e.g. maternity care
- Urgent treatment (can’t wait until patient leaves UK) – not essential to secure payment beforehand
Who has to pay?

How NHS overseas visitor charges apply to migrants and asylum seekers in England

The National Health Service (NHS) is free to anyone who is 'ordinarily resident'. Those who are not ordinarily resident in the UK can be charged for using some NHS services.

There are exemptions from NHS charges for specific types of treatment and also specific groups of people. In addition, there are rules to make sure that no one is denied life-saving and urgent treatment (but some patients will still be asked to pay for this treatment).

This is a factsheet about the NHS in England. However, HIV and sexual health testing, treatment and care is available free of charge from the NHS throughout the UK, regardless of Immigration status.

Types of treatment which are always free

NHS overseas visitors charges apply to most secondary care (hospital services) – but some NHS services are always free.

Download at www.nat.org.uk
Conclusions

• Excellent joint meeting with BASHH
• HIV cure strategy: realistic phase
• Acceptability of generics and savings
• Switching is safe
• New drugs, 2 Drug regimen strategy & long acting
• PREP; improve awareness and knowledge
  • Service re-provision to cope with PREP demand
• Need to meet the needs of users; identify gaps
• Improve access to care, in particular those with irregular status