HIV Update

Chairs:
Dr Tristan Barber & Liz Foote

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HIV update for Autumn BHIVA

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British HIV Association Chair
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Disclosures & disclaimers

- Investigator on clinical trials sponsored by Janssen & Gilead
- Speaker/advisory fees: Viiv, Gilead, Janssen, MSD, Cipla & Mylan
Most important disclosure

• You will have seen much of the data behind this talk ad nauseum
• Therefore my remit is to provoke thought & encourage all is us to QUESTION that data
Content

• Injectables
  – Scotland
  – England
• Pipeline
• The grand reveal (ish)
11th October 2021

cabotegravir 600mg prolonged-release suspension for injection (Vocabria®)
ViiV Healthcare
Key points

• 74% predicted oral adherence in the model is not appropriate to people living with HIV in Scotland
• Additional benefit uncertain: SF-6D, an acceptable measure, may differ from more commonly used EQ-5D
• Potential issue as administration cost was based on 15 minutes of nurse time, most likely an underestimation
• Could help remove the fear of hiding pill-based treatments and give greater freedom from rigorous treatment plans
For every 50 patients on injectables we’ll need to run an extra clinic a week
NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Cabotegravir with rilpivirine for treating HIV-1
18 November 2021

Today’s draft guidance is the first time NICE has made recommendations about the use of an HIV treatment since these came under NICE’s remit in 2019.

It is estimated that around 13,000 people will now be eligible for treatment with cabotegravir with rilpivirine in England.

“We’re pleased therefore to be able to recommend cabotegravir with rilpivirine as a valuable treatment option for people who already have good levels of adherence to daily tablets, but who might prefer an injectable regimen with less frequent dosing.”
I have NEVER seen anything like it!
From: WATERS, Laura Jane (CENTRAL AND NORTH WEST LONDON NHS FOUNDATION TRUST) <lwaters@nhs.net>
Sent: 18 November 2021 11:49
Subject: [EXTERNAL]:URGENT: OMFG

I'm sure you appreciate the difficulty for surprised services dealing with multiple enquiries.

BHIVA shall indeed be reviewing vthe document in detail but I stand by my view that NICE could have made it clearer that the drugs are not available right now.
The 13,000 are total potentially eligible people that were estimated from the company originally. This is not the estimate of the number of people we expect to have treatment per year. Simply put, the true number of people receiving treatment will be much lower each year, and something we’ve had a dialogue with NHS England with.

If no appeals,...statutory 3-month clock starts on 5th January 2022 to be implemented from April
Clinical trial results show that cabotegravir with rilpivirine is as effective as oral antiretrovirals at keeping the viral load lower than 50 copies/ml of blood. It is unclear whether there would be a difference in adherence between long-acting injections and daily oral tablets. The most likely cost-effectiveness estimate is likely to be within what NICE normally considers an acceptable use of NHS resources. So cabotegravir with rilpivirine is recommended.
Vocabria (cabotegravir)
An overview of Vocabria and why it is authorised in the EU

Rekambys (rilpivirine)
Clinical trial results show that cabotegravir with rilpivirine is as effective as oral antiretrovirals at keeping the viral load lower than 50 copies/ml of blood. It is unclear whether there would be a difference in adherence between long-acting injections and daily oral tablets. The most likely cost-effectiveness estimate is likely to be within what NICE normally considers an acceptable use of NHS resources. So cabotegravir with rilpivirine is recommended.
Prior to starting REKAMBYSC, the healthcare professional should carefully select patients who agree to the required injection schedule and counsel patients about the importance of adherence to scheduled dosing visits to help maintain viral suppression and reduce the risk of viral rebound and potential development of resistance associated with missed doses.

2 of these factors = more VF
- Proviral RPV RAMs
- Subtype A6/A1 (assoc with L74I)
- BMI ≥30 (assoc with CAB PK)

ATLAS-2M week 48
- CVF: 1.5% on Q8W & 0.4% on Q4W
- RAMs: 1% on Q8W, 0.4% on Q4W

Overall Summary of CVFs through Week 96

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>CVFs (%)</th>
<th>CVFs with RPV RAMs*</th>
<th>RPV RAMs observed at failure</th>
<th>CVFs with RAM*</th>
<th>IN RAMs observed at failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q8W</td>
<td>522</td>
<td>1 (1.9)</td>
<td>7/9</td>
<td>K101E, M230L</td>
<td>5/9</td>
<td>Q148R, N155H</td>
</tr>
<tr>
<td>Q4W</td>
<td>523</td>
<td>2 (0.4)</td>
<td>1/2</td>
<td></td>
<td>2/2</td>
<td>E138K, Q148R, N155N/H</td>
</tr>
</tbody>
</table>

100% ADHERENCE
<table>
<thead>
<tr>
<th>Virologic Outcome at Month 12, n (%)</th>
<th>Patients (N = 115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic success (&lt;50 copies/mL)</td>
<td>101 (88)</td>
</tr>
<tr>
<td>Virologic nonresponse (≥50 copies/mL)</td>
<td>0</td>
</tr>
<tr>
<td>No virologic data</td>
<td></td>
</tr>
<tr>
<td>▪ Discontinued due to AE or death</td>
<td>14 (12)</td>
</tr>
<tr>
<td></td>
<td>5 (4)*</td>
</tr>
<tr>
<td>▪ Discontinued for other reasons</td>
<td>8 (7)</td>
</tr>
<tr>
<td>▪ On study but missing data in window</td>
<td>1 (1)†</td>
</tr>
<tr>
<td>Scheduling injection visits</td>
<td>2</td>
</tr>
</tbody>
</table>

2% withdrew for ISR

Time in clinic:
- Month 1: 57 min
- Month 11: 34 min
HPTN 083: IM CAB vs TDF/FTC

Crucial point

• Adherence
  – IM CAB 92%
  – PO TDF/FTC 74% had PK consistent with daily dosing

• Incident HIV infections
  – IM CAB: 4/12 with target plasma CAB concentrations & on-time dosing
  – TDF/FTC: 37/39 had suboptimal or non-adherence

Gilead Announces Decision Not to Pursue Marketing Authorization for Descovy® for Pre-Exposure Prophylaxis in the European Union

Foster City, Calif., October 20, 2021 – Gilead today announced it will not pursue a marketing authorization for Descovy® (emtricitabine 200 mg/tenofovir alafenamide 25 mg) for pre-exposure prophylaxis (PrEP) in the European Union (EU) at this time. Conversations with healthcare professionals, payers and other stakeholders across Europe have confirmed there is a lack of demand for innovative daily PrEP options given the broad availability of generic alternatives. Policies and decisions made by national governments relating to reimbursement can adversely impact the feasibility of pursuing marketing authorization in each market. This is the case in the EU.

The pipeline is a bit smaller than it was

- **MK-8507**
  - Decreases in TLC & CD4 on islatravir (ISL) + MK-8507
  - External Data Monitoring Committee (eDMC):
    - Effect related to the **combination** of ISL+MK-8507;
    - Greatest decreases on highest doses of MK-8507
    - Recommended trial cessation
  - MSD announced on 18\textsuperscript{th} November 2021
    - Paused development of MK-8507
    - Remains confident in ISL
Maybe not all that confident?

Gilead and Merck Announce Temporary Pause in Enrollment for Investigational Once-Weekly Oral Combination Treatment Regimen of Islatravir and Lenacapavir in People Living with HIV who are Virologically Suppressed on Antiretroviral

Paused due to an “abundance of caution”

Press release 23rd November 2021
ViiV
IL-6 & SNAE risk: 2DR vs 3DR
Markov modelling from TANGO & AIR

The INSIGHT trials network showed that elevated inflammatory markers (including IL-6) are associated with a higher risk of SNAE or death*.\(^1\)

- Findings predicted that a 16% increase in IL-6 may increase the risk of SNAE by ~16% – the difference in IL-6 level observed in TANGO at Week 48.

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IL-6 Levels in TANGO and SALSA Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Switch</th>
<th>Change in IL-6 level after switching from 3DR to 2DR</th>
</tr>
</thead>
</table>
| TANGO   | Switch to DTG/3TC vs. continuing a TAF-based 3DR | Week 48: \(P = 0.006\) in favor of 3DR\(^2\)  
Week 96: Numerical difference but not statistically significant\(^3\)  
Week 144: \(P = 0.039\) in favor of 3DR\(^4\) |

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AIR: Serum IL-6 After Switching From 3DR to 2DR\(^6\)

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*Cardiovascular, hepatic, renal or malignancy event

On vs off ART comparisons

% vs absolute value?

Confounders? Adherence, statins

Causation vs association

Plasma Levels of Soluble CD14 Independently Predict Mortality in HIV Infection

Netanya G. Sandler, Handan Wand, Annelys Roque, Matthew Law, Martha C. Nason, Daniel E. Nixon, Court Pedersen, Kiat Ruxrungtham, Sharon R. Lewin, Sean Emery, James D. Neaton, Jason M. Brenchley, Steven G. Deeks, Irini Sereti, and Daniel C. Douek, for the INSIGHT SMART Study Group
### Recommended 1st line regimens

<table>
<thead>
<tr>
<th>Option 1</th>
<th>Option 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bictegravir/emtricitabine/tenofovir-AF</td>
<td>Doravirine/lamivudine/tenofovir-DF</td>
</tr>
<tr>
<td>Dolutegravir/abacavir/lamivudine</td>
<td>Doravirine + emtricitabine/tenofovir-AF</td>
</tr>
<tr>
<td>Dolutegravir + emtricitabine/tenofovir-AF</td>
<td>Darunavir/b + emtricitabine/tenofovir-AF</td>
</tr>
<tr>
<td>Dolutegravir + emtricitabine/tenofovir-DX</td>
<td>Darunavir/b + emtricitabine/tenofovir-DF</td>
</tr>
<tr>
<td>Dolutegravir/lamivudine</td>
<td></td>
</tr>
<tr>
<td>Raltegravir + emtricitabine/tenofovir-AF</td>
<td></td>
</tr>
<tr>
<td>Raltegravir + emtricitabine/tenofovir-DF</td>
<td></td>
</tr>
</tbody>
</table>
Regimen A vs regimen B

VIROLOGICAL SUCCESS  
FAVOURS A  FAVOURS B

VIRAL FAILURE  
FAVOURS A  FAVOURS B
Regimen A vs regimen B

Virological Success

Viral Failure

Favours A  Favours B

Favours A  Favours B
Regimen A vs regimen B

VIRAL FAILURE

FAVOURS A  FAVOURS B

VIRAL FAILURE WITH RAMs

FAVOURS A  FAVOURS B
Conclusions

• Injectables are here
  – We must ensure those in greatest need get access
  – We must manage expectations realistically
• New drugs can still stutter
• Interpret single biomarker extrapolations cautiously
• BHIVA ART guidelines out for consultation soon
Thank you!

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