25th Annual Conference of the British HIV Association
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Hepatitis: Lessons learned from the Hepatitis A outbreak, Hepatitis C etc...

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COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:
Andrew Ustianowski: has acted in a Consultancy/speaker capacity for Abbvie, Gilead, Janssen, MSD & ViiV. His research unit has also received grants for research from Abbvie & Gilead.
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Outline

• Hepatitis A (HAV)
  • Background & guidelines
  • HAV Outbreaks
    • In MSM & PLWH
    • What interventions might help?

• Hepatitis C
  • Current issues
  • Elimination…?

• Other issues in viral hepatitis
Hepatitis A
Background

- Faeco-oral spread
  - Oro-anal
  - Digital-rectal

- Incubation
  - 15-45 days generally

- Presentation:
  - May be asymptomatic
  - Severity increases with age:
    - Jaundice in 70-80% of adults
      - <1% fulminant - with mortality of 45%
    - Prolonged and relapsing cases increasingly recognised

1. Lemon et al. J Hepatol. 2017
Control

- No specific treatment for active cases

Prevention:
- Human Normal Immune Globulin
- Hepatitis A Vaccination
  - Monovalent vaccines
    - Four available - Havrix®, Vaqta®, Avaxim®, Epaxal®
      - Different strains of the hepatitis A
      - Can be used interchangeably
  - Combined HAV and HBV vaccines
    - Two available - Twinrix®, Ambirix®
  - Combined HAV and Typhoid vaccines
    - Two available - ViATIM®, Hepatyrix®
Guidelines in HIV and MSM

- **BHIVA Monitoring Guidelines (2019 interim update)**
  - We recommend that all new patients should be screened for hepatitis A immunity (1A)

- **BHIVA Use of Vaccines Guidelines (2015)**
  - Vaccinate HIV+ individuals at risk of infection

- **BASSH Viral Hepatitis (2019 interim update)**
  - Screening for pre-existing hepatitis A exposure before vaccination may be performed, depending on factors such as funding/clinic access (2B)
  - All unvaccinated/non-immune MSM attending GUM and HIV clinics should be offered full vaccination (1B)

Outbreaks occur

What does the Green Book say for general public?

- **Post-Exposure**
  - **Passive:**
    - Human Normal Immunoglobulin (HNIG)
      - Protection if given within 14 days of exposure
      - Lasts 4-6 months
  - **Active:**
    - Hepatitis A vaccination
      - 79% protection when given within 8 days of exposure\(^2\)
    - ➔ HepA vaccination <7 days, HNIG if 7-14 days

- **Outbreaks**
  - Hep A vaccination in more prolonged outbreaks
Outbreak of hepatitis A associated with men who have sex with men (MSM), England, July 2016 to January 2017

Kazim Beebeejaun, 1 Srilaxmi Degala, 2 Koye Balogun, 1 Ian Simms, 3 Sarah Charlotte Woodhall, 3 Ellen Heinsbroek, 4 Paul David Crook, 4 Ishani Kar-Purkayastha, 5 Juli Treacy, 5 Kate Wedgwood, 6 Kate Jordan, 7 Sema Mandal, 1 Siew Lin Ngui, 8 and  Michael Edelstein 1
Hepatitis A outbreak among men who have sex with men (MSM) predominantly linked with the EuroPride, the Netherlands, July 2016 to February 2017
Outbreak of hepatitis A linked to European outbreaks among men who have sex with men in Osaka, Japan, from March to July 2018

Satoshi Tanaka,1† Tomomi Kishi,2† Akio Ishihara,1 Dai Watanabe,2 Tomoko Uehira,2 Hisashi Ishida,1 Takuma Shirasaka2 and Eiji Mita1
Total numbers?

- **European Centre for Disease Prevention and Control (ECDC)**
  - June 2016-June 2017:
    - 1,500 confirmed hepatitis A (HAV) cases
    - 2,660 probable or suspected cases
    - Predominantly among adult men who have sex with men (MSM)
  - 3 separate clusters
    - Cluster RIVM-HAV16-090 (‘Europride Strain’) initially linked to MSM at EuroPride
    - Cluster VRD_521_2016 (‘Spanish Strain’) initially linked to travel to Spain
    - Cluster V16-25801 (‘Berlin Strain’) initially reported in Berlin

- **Public Heath England**
  - July 2016 and April 2017
  - 266 cases
    - 74% MSM
    - 63% in London
But it is not only EuroPride

- Outbreaks long recognised in MSM\(^1,2\)

1. Reintjes et al., 1999; 2. Bell et al., 2001
IVDU, Homeless etc.

- IVDU & Homeless:
  - Multiple outbreaks

- Why?
  - Close contact
  - Poor hygiene
  - Possible faecal contamination of shared injecting equipment/drugs

Roy et al., 2004; O’Donovan et al., 2001; Syed et al., 2003; Perrett et al., 2003; MMWR Feb 2019
Potential interventions - vaccination

HAV Vaccine in PLWH

- Seroconversion rates\(^1\)
  - 88.3% who get 2 doses (6 months apart)
  - 83.2% after just one dose
  - Though earlier data suggested <50% with one & 70% after two doses\(^2-7\)

- But loss of sero-response in 3.9% over median 611 days\(^a\)
  - More likely in:
    - Higher weight
    - HIV viraemia at time of vaccination
    - Lower CD4 count

- However some data that a booster can work
  - Single dose of HAV revaccination provided rapid and ‘sufficient’ seroresponses during outbreak of acute hepatitis A\(^b\)

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UK Guidance

• **BHIVA Use of Vaccines (2015)**
  - CD4>350
    - 2 vaccines 6 months apart (1A)
  - CD4<350
    - 3 vaccines at 0, 1 and 6 months (1C)
  - Those at continuing risk:
    - Booster every 10 years (1C)

• **BASHH Viral Hepatitis (interim 2019 update)**
  - 2 doses – 0 and 6-12 months (1A)
  - Revaccinate after 10 years (1B)
    - However increasing evidence that immunity may last >20 years or possibly lifelong in the immunocompetent so may not be required

Potential interventions - vaccination

- **Herd immunity plays a role....**
  - In San Diego an outbreak was ‘not as expected’¹
    - HAV IgG+ in 81% of HIV-negative MSM in community
  - Lack of routine vaccination implicated in on-going outbreak in North France²
    - Only 3/49 cases had been vaccinated
  - In Italy³
    - 42.8% of MSM were HAV IgG+

- **How are we doing in the UK?⁴**
  - 74% of HIV-negative MSM were screened
  - Antibodies **not** detected in 57.4%
  - 48% of eligible individuals then vaccinated
    - Suggestion in paper: universal vaccination....

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Is seroconversion actually an adequate endpoint?

CASE REPORT

Acute hepatitis A infection after hepatitis A immunity in a HIV-positive individual

Ming Jie Lee, Sam Douthwaite, Ranjababu Kulasegaram

Lee et al., Sex Transm Infect 2018;94:30-31; Fritsche et al., Infection 2018:46(4):565-7
Vaccination in an outbreak setting?

- **Green Book:**
  - **MSM with multiple sexual partners** need to be **informed about the risks** of hepatitis A, and about the need to maintain high standards of **personal hygiene**
  - **Immunisation should be offered** to such individuals, particularly during periods when outbreaks are occurring

- 2 dose schedule in those on ART was effective in a Taiwan outbreak
  - Cases: 3.7 vs 99.3 per 1,000 person-years
    - Vaccine effectiveness of 96.3%

Other issues… those on PrEP

- And others have seen similar and suggested HAV vaccination is an important component of PrEP programmes

**CASE REPORT**

Hepatitis A infections in men who have sex with men using HIV PrEP in Paris

Pauline Penot, Marie-Alice Colombier, Sarah Maylin, Jean-Michel Molina

Penot et al., BMJ Case Rep 2018; Ismail et al., AIDS 2018;32(5):675-6
Hepatitis C
Hepatitis C - recap

And there were very few negatives

NS3A Protease Inhibitor
NS5A Inhibitor
NS5B inhibitor
What is the key current issue in the UK?
Micro-Elimination in HIV?

- Relatively small numbers
- Already engaged with robust health system
- Cost effective

- Re-Infection (perhaps 2-20 fold baseline groups)
Modelling ‘What could be achieved’
Modelling ‘What could be achieved’

Really need scale up AND risk reduction in this model

Martin et al., CID 2016;62(9):1072-80
Modelling ‘Elimination’

- Need to be able to treat acute infection
- Need to be able to treat re-infection
- Also need to be better at risk reduction and behavioral change
  - But little evidence-base to guide this
Real World?: The Netherlands Experience

A

B

Boerekamps et al., CID 2018;66(9):1360-5
And in the UK?

Incidence Rate per 1000 HIV+ MSM

Year

- Incidence of all infections

- First infection

- All infection

68% reduction

79% reduction

See Lucy Garvey’s oral presentation

Garvey et al., CROI 2019 abstract 0085
Joined up…

- As in HAV we are not an island… We need to do this joined-up with others…

Phylogenetic Tree

* Incident Swiss HCV Infections in HIV+ MSM
* Chronic from Switzerland
* UK
* Germany
* The Netherlands
* Other Countries in Europe
* Outside Europe
* Unknown
Hepatitis B
The pipeline is strong...

Pathogen sensing

Interferon loop

IFNβ

HBV (x and pol)

HBV (pol)

RIG-1

ISG expression

HBV

HBV (HBsAg/HBeAg)

IFNβ

ISG expression
And then there is Hepatitis E
Recognition, diagnosis, treatment….
Summary

- Hepatitis A outbreaks have occurred
  - But we can do our bit to prevent them
    - Follow guidelines...

- We may have easier access to Hepatitis C therapies soon
- Micro-elimination is what we should be planning

- Hepatitis B has a rich pipeline
  - Watch this space

- Don’t forget Hepatitis E