British HIV Association
BHIVA

Professor Anna Maria Geretti

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COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Prof Anna Maria Geretti	Has received speaker's and consultant's fees from Gilead, GSK, Janssen, MSD, Roche, Qiagen, ViiV and research funding from Janssen, Quagen and ViiV.
Date	**October 2014**

BHIVA Immunisation Guidelines

Anna Maria Geretti

Themes

- Hepatitis B Virus (HBV)
- Shingles / Herpes Zoster (HZ)
- Pneumococcus
- Human Papilloma Virus (HPV)

Which of the following best describes your current practice regarding hepatitis B vaccination for HIV-positive adults?

1. I offer high-dose vaccination to all patients, regardless of CD4 cell count

2. I offer standard dose vaccination to all patients, regardless of CD4 cell count

3. I am confused by the current terminology – e.g., “high-dose”, “double-dose” etc.

4. 1+3 apply

5. 2+3 apply

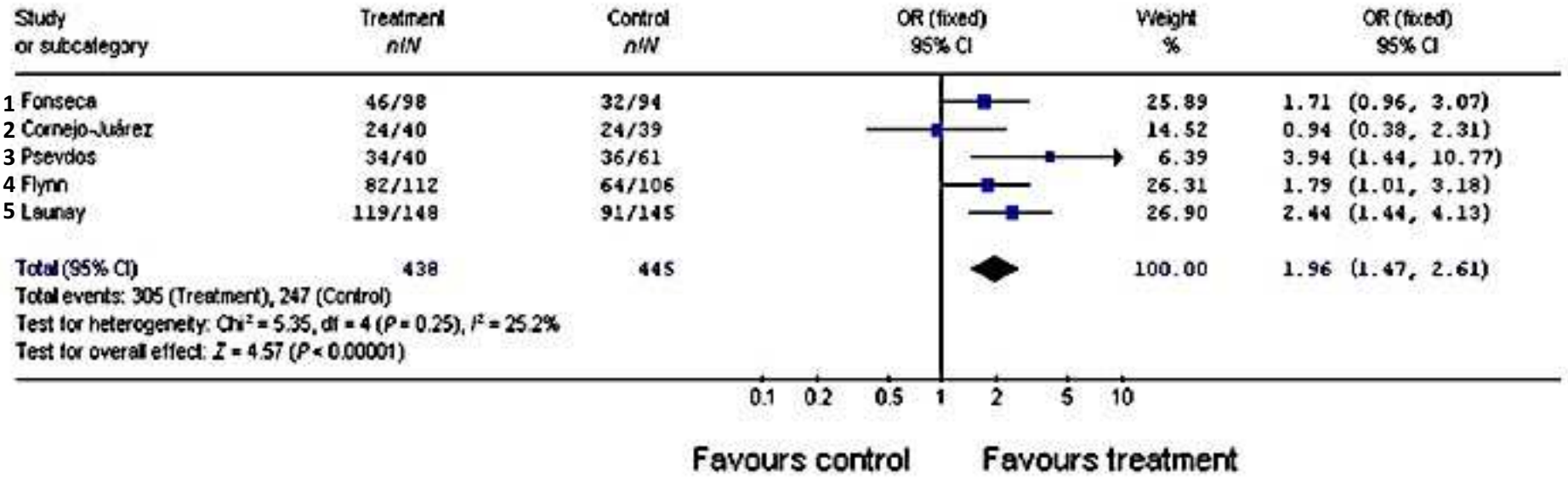
HBV vaccine recommendations

We recommend

- All non-immune individuals are immunised against HBV **[1A]**
- High dose (40 µg) vaccine strength is used for all patients **[1A]**

Meta-analysis favours high-dose HBV vaccines

Five studies (n=883), four including only vaccine-naive patients
Standard-dose vaccination (controls) compared with high-dose vaccination
No study heterogeneity found[1]



1 + 4: Engerix 20µg vs. 40µg
2: Recombivax 10µg vs. 40µg
5: GenHevac 20µg vs. 40µg

3: Previous failure to respond

UK Vaccine	Standard dose	Recommended dose
Engerix B®	20 µg	Double (40 µg)
HBvaxPRO®	5, 10, 40 µg	High (40 µg)
Fendrix®	20 µg	20 µg?[2]

1. Ni et al. Int J STD AIDS 2013; 2 De Silva et al. J Infec 2014

HBV recommendations

We recommend

- All non-immune individuals are immunised against HBV **[1A]**
- High dose (40 µg) vaccine strength is used for all patients **[1A]**
- Four doses are given at 0, 1, 2, 6 months **[1B]**
- Anti-HBs levels are measured 4–8 wks after the last dose **[1B]**
  - <10 IU/L: 3 further (40 µg) doses at monthly intervals **[2B]**
  - ≥10 but <100 IU/L: one further (40 µg) dose **[2B]**
- If anti-HBs levels ↓ <10 IU/ml, offer booster dose (40 µg) **[1B]**

We suggest

- Frequency of subsequent anti-HBs screening can be guided by anti-HBs levels: yearly if 10-100 IU/L; every 2 yrs if >100 IU/L [GPP]

Which of the following best describes your opinion in relations to shingles vaccination for HIV-positive adults?

1. Safety data are limited and I am concerned that the vaccine may cause excess side effects

7%

2. Efficacy data are limited and I am not convinced that the vaccine would be beneficial

18%

3. Provided it is safe, I would offer vaccination to all patients aged 50 or 60 years and above

42%

4. Shingle is a condition best prevented and managed in primary care and national guidance applicable to the general population should be followed for vaccination

33%

Shingles - What is new?

- **Zostavax:** high dose live attenuated VZV vaccine, ≥14 times more potent than the varicella vaccine
- Licensed for immune competent adults aged ≥50 yrs
- Boosts natural immunity, reduces incidence of herpes zoster by at least half and frequency of post-herpetic neuralgia by ~ two thirds - *Protection expected to last for ≥5 years*[1]
- No major safety concerns - *Contraindicated in significant immune deficiency*
- In Sept 2013, JCVI recommended routine shingles vaccination for people aged 70 yrs & catch-up programme in 78-79 yrs old

VZV = Varicella Zoster Virus

JCVI = Joint Committee on Vaccination & Immunisation

1. Gagliardi et al. Cochrane 2012

Shingles vaccine for HIV-positive adults

- Annual incidence of HS per 100 p-yrs ↓ from 6.3 episodes in 1987 to 1.0 episode in 2011 in the U.S.[1]
- Disease burden reduced by ART, but expected to remain higher than in HIV-negative people[2-4] - *UK burden unknown*
- Greater HS risk at low CD4 counts vs. no vaccine safety data at low CD4 counts
- Additional risk factors may include prior shingles[5], crack cocaine use, age >60 yrs (>40 in crack cocaine users)[4]
- ACTG phase 2 randomised placebo-controlled trial of 395 HIV-positive adults on ART with CD4 >200: vaccine safe and immunogenic - *abstract*[6]
- Duration of response, clinical/cost-effectiveness unknown

1. Moanna et al. Clin Infect Dis 2013; 2. Vanhems et al. J AIDS 2005; 3. Levin et al. J AIDS 2009; 4. Nacher et al. PlosOne 2013; 5. Shearer et al. Int J Infect Dis 2014; 6. Benson et al. CROI 2012

Recommendations

- We recommend that shingles vaccination should be offered to HIV-positive adults on ART with a CD4 count >200 according to the national programme (currently adults aged 70 and 78/79 **[1D]**
- Benefit plausible, but insufficient evidence to extend to younger ages (e.g., >60 yrs) or those with additional factors (e.g., previous shingles, crack cocaine use)

Which of the following best describes your current practice in relation to pneumococcus vaccination for HIV-positive adults?

1. I am no longer concerned about preventing pneumococcal disease in HIV-positive patients


3%

2. I offer vaccination routinely to all patients


57%

3. I offer vaccination to selected patients based upon additional risk factors for severe pneumococcal disease (e.g., chronic pulmonary disease)


35%

4. I am not convinced the pneumococcus vaccine is efficacious and I do not usually offer it


5%

Pneumococcus vaccination - What is new?

- **Pneumococcal conjugate vaccines (PCV-7 → PCV-13)**
- Immunogenic and clinically effective in HIV-positive adults, PCV could be offered to all patients, at all CD4 counts, +/- ART, +/- additional risk factors for pneumococcal disease*
- *Tempering factors:*
  - routine PCV use in UK infant vaccine programme ↓ disease burden due to PCV13 serotypes ↓ clinical effectiveness
  - Uncertainty over the burden of PCV13 serotype disease in HIV-infected adults

Kroon et al. Vaccine 2000; Feikin et al. Vaccine 2001; Lesprit et al. AIDS 2007; Crum-Cianflone et al. JID 2010; Penaranda et al. AIDS 2010; Sogaard et al. AIDS 2010; French et al. NEJM 2010; Ho et al. Vaccine 2013; Slayter et al. Int J STD AIDS 2013; Lu et al. Vaccine 2014

***Risk factors for pneumococcus disease:**

- **Age >65 yrs; alcoholism; malnutrition**
- **Chronic cardiovascular, pulmonary, or renal disease; cirrhosis; diabetes; cancer; immunodeficiency; asplenism; hypogammaglobulinaemia**

Pneumococcus vaccination - Recommendations

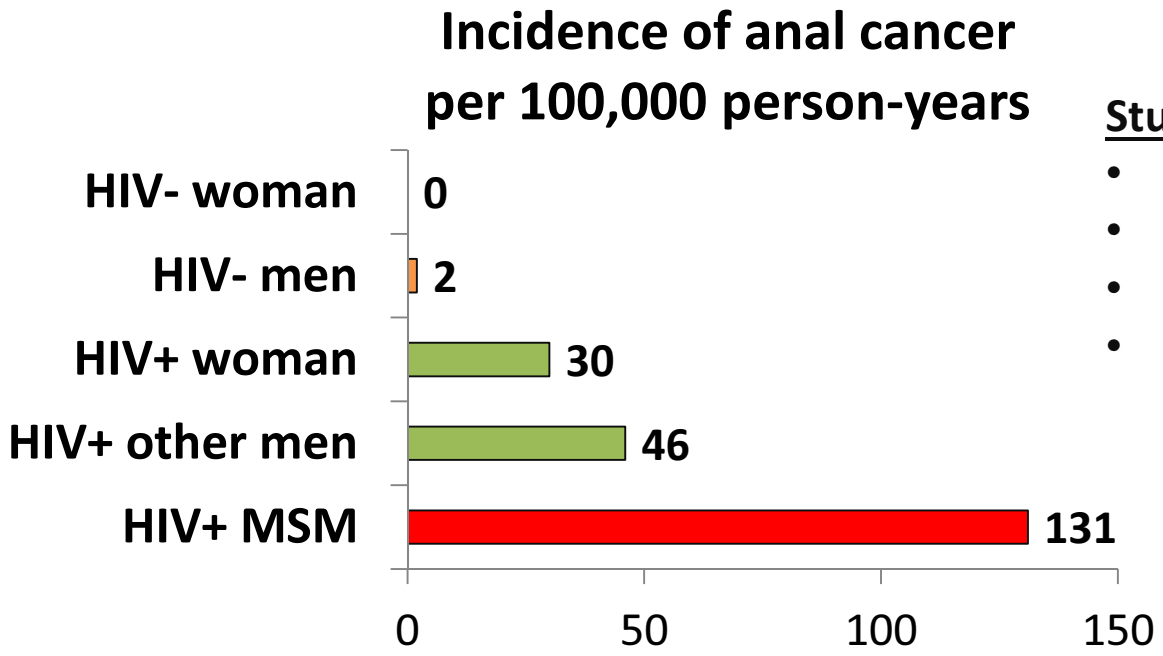
- We recommend that all HIV-positive adults receive a single dose of **PCV13**, irrespective of CD4 count or ART use **[1B]**
  - *Repeat PCV dosing not recommended* **[1B]**
- We suggest that post PCV13, a single dose of **PPV23** may be considered for individuals with CD4 ≥500 and additional risk factors for pneumococcal disease*, as per national guidelines **[2C]**
  - *Repeat PPV23 dosing not recommended* **[1C]**
- To be reviewed in light of evolving epidemiology data

***Risk factors for pneumococcus disease:**

- **Age >65 yrs; alcoholism; malnutrition**
- **Chronic cardiovascular, pulmonary, or renal disease; cirrhosis; diabetes; cancer; immunodeficiency; asplenism; hypogammaglobulinaemia**

HPV in people with HIV: High disease burden, only partially ameliorated by ART

- Genital warts more common, often resistant to treatment
- Higher risk of cervical cancer (~4 fold)[1-3]
- Higher risk of anal cancer (MSM > Other men = Women)[4]



Study population (U.S.)

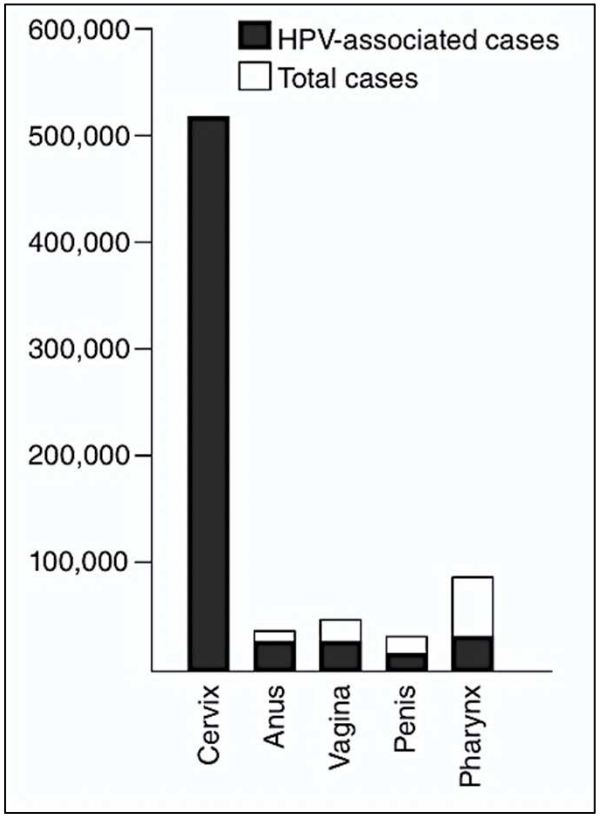
- **34,189 HIV-positive**
- **114,260 HIV-negative**
- **Follow-up 1996-2007**
- **Rates increased in the early HAART era then plateaued**

1. Adler DH. Curr HIV Res 2010; 2. Chen et al. AIDS 2014; 3. Denslow et al. Int J STD AIDS 2014; 4. Silverberg et al. Clin Infec Dis 2012

HPV Vaccines

- Virus-like particle (VLP)
  - ***HPV2 (Cervarix: HPV types 16, 18)***
  - ***HPV4 (Gardasil: HPV types 6, 11, 16, 18)***
- Excellent efficacy for preventing infection and disease in HIV-negative females & males[1,2]
  - *No therapeutic efficacy*
  - *No safety concerns*
- National programme:
  Targets girls aged 12-13 yrs
  + catch-up through 18 yrs, including any unvaccinated or partially vaccinated female (e.g., from overseas) – *HPV4 given in 2 or 3 doses*

Annual number of cancer cases worldwide[3]



1. Bosch et al. Vaccine 2013; 2. Dochez et al. Vaccine 2014; 3. Cachay et al. AIDS Rev 2014

HPV Vaccines: Other populations

- Feb 2014, Joint Committee on Vaccination & Immunisation: "Not yet in a position to advise on targeted vaccine use in MSM or on extension of the routine programme to adolescent boys"

- DoH Green Book: "People with HIV (regardless of CD4 counts) should be managed in accordance with the national programme. They may not develop a full antibody response to the vaccine and re-immunisation should be considered after immune recovery has occurred. Specialist advice may be required"

MSM = Men who have sex with men
DoH = Department of Health

U.S. Advisory Committee on Immunization Practices – HPV vaccine *Aug 2014*

- All males (HPV4) and females (HPV2 or HPV4) aged 11-12 yrs
- Unvaccinated/partially vaccinated people in the groups:
  - Females 13-26 yrs
  - Males 13-21 yrs (males 22-26 yrs may be vaccinated)
  - **MSM and HIV-positive people ≤26 years**

"Although vaccine effectiveness would be lower in those who are sexually active, and would decrease with older age and likelihood of previous HPV exposure, only a small percentage in the above age groups have been infected with both HPV 16 and HPV 18 or all four vaccine types and the majority will derive at least partial benefit"

HPV vaccines not licensed in the US for persons >26 yrs

Markowitz et al. MMWR Recomm Rep 2014

HPV vaccines in HIV-positive people

- Safe and immunogenic in 5 clinical studies (Table)[1-5]
- HPV4 seroconversion rates similar between HIV-negative and HIV-positive people aged 13-27 yrs *(85% vs. 91%; p=0.52)*[6]
- CD4 <200 associated with lower seroconversion rates in one study but not in others; ART improves responses
- No long-term immunogenicity data, no clinical outcome data

Location	Design	*N*	Vaccine	Outcomes
US	Randomised double-blind	*126*	HPV4	Safe, immunogenic
US	Single-arm open-label	*112*	HPV4	Safe, immunogenic
US, Puerto Rico	Open-label multicentre	*99*	HPV4	Safe, immunogenic
Denmark	Randomised double-blind	*92*	HPV4 vs. HPV2	Safe, equal rates of seroconversion
India	Single-arm open-label	*150*	HPV4	Safe, immunogenic

1. Markowitz et al. MMWR Recomm Rep 2014; 2. Cachay et al. AIDS Rev 2014;
3. Denny et al. Vaccine 2013; 4. Wilkin et al. J Infect Dis 2010; 5. Kahn et al. Clin Infect Dis 2013; 6. Giacomet et al. Vaccine 2014

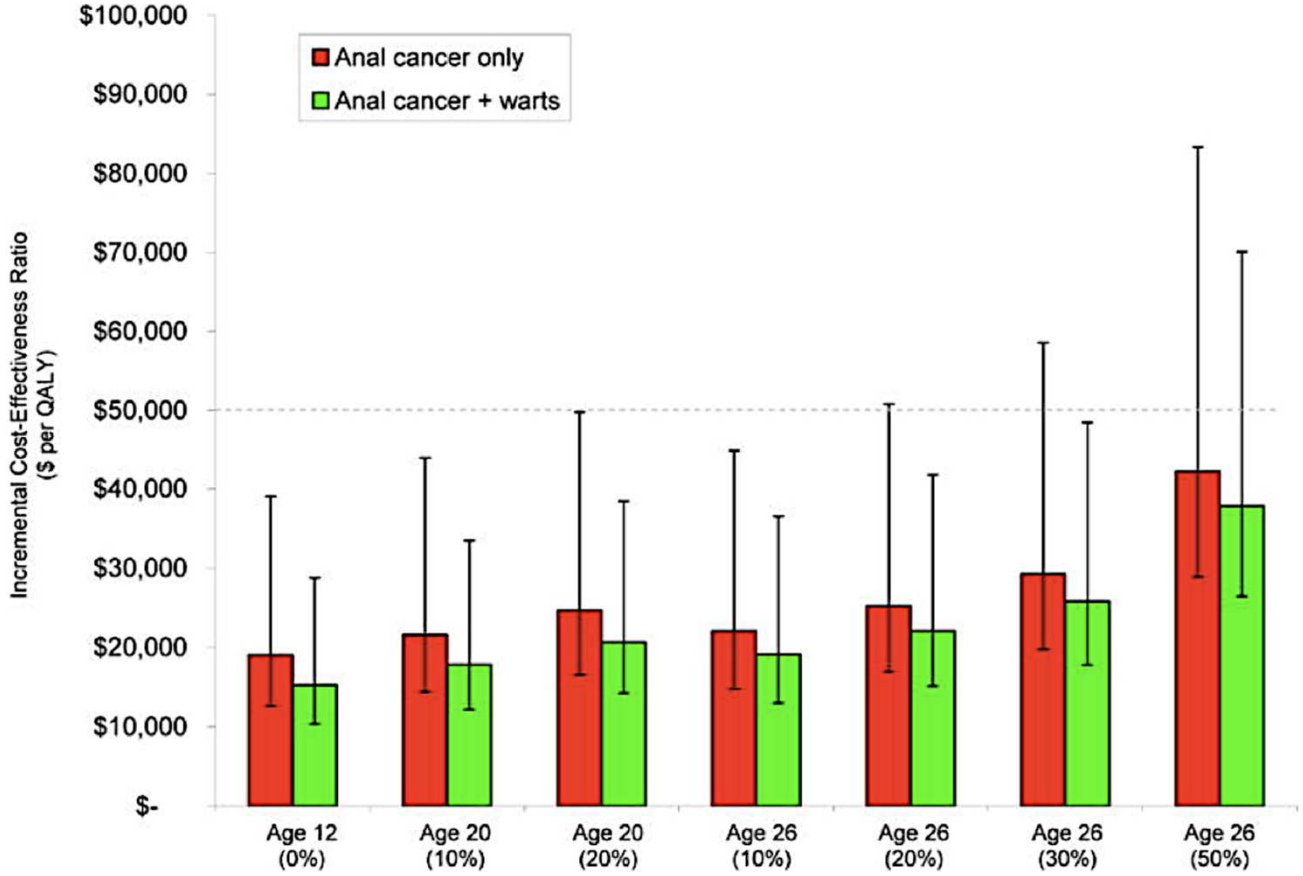
Cost-effectiveness of HPV vaccination

Population	*Cost-effectiveness*	
Young females	*High*	
Older females	*Lower*	Pre-existing infection likely; upper age for loss of benefit uncertain (15-26 years in different studies)
Young males	*Lower*	Lower burden of disease in men than in women; protected by herd immunity, particularly if high vaccine coverage in females
MSM ≤26 years	*Probable*	Higher burden of disease than other men, not protected by herd immunity, a subset has HIV
Older MSM	*Unknown*	Pre-existing infection likely; higher burden of disease than in other men, not protected by herd immunity, a subset has HIV

Markowitz et al. MMWR Recomm Rep 2014; Cachay et al. AIDS Rev 2014; Desai et al. STD 2011

Cost-effectiveness of HPV vaccination in MSM: Impact of age, prior exposure to vaccine types, & HIV prevalence

Base case assumptions: 50% coverage, 90% efficacy, 25% HIV-positive
Error bar limits refer to HIV prevalence: upper 8%, lower 40%



Kim JJ. Lancet Infect Dis 2010

Summary of rationale for HPV vaccine recommendations in HIV-positive adults

- Same HPV types cause disease in HIV-negative and HIV-positive people *(HPV 16, HPV 18 predominant oncogenic types)*
- Higher carriage of HPV vaccine types than HIV-negative people, but exposure not universal and appreciable incidence demonstrated through maturity, especially among MSM[1-4]
- High disease burden

HPV vaccines:

- Safe and immunogenic
- Cost-effective in HIV-negative women ≤26 yrs
- Cost-effective in MSM ≤26 yrs, greater benefit if HIV-positive
- No data on clinical- and cost-effectiveness in HIV-positive men, women, and MSM populations aged >26 yrs

1. Sadlier et al. HIV Med 2014; 2. Poynten et al. STD 2012; 3. Sharma et al. J AIDS 2013; 4. Hernandez et al. 2014

What is your opinion regarding what BHIVA should recommend about HPV vaccination for HIV-positive adults?

1. Follow U.S. practice and recommend vaccination for all unvaccinated HIV-positive females & males ≤26 years

2. Recommend targeted vaccination for women and MSM ≤26 years based upon likely cost-benefit

3. Recommend vaccination for women and MSM ≤45 years based upon lack of harm and possible benefit

4. Recommend vaccination for all HIV positive people ≤45 years based upon lack of harm and possible benefit

5. Do nothing and wait for more evidence

Panel

- Anna Maria Geretti (Chair)
- Gary Brook
- Claire Cameron
- David Chadwick
- Neil French
- Robert Heyderman
- Antonia Ho
- Michael Hunter
- Shamez Ladhani
- Mark Lawton
- Eithne MacMahon
- John Mc Sorley
- Anton Pozniak
- Alison Rodger

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