Professor Fiona Mulcahy
St James’s Hospital, Dublin, Ireland

COMPETING INTEREST OF FINANCIAL VALUE £1,000:

<table>
<thead>
<tr>
<th>Speaker Name</th>
<th>Statement</th>
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<tbody>
<tr>
<td>Prof Fiona Mulcahy:</td>
<td>Professor Mulcahy has received grants and research support from MSD, Abbott, BMS, VIVVE, GSK, and Jannsen. She has also undertaken speaker, advisory board and consultancy work for MSD, Abbott, GSK, BMS, Jannsen and Gilead</td>
</tr>
<tr>
<td>Date</td>
<td>April 2012</td>
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</tbody>
</table>
10 Top Papers 2011-2012

Prof Fiona Mulcahy
Prevention of HIV infection with early antiretroviral therapy


HPTN052: STUDY DESIGN

- 1763 stable, healthy, sexually active, serodiscordant couples
- 890 HIV-positive men and 873 HIV-positive women from sub-Saharan Africa (n = 954), Asia (n = 531), Latin America (n = 276) and the USA (n = 2)
- CD4 cell count: 350–550 cells/mm³

Randomization

Immediate ART (886 couples)

Primary transmission endpoint
Virally linked transmission events

Delayed ART (877 couples)

Primary clinical endpoint
WHO Stage 4 clinical events, pulmonary tuberculosis, severe bacterial infection and/or death

WHO = World Health Organization
HPTN052: EARLY ART PREVENTS HIV TRANSMISSION TO SEXUAL PARTNERS

- **28/39 transmission events were linked**
  - One in the ART immediate arm and 27 in the ART delayed arm (p < 0.001)
  - 23/28 (82%) transmissions in sub-Saharan Africa
  - 18/28 (64%) transmissions from infected participants with CD4 cell count > 350
  - 18/28 (64%) transmissions from female to male partners

- **Viral suppression in treated individuals**
  - Immediate arm: after 1 year, 90% of total had viral suppression
  - Delayed arm: after 1 year, 93% of total had viral suppression

HPTN052: PRIMARY CLINICAL EVENTS

- **Median follow-up: 1.7 years**
- **105 individuals experienced at least one primary clinical endpoint**
  - 40 immediate arm: incidence 2.4/100 PY (95% CI: 1.7–3.3)
  - 65 delayed arm: incidence 4.0/100 PY (95% CI: 3.1–5.0)
Implications

• Patient information

• Transmission prevention

• PEP guidelines

• Pregnancy options
Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study

- Prospective study of 3790 heterosexual, HIV-1 serodiscordant couples from seven African countries:
  - Injectable contraception was more commonly used than oral pills
  - Analysis controlled for age, pregnancy, condom use and HIV plasma concentrations
- Subgroup analysis showed
  - Significantly increased HIV risk with injectable contraceptive use
  - Non-significant increase with oral contraceptive use

![Graph showing rate of HIV-1 acquisition per 100 person-years for female and male HIV-negative individuals with hormonal contraception and no hormonal contraception.]

aHR = adjusted hazard ratio


Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study

<table>
<thead>
<tr>
<th>Detection of any genital HIV-1 RNA</th>
<th>Quantity of genital HIV-1 RNA detected (log copies/mL)</th>
<th>Adjusted regression coefficient (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>Median [IQR]</td>
<td>1.51 (1.20-1.82)</td>
<td>0.002</td>
</tr>
<tr>
<td>No hormonal contraception</td>
<td>Median [IQR]</td>
<td>1.51 (1.20-1.82)</td>
<td>0.002</td>
</tr>
<tr>
<td>Any hormonal contraception</td>
<td>Median [IQR]</td>
<td>1.51 (1.20-1.82)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Transmission may be explained by raised HIV concentration in endocervical secretions

- Heffron R et al. Lancet 2012:12;19-26
When to Start Antiretroviral Therapy in HIV-Associated Tuberculosis

M. Estée Török, M.D., Ph.D., and Jeremy J. Farrar, M.D., Ph.D.
Earlier versus Later start of Antiretroviral Therapy in HIV-infected Adults with Tuberculosis


- 661 pts randomised to early ART (D4T/3TC/EFV) @ 2 vs 8 weeks post TB Rx initiation
- Median CD4 25x10^6/ml
- Median HIV VL 5.64 log
- TB Rx Inah/rif/PYZ/Eth x 2 months, followed by rif/inah x4 months.
- Prophylaxis with co-trimoxazole and fluconazole (CD4<200)
Results

- **Survival Rate** Earlier-ART group vs later-ART group (P=0.004 by the log-rank test) Death rate was 8.28 / 100 pys (95% confidence interval [CI], 6.42 to 10.69) in the earlier-ART group, vs 13.77/100 pys (95% CI, 11.20 to 16.93) in the later-ART group (P=0.002).

- In the multivariate analysis, the **adjusted hazard ratio for death** in the earlier-ART group, vs the later-ART group, was **0.62** (95% CI, 0.44 to 0.86; P=0.006).

- **Tuberculosis-associated IRIS** was significantly increased 110 events in the earlier-ART group, vs 45 events in the later-ART group (hazard ratio, 2.51; 95% CI, 1.78 to 3.59; P<0.001).

- Six deaths were directly related to tuberculosis-associated IRIS, all occurring in the earlier-ART group.
Implications

• Benefit of early initiation of ART in patients with higher CD4+ T-cell counts ?

• Benefit in patients other than those with pulmonary tuberculosis, ??

• IRIS in patients with pulmonary tuberculosis is rarely life-threatening. But in patients with more severe forms of disease, such as tuberculous meningitis, mortality is much higher and intracranial IRIS may prove fatal.

Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)-associated Tuberculous meningitis.


• Randomized, double-blind, placebo-controlled trial

• 253 Vietnamese patients with tuberculous meningitis,

• ART was given within 1 week or was deferred until 8 weeks after presentation.

• Results:
  – no reduction in mortality
  – increased frequency of severe adverse events in the group that received ART within 1 week after presentation.
New Regimens to Prevent Tuberculosis in Adults with HIV Infection

Neil A. Martinson, M.B., B.Ch., M.P.H., Grace L. Barnes, B.S.N., M.P.H., Lawrence H. Moulton, Ph.D., Reginah Msandiwa, R.N., Harry Hausler, M.D., Ph.D., Malathi Ram, Ph.D., James A. McIntyre, M.B., B.Ch., Glenda E. Gray, M.B., B.Ch., and Richard E. Chaisson, M.D.
• 1148 pts (S AFRICA)
  • Median CD4 484
  • >18 yrs
  • 5mm+ tuberculin skin test

Exclusion factors:
  • active TB
  • TB Rx >2/12
  • ART
  • CD4 < 200

Four regimens:
  once-weekly INH 900 mgs-RPT 900mgs DOT x12/52
  twice-weekly INH 900mgs-RIF 600mgs DOT x 12/52
  daily self-supervised INH 300mgs x 6/12
  daily self-supervised INH 300mgs indefinitely

Median follow-up duration was approximately 4 years.

• The incidence rates of TB were 1.4–2.0 per 100 person-years, without significant differences between the four regimens.

• Treatment completion was greater for the two rifamycin-containing regimens, and grade 3 or 4 adverse effects were more common for INH taken indefinitely.
What Regimen should we use?

Table 1. Latent TB Infection Treatment Regimens

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Duration</th>
<th>Interval</th>
<th>Minimum doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>9 months</td>
<td>Daily</td>
<td>270</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly*</td>
<td>76</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>6 months</td>
<td>Daily</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly*</td>
<td>52</td>
</tr>
<tr>
<td>Isoniazid and Rifampin</td>
<td>3 months</td>
<td>Once weekly**</td>
<td>12</td>
</tr>
<tr>
<td>Rifampin</td>
<td>4 months</td>
<td>Daily</td>
<td>120</td>
</tr>
</tbody>
</table>

*Use Directly Observed Therapy (DOT)
Efficacy of Quadravalent HPV vaccine against HPV infection and Disease in males

*Giuliano AR et al N Eng J Med 2011 :364;401-11*
HPV vaccine against Anal HPV Infection and Anal Intraepithelial Neoplasia

• 602 MSMs enrolled
  – 299 vaccinated with qHPV
  – 299 placebo

• Age 16 to 26 years

• 5 or fewer lifetime sexual partners

• Insertive or receptive anal intercourse or oral sex within the past year.

Exclusion criteria:
• History or presence of clinically detectable anogenital warts or lesions suggesting other STI.
• HIV positive

Serum specimens for HPV serologic testing:
Obtained on study day 1 and month 7.

Detailed anal examination:
Day 1, months 7, 12, 18, 24, 30 and 36.

Each visit:
Dacron swabs – anal cytologic analysis
HPV DNA – PCR assays
Digital rectal examination and standard anoscopy
RESULTS

71.8% completed the 36 months follow-up period.

2/3 included in the pre-protocol efficacy population.

- Subjects (Pre-Protocol Efficacy)
  - were seronegative on day 1
  - PCR-negative for both swab and biopsy specimens from day 1 through month 7 for the relevant vaccine HPV type (or types)
  - did not have any protocol violations
  - received all 3 vaccinations within 1 year
  - had 1 or more follow-up visits after month 7

- Case counting commenced at month 7

- 194 qHPV recipients and 208 placebo were eligible for the pre-protocol efficacy analysis of HPV – 6, 11, 16 or 18 – related AIN end point.

- HPV- DNA positive: 27.4% HPV 6 or 11
  16.4% HPV 16
  11.3% HPV 18

| Table 1. Vaccine Efficacy against Anil Intraepithelial Neoplasia (AIN) and Anal Cancer in the Intention-to-Treat Population. |
|---|---|---|---|---|---|---|---|
| End Point | qHPV Vaccine (N=299) | | | Placebo (N=299) | | | |
| | No. Included in Analysis | No. of Affected Participants Person-Yr at Risk | Events per 100 Person-Yr at Risk | No. Included in Analysis | No. of Affected Participants Person-Yr at Risk | Events per 100 Person-Yr at Risk |
| AIN due to any HPV type | 275 | 74 | 369.0 | 13.0 | 276 | 103 | 588.4 | 17.5 | 25.7 (1.1 to 45.6) |
| HPV-6, 11, 16, or 18 | 275 | 78 | 407.4 | 9.3 | 276 | 77 | 611.9 | 12.4 | 59.2 (22.7 to 96.7) |
| HPV-16 or 18 | 275 | 12 | 662.7 | 1.8 | 276 | 27 | 668.3 | 4.0 | 52.2 (8.5 to 79.3) |
| AIN due to a specific HPV type | | | | | | | |
| HPV-6 | 275 | 18 | 644.8 | 2.8 | 276 | 47 | 645.3 | 7.3 | 61.7 (32.8 to 79.1) |
| HPV-11 | 275 | 19 | 653.3 | 3.0 | 276 | 35 | 600.5 | 3.8 | 47.3 (27.4 to 71.9) |
| HPV-16 | 275 | 8 | 668.7 | 1.2 | 276 | 18 | 678.6 | 2.7 | 54.9 (9.0 to 83.0) |
| HPV-18 | 275 | 5 | 671.9 | 0.7 | 276 | 11 | 684.5 | 1.6 | 53.7 (44.6 to 62.4) |
| AIN grade 2 or 3 | | | | | | | |
| Condyloma Laminatum | 275 | 13 | 653.1 | 2.0 | 276 | 31 | 664.2 | 4.7 | 57.2 (15.9 to 79.7) |
| Flat lesion | 275 | 27 | 636.0 | 4.2 | 276 | 48 | 641.3 | 7.5 | 43.3 (7.3 to 66.0) |
| AIN grade 2 or 3 | 275 | 18 | 660.1 | 2.7 | 276 | 39 | 655.2 | 6.0 | 54.2 (18.0 to 75.3) |
| Grade 2 | 275 | 11 | 668.0 | 1.6 | 276 | 29 | 671.5 | 4.3 | 61.9 (21.4 to 81.8) |
| Grade 3 | 275 | 10 | 665.9 | 1.5 | 276 | 19 | 672.8 | 2.8 | 46.8 (10.2 to 77.9) |
| Anal cancer | 275 | 0 | 678.4 | 0.0 | 276 | 0 | 694.8 | 0.0 | NA |

* The intention-to-treat population consisted of study participants who received at least one dose of the study drug. A participant may have been counted more than once if multiple lesions in different categories developed. NA denotes not applicable.
### Efficacy against HPV 6/11/16/18 Anal Intraepithelial Neoplasia (AIN)

**Young Men (16 – 26 years) Per Protocol Efficacy Population ~3 years of Follow Up**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>qHPV N = 299</th>
<th>Placebo N = 299</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n # Cases</td>
<td>PY at risk</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-----------</td>
<td>------------</td>
</tr>
<tr>
<td>HPV 6/11/16/18-related AIN/Anal Cancer</td>
<td>194 5</td>
<td>381.1</td>
</tr>
<tr>
<td>AIN1</td>
<td>194 4</td>
<td>383.1</td>
</tr>
<tr>
<td>AIN2 or Worse</td>
<td>194 3</td>
<td>383.9</td>
</tr>
</tbody>
</table>

Evaluation of the Efficacy of qHPV against AIN was studied in Men having Sex with Men (MSM) to ensure adequate end points during the period of follow up.


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Multiple Infections occurred frequently. At least 3 cases likely to be not due to HPV 6/11/18.
Efficacy against HPV 6/11/16/18 Persistent Infection (Anal)

Young Men (16 – 26 years) Per Protocol Efficacy Population ~3 years of Follow Up

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>qHPV (N=299)</th>
<th>Placebo (N=299)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td># of Cases</td>
<td>PY At Risk</td>
</tr>
<tr>
<td>HPV 6/11/16/18</td>
<td>193</td>
<td>2</td>
</tr>
</tbody>
</table>

Evaluation of the Efficacy of qHPV against Persistent Infection (Anal) was studied in Men having Sex with Men (MSM) to ensure adequate end points during the period of follow up.


Implications

• Study shows efficacy of the qHPV against HPV- 6, 11, 16 or 18-related AIN grade 1,2 or 3, against persistent anal infection with each of the four HPV strains, and against anal detection at any time of DNA of each of the 4 HPV types, in both pre- protocol efficacy and the intention –to- treat population.

• The proportion of participants who reported serious adverse events was relatively low and was similar in both groups.

• Does this apply to our HIV+ pts???
  – age of the participants,
  – short follow-up time,
  – limited sexual activity of participants.
Clinical features and outcome in HIV-associated Multicentric Castlemans Disease


- 61 pts with MCD
- 53 (87%) male, median age 42 yrs
- Median interval HIV and MCD DX 2.4 yrs (0-24)
- Median follow up 4.2 yrs
- 49 pts RX Rituximab +/- etoposide
  - 2yr survival 94% (CI 87-100%) vs 42% (14-70%) pre rituximab
  - 5yr survival 90% (CI 81-100%) vs 33% (6-60%) pre rituximab
  - P< .001
  - 8/46 pts with clinical remission relapsed
Kaplan-Meier curve showing the overall survival for all 49 patients treated with rituximab-based therapy for HIV-associated multicentric Castleman's disease.

Bower M et al. JCO 2011;29:2481-2486

Frequency of clinical criteria defining active Castleman's Disease

<table>
<thead>
<tr>
<th>criteria</th>
<th>% of patients</th>
<th>criteria</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>fever</td>
<td>98</td>
<td>cough</td>
<td>61</td>
</tr>
<tr>
<td>C-reactive protein &gt; 20 mg/L in the absence of any other aetiology</td>
<td>92</td>
<td>Nasal obstruction</td>
<td>40</td>
</tr>
<tr>
<td>Peripheral lymphadenopathy</td>
<td>100</td>
<td>Xerostomia</td>
<td>40</td>
</tr>
<tr>
<td>splenomegaly</td>
<td>95</td>
<td>Rash</td>
<td>62</td>
</tr>
<tr>
<td>oedema</td>
<td>18</td>
<td>Neuro features</td>
<td>66</td>
</tr>
<tr>
<td>thrombocytopenia</td>
<td>33</td>
<td>hypoalbuminaemia</td>
<td>70</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>18</td>
<td>Jaundice</td>
<td>14</td>
</tr>
<tr>
<td>Acsites</td>
<td>8</td>
<td>Autoimmune hemolytic anemia</td>
<td>43</td>
</tr>
</tbody>
</table>

Patients require a fever, raised serum C-reactive protein, and three of 12 additional clinical findings (ANRS)
Host Genomics and HCV treatment response
Clark PJ, Thompson A J Gastroenterol Hepatol 2012:2,212-22

- Human genome >3 billion nucleotide base pairs with 90% identical between individuals

- Most common genetic variation is a single nucleotide polymorphism (SNP)

- Genome wide ass studies (GWAS) now widely available
  - Major limitations
  - Necessitates very large well characterised cohort
  - Do not include rare variants
  - High no of ass tests required
Genotype 1 HCV and Peg-ifn/RBV treatment response

IDeAL Study

- 1137/1671 pts pharmacogenomic analysis included in analysis
- SNP rs12979860 biallele (C/T) with 3 genotypes CC, CT, TT
- SNP rs12979860/IL28B CC genotype ass with 2-3 increase in SVR in 3 ethnic groups
- Also ass with RVR and EVR
- Freq of IL28B allele lower in AA 64% vs 89% Caucasian pts.
- 6 other SNPs on a common haplotype also ass with SVR
- Other studies G allele of rs8099917 ass with non response to treatment, both tag a common haplotype

- Spontaneous clearance increased with favourable IL28B allele
  - CC 64% vs CT 24% vs TT 6%
- More likely to present with jaundice
- Poor IL28B alleles ass with more severe steatosis and LDL-C levels, elevated ALT
- HIV does not modulate the association
- Response rates to IFN RX post transplant improve where donor or recipient carry the good response variant!! The effect is additive!
Non–Genotype -1HCV

• No significant ass between genotype and SVR in Genotype 2/3 HCV

• Possibly in genotype 4/6 HCV

Implications

• IL28B most important re Neg Predictive Value (NPV)

• In poor responders delay for DAAs?

• Treat seroconverters with poor allele with IFN/RBV?

• Choose optimum transplant donor organs?

• Other alleles may prove more important
Rilpivirine versus Efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE)
Cohen C et al Lancet 2011;378;229-36

Rilpivirine versus Efavirenz with Tenofovir and Emtricitabine in treatment-naive adults infected with HIV-1 (ECHO)
Molina JM et al Lancet 2011;378;238-46
**ECHO and THRIVE: Double-blind, ARV treatment-naïve adults**

- **Primary objective:** To demonstrate non-inferiority (12% margin) vs EFV in confirmed virologic response (VL <50 copies/mL, ITT-TLOVR) at Week 48.
- **Main inclusion criteria:** VL ≥5000 copies/mL; no NNRTI RAMs †; sensitivity to the N(t)RTIs ‡.
- **RPV/RPV placebo taken with food; EFV/EFV placebo taken on an empty stomach, at bedtime.**

**RPV 25 mg qd + TDF/FTC qd + EFV pbo qd (N=346)**

**EFV 600 mg qd + TDF/FTC qd + RPV pbo qd (N=344)**

**RPV 25 mg qd + 2 N(t)RTIs* + EFV pbo qd (N=340)**

**EFV 600 mg qd + 2 N(t)RTIs* + RPV pbo qd (N=338)**

*Investigator’s choice: TDF/FTC (60%); AZT/3TC (30%); ABC/3TC (10%)

**ECHO and THRIVE Week 48 analysis:**

- **VL <50 copies/mL by baseline VL (ITT-TLOVR)**

  - **RPV**
    - ≤100,000 copies/mL: 90% (162/181), 91% (172/187), 90% (323/360), 84% (332/388)
    - >100,000 copies/mL: 76% (129/169), 79% (121/153), 77% (246/318), 81% (285/352)

  - **EFV**
    - ≤100,000 copies/mL: 92% (162/181), 94% (172/187), 90% (323/360), 84% (332/388)
    - >100,000 copies/mL: 82% (129/169), 80% (121/153), 84% (246/318), 81% (285/352)

  *Difference in response rates (95% CI)

- **N(t)RTI background had no effect on virologic response**
- **No differences between treatment groups in virologic response by gender, region, or race**
Pooled ECHO and THRIVE Week 48 analysis: ITT-TLOVR outcome at Week 48 by baseline VL

Pooled ECHO and THRIVE Week 96 analysis: ITT-TLOVR outcome at Week 96 by baseline VL

Cohen C, et al. 6th IAS 2011; Abstract TULBPE032
Stellbrink HJ, et al. 13th EACS 2011; Poster PE7 3-5
Osteoporotic fracture risk associated with cumulative exposure to Tenofovir and other antiretroviral agents

Bedimo R et al AIDS 2012, 26:

- 56,660 HIV pts
- Risk of OF was examined by
  - Univariate analysis: UV
  - Multivariate analysis: MV1 (controlling for race, age, tobacco use, diabetes, BMI, HepC)
  - MV2 (controlling for MV1 variables + concomitant ARV exposure)
ARV exposure and OF risk 1996-2009

Fig. 2. Antiretroviral Exposure and Risk of Osteoporotic Fractures 1996–2009. ABC, Abacavir; AZT/3TC, Zidovudine or Stavudine; NNRTI, Non-nucleoside reverse transcriptase inhibitors; rPI, ritonavir-boosted protease inhibitors; TDF, Tenofovir. Drug name followed by 1: Multivariate model 1; controlling for CKD, age, sex, tobacco use, diabetes and BMI (Model 1); Drug name followed by 2: Multivariate model 2; controlling for Model 1 variables and concurrent exposure to other antiretrovirals.
Single Center Study

- 1557 women analyzed (519 infected and 1038 non-infected)
- Excluded Hx of &risk factor for PTD, active IVDU, multiple gestation
- Iatrogenic preterm delivery: delivery < 37 weeks due to the following reasons: preeclampsia, intrauterine growth restriction, fetal distress or intrauterine fetal death
- Spontaneous preterm delivery: delivery < 37 weeks including premature rupture of membranes

Incidence of preterm delivery: 19.7% in HIV+ group vs 8.5% in controls (OR 2.6 95%CI 1.9-3.6; p<0.001)

Incidence of each type of prematurity by HAART use

- Significant association between use of HAART in the second half of pregnancy and iatrogenic preterm delivery (OR 6.2 CI 4.4-26.8 p=0.015)
- No association between spontaneous preterm delivery and use of HAART

Lopez et al. AIDS 2011
Own white coats versus newly laundered short sleeve uniforms.
Rate of bacterial colonisation of newly laundered uniforms

No differences in:
- in cfu from white coats vs newly laundered uniforms, P=0.61
- in no. MRSA contaminated
- in bacterial or MRSA wrist contamination