Dr Julie Fox
St Thomas’ Hospital, London

<table>
<thead>
<tr>
<th>Speaker Name</th>
<th>Statement</th>
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<tbody>
<tr>
<td>Dr Julie Fox</td>
<td>Dr Julie Fox has received grant support from xxx for research and/or for travel to international conferences.</td>
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Date
April 2015
Translating recent research into clinical practice

Julie Fox
Guy’s and St Thomas’ NHS trust
Kings College London
Aim

- Review published research from past 12 months and discuss how they might impact clinical practice
  - Immediate
  - Medium term
  - Long term
Method

- Ask colleagues (community and clinic based)
  - Thank you!

Consensus expert opinion

DISCLAIMER Red = Fox opinion
Immediate impact on clinical practice
1. Expect a normal life expectancy:
   May et al. AIDS 2014

- UK CHIC: 21 388 people started ART 2000-2010

- Estimated the impact of ART (CD4 count and VL response) on life expectancy of HIV positive people
## Results

### If 35 year old man started ART:

<table>
<thead>
<tr>
<th>CD4</th>
<th>Baseline</th>
<th>1 year ART</th>
<th>5 years ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200</td>
<td>71</td>
<td></td>
<td>&amp; VL&gt;50 54</td>
</tr>
<tr>
<td>200-349</td>
<td>78</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>&gt;350</td>
<td>77</td>
<td>81</td>
<td>&amp; VL&lt;50 80</td>
</tr>
<tr>
<td>General population</td>
<td>78</td>
<td></td>
<td></td>
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</tbody>
</table>

**Conclusion:** If diagnosed, in care and on effective ART: life expectancy is normal

Great information to give to people newly diagnosed and encourage good adherence
2. Super infection: does not matter Ronen et al. AIDS 2014

- Female sex worker cohort, Mombasa n= 146 HIV seroconversions (median follow-up 5 years)
- Sequenced gag, pol and env genes to identify individuals were super-infected

- 21/146 (14%) women had superinfection

- Superinfection was associated with:
  - Faster ↑ in VL (0.009 log10 /month  (p=0.0008)
- Superinfection was NOT associated with:
  - CD4 decline (p=0.06)
  - Clinical event ( CD4 <200, initiating ART or death) (hazard ratio 1.07, CI: 0.60 – 1.89; p = 0.76)

Reassuring for patients

- Low VL more likely to get superinfected (p=0.05)

Who gets super-infected important for vaccine research
3. Efavirenz & suicidality  

- Efavirenz
  - abnormal dreams, mood changes, anxiety, dizziness
  - Relationship with suicide not well defined.

- ACTG analysed **4 ART naïve Efavirenz RCTs**:

<table>
<thead>
<tr>
<th>Study</th>
<th>EFZ n=3214</th>
<th>Comparator n= 2091</th>
<th>Open/blinded</th>
<th>Study duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>A5095</td>
<td>Kivexa + EFZ</td>
<td>Trizivir</td>
<td>Blinded</td>
<td>96</td>
</tr>
<tr>
<td>96A5142</td>
<td>NRTIs + EFZ</td>
<td>NRTIs + LPV/r</td>
<td>Open</td>
<td>96</td>
</tr>
<tr>
<td>A5175</td>
<td>NRTIs + EFZ</td>
<td>ATZ+ddI-EC +FTC</td>
<td>Open</td>
<td>96</td>
</tr>
<tr>
<td>A5202</td>
<td>NRTIs + EFZ</td>
<td>NRTIs + ATZ/r</td>
<td>Open</td>
<td>96</td>
</tr>
</tbody>
</table>

Limitations: ¾ studies open, not powered to investigate suicide
Primary outcome: suicidality (suicidal ideation, attempt or complete suicide)

- Suicidality was 2.3 x high in EFZ regime compared to a EFZ free regimen:
  - Risk was higher in the 1\textsuperscript{st} 6 months HR 3.69 (CI 1.41 to 9.63)

- Overall, suicidality was associated with:
  - taking efavirenz, history of injecting street drugs or history of mental health/ severe emotional disorders (all p<0.001)

<table>
<thead>
<tr>
<th></th>
<th>Events (Incidence per 1000 person-yrs)</th>
<th>Hazard ratio</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>EFZ</td>
<td>EFZ free</td>
</tr>
<tr>
<td>Attempts &amp; completed</td>
<td>17 (2.90)</td>
<td>5 (1.22)</td>
</tr>
<tr>
<td>suicide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suicidality (suicidal</td>
<td>47 (8.08)</td>
<td>15 (3.66)</td>
</tr>
<tr>
<td>ideation, attempt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or complete suicide</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Efavirenz & suicide risk

- Results worrying
- Must monitor for suicidality
  - New starters ok seen regularly
  - Stable patients only seen 6 monthly – is this enough to pick up risk?
- Given these results should EFZ still be first line?

Raffi, Pozniak et al. J. Antimicrob. Chemo 2014
Ford N et al. JAIDS May 2015
Efavirenz: change the dose?

- ↓ side effects and cost
Randomised, double-blind, non-inferiority trial
ART-naïve, HIV+ adults

**Randomisation:**
- TDF/FTC + EFV 400 mg QD
- TDF/FTC + EFV 600 mg QD

N=636

**4. ENCORE 1:** Efficacy of 400mg EFZ versus 600mg in ART naïve individuals- 96 week: *Lancet ID April 2015*
Low dose EFZ non inferiority virologically and less EFZ related AE

Virological non inferiority for VL < 400, < 200 and <50 copies/ml irrespective of baseline viral load

<table>
<thead>
<tr>
<th></th>
<th>EFV 400 mg N =324 (%)</th>
<th>EFV 600 mg N=312 (%)</th>
<th>Difference (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion VL &lt;200</td>
<td>90.0</td>
<td>90.6</td>
<td>-0.6 (-5.2, 4.0)</td>
<td>0.72</td>
</tr>
<tr>
<td>Developed NNRTI resistance</td>
<td>0.6</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. pts with AEs</td>
<td>287 (89.4)</td>
<td>276 (89.3)</td>
<td>0.1 (-4.7, 4.9)</td>
<td>0.97</td>
</tr>
<tr>
<td>No. pts with EFV-related AE*</td>
<td>121 (38)</td>
<td>148 (48)</td>
<td>-10.2 (-17.9, -2.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>No. pts ceasing EFV due to EFV-related AE*</td>
<td>10 (8)</td>
<td>23 (16)</td>
<td>-7.3 (-14.9, 0.4)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

No difference in adherence, QOL, depression or anxiety scores
Conclusion

Low dose EFZ 400mg was virologically efficacious up to 96 weeks & had less EFZ related side effects:

- This one third reduction in active drug would have large cost savings

But not being prescribed:

- No drug interaction data for the low dose with rifampicin or in pregnancy,
  - vital for high TB, high pregnancy settings
  - unable to get funds to do the drug interaction analysis

- Lancet editorial this week: suggested low dose could be used for all except TB and pregnancy.
  - BUT WHO keen for one treatment for all
  - fixed dose combinations available cheaply only include 600mg EFZ
5. Integrases

Rapid virological response, low levels of side effects, high genetic barrier to resistance; no booster required (Review Raffi AIDS 2015)

Key groups who might benefit most:
- NEAT study: high CV risk (Pozniak)
- BESTT study: older women (Post)
- SWORD: NRTI sparing therapy

A Carr PLOS 1 2014: Met-analysis of 114 studies with up to 144 weeks follow up - Greatest efficacy was associated with Integrase inhibitors (vs other 3rd drug classes) and Truvada (vs other NRTI backbones)
Medium Term
Do we need more drugs? Yes: Fletcher PNAS 2014

Measured ARV drug levels in blood and tissue in 12 people starting ART

ART naive

Truvada/ Efavirenz
N=6

Truvada/ Atazanavir /ritonavir
n=4

Truvada/ Darunavir/ Ritonavir
N=2

Monthly bloods
Biopsies (inguinal lymph node, ileum, rectum) 0,1,3,6 months
Results

With the exception of TFV-DP (in ileum and rectum) and DRV (ileum only)
- All ARV concentrations much lower in tissue compared to plasma.
- ATZ particularly poor (green bars)
Results: VL decay in tissues

- VL in lymph tissue declined rapidly in 1st month and then slowed or ↑ thereafter in all drugs except TFV-DP (0.0242) (light blue) & FTC-TP (0.0204)(orange)

- suggests continued virus production
Fletcher: Conclusion

- [ARV] in lymph tissue do not fully suppress viral replication and this may maintain immune activation

- Newer drugs and drug combinations are required to fully suppress viral replication in lymph tissue

Agree, tissue penetration may become important in determining long term morbidities of HIV and improving cure strategies

Further analysis of integrases and TAF now planned
Medium term impact: Costs and adherence

• Should we switch to generic drugs as they come available?
  • In UK, this strategy would save NHS £1.25 billion pounds over 5 years (Hill Glasgow 2014)
  • In USA, switch from STR to 3-pills od would save $920 million dollars per year (Walensky Ann Int Med 2013)

• Before do this, must decide:
  • Is pill burden a real issue for virological suppression
  • Is once a day regimen better than twice a day?
Does Pill Burden and od v bd matter: Cohen
BMJ open 2013

- Medicaid analysis of 7381 HIV + individuals on ART:
  - Compared a once-daily single-tablet regimen (STR) with two or more pills per day

- STR associated with
  - 23%↓ hospitalisations
  - 17% ↓ hospital cost
  - ↑ p( ≥95%) adherence

X sectional cohort study
USA healthcare

Risk of Channelling bias??
Does Pill Burden and od v bd matter: Nachega CID 2014

- Meta-analysis of 19 RCTs investigating this
- N = 6312 adult patients (ART naive and switch studies)

**Virological suppression:**
- No difference between od and bd (RR = 1.01; 95% CI 0.99 - 1.03; p = 0.57)
- Increased pill burden was associated with increased virological failure in both od (p=0.005) and bd (p<0.0003) dosing
- Suppression decreased over time in both od (-0.71 - 0.83 to -0.362; p=0.001) and bd dosing (-0.6 - 0.88 to -0.33; p=0.002)

**Adherence:**
- lower in bd compared to od regimens (weighted mean difference = 2.55%; 95% [CI], 1.23 to 3.87; P = .0002)
  - Driven by those switching to bd for virological failure on od (WMD=5.9% 0.6-9.96; p=003) and ART naïve (WMD=3.9% 1.42-6.47; p=0.002)
Conclusions

- Lower pill burden was associated with better virological suppression but no difference in between od and bd regimens

Supports current BHIVA guidelines
To save money, in 2011 area around Copenhagen changed treatment guidelines to:

- ART naïve patients suitable for Atripla started Tenofovir/3TC/Efavirenz (3 pills) instead
- People on Atripla were switched to Tenofovir/3TC/Efavirenz (3 pills)

Clinics responded: >96% on Atripla switched to TTR (Triple tablet regimen)

Two 48 week time periods before and after guideline change were compared.
Compared 2 time periods before and after guideline change over 48 weeks

Starting ART

no difference between the two time periods in:
- % virological failure (<500 copies/ml)
- number new 184V/1I mutation (1 person)
- risk of switch to a non EFZ based regime

On ART
Conclusion:

A switch from STR to triple tablet 3TC containing regimen can be done with negligible short-term risk of adverse outcomes.

- No longer term data why?
  - the company reduced price of Atripla and Atripla prescribing resumed!
  - interesting and important approach by Denmark
Treatment AS Prevention (TASP)

- TASP important again in 2015:
  - Partner study; Partners Prep demonstration project (TASP with Prep); 052 IAS

- 052 showed ART ↓ risk of transmission within a couple by 96% (Cohen NEJM 2012)
  - The effect on population level HIV incidence unknown
  - Especially in sub-Saharan Africa where
    - stable discordant couples are often not the norm
      - HIV acquisition can occur outside the relationship (Cohen NEJM 2012)
    - role out of ART to whole communities problematic
Population based analysis of 16,667 HIV negative people followed up in KwaZulu-Natal 2004–12

- 1413 HIV seroconversions occurred

- Mathematical modelling investigated impact of changing ART coverage on HIV incidence
  - whilst controlling for known risk factors for HIV (marital status, household wealth, no. sex partners in past 12 months)
Tanser results

Overall, the risk of HIV was much lower in areas of high ART coverage.

For each 10% increase in household ART coverage, the HIV acquisition hazard was reduced by 6% (95% CI 2–9).
Tanser conclusion

- The first real-world evidence that ART coverage ↓ HIV incidence

- The effect of ART on HIV incidence must be included in ART costing models.
Oral PreP (pre PROUD era): iPrEx

- **Placebo** controlled RCT in 2499 MSM and transgender women to receive oral daily FTC/TDF or placebo

- **Truvada** reduced HIV incidence by **44%** (CI 15% to 63%: p = 0.005)
  - Lower reduction than expected
  - Until now little understanding of:
    - Adherence patterns
    - Factors associated with poor adherence
Drug levels measured in Truvada arm

1. Cross sectional random n=470 at week 8.
   - 55% had drug detected.
   - Drug detection associated with older age and site location (90% San Fran, 35% Lima). ‘Research literacy’

2. Longitudinal analysis n=303 over 72 weeks.
   - Detection rates declined over time.
     - 31% never had drug detected: target for adherence support
     - 30% always had drug detected,
     - 39% had an inconsistent pattern – similar to Ipergay

Drug detection associated with older age, high sexual risk and responding “don't know” to a question about belief of PrEP efficacy (0–10 scale).
Open Label Extension of iPrEx
- First PrEP demonstration project
- Drug levels measured on EVERYONE
HIV Negative MSM/Transgender
N=1603 (65% from IPREX)

Chose PreP
1225 (76%)

HIV incidence 28/1225 (2.3%)
7 had stopped PreP completely >2months earlier
(1.7%)

Chose no Prep
N=378 (24%)

HIV incidence 13/378 (3.4%)

- IPREX OLE PreP group had:
  - 49% reduction HIV risk compared to OLE no PrEP group
  - 51% reduction HIV risk compared to placebo IPREX arm

- but underestimates as much higher risk behaviour
Adherence predicts protection

- 100% protection if took 4 or more doses per week
  - But only one third had this drug level (IPREX /IPERGAY)
- 84% protection if take 2-3 doses per week

- Adherence associated with
  - ↑ level education (PROUD)
  - older age (PROUD)
  - high HIV risk (PROUD)
  - recently starting PreP

- BUT High early drop out, especially in young people
Compare adherence results from IPREX/IPREX OLE/IPERGAY

- Truvada usage similar across all 3 studies
  - ie converge to 3-4 doses per week

- Adherence associated with:
  - age, risk, education & duration of Prep use
  - high adherence in those reporting highest risk may increase the impact and cost-effectiveness of PrEP

- Target the right people and give adherence support to those who need it
Do we need PreP: aren’t condoms enough?

• PROUD deferred arm tells us the answer: without Prep high risk MSM get HIV.

• Despite knowing they were high risk for HIV, knowing that PreP works and knowing that they were not on it- PROUD participants could not reduce risk practices for the 12 month required until PreP received

McCormack CROI 2015
Long active Prep: 744 / cabotegravir
12 Female pigtail macaques exposed to intravaginal inoculations of SHIV twice a week for up to 11 weeks

monthly 744 injection = 6
monthly placebo injection n = 6

1 2 3
months
Results

100% protection

All 6 macaques protected from SHIV

Drug levels stable

- 744 levels stable over time
- Levels in vagina and rectum 7-28% lower than plasma (p=0.002)
- But all above PA-IC90
- Results comparable with quarterly injections 800mg im in humans (Spreen JAIDS 2014)
Conclusion

- These data support advancement of GSK744 LA as a PrEP candidate for women.

efficacy studies in development
Long term impact: HIV cure

2x Boston adults rebounded after stopping ART following BM transplant

Not a good year
Rapid seeding of SIV viral reservoir in rhesus monkeys
Whitney Nature 2014

Investigated how quickly reservoir established after infection

- inoculated 20 Rhesus monkeys intra-rectally with high dose SIV
- randomised to start ART (TNF/FTC/dolutegravir) days later
  - 3 days
  - 7 days
  - 10 days
  - 14 days
- Stopped ART week 24
### on ART

<table>
<thead>
<tr>
<th></th>
<th>Day 3</th>
<th>Day 7</th>
<th>Day 10</th>
<th>Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma RNA ever</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Plasma proviral DNA ever</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Immune responses (cellular and humoral) ever</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>viral evolution</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissue proviral DNA</td>
<td>+ v.low and ↓ over time (absent in ¼ week 20)</td>
<td>+++ stable after week 12</td>
<td>+++ stable after week 12</td>
<td>+++ stable after week 12</td>
</tr>
</tbody>
</table>
Off ART: All rebounded

- Day 3 ART group had a 3 fold delay in viral rebound viraemia
- Rebound RNA set point was lower in all groups compared to ART naïve controls (with no difference between randomisation groups)
Conclusion

- Viral reservoir seeding occurs very early in rhesus monkeys—during eclipse phase, before plasma viraemia.

- Creates new “challenges” for HIV eradication strategies.

Disappointing results

Suggests that ARV alone even if very early not enough

More understanding of VISCONTI group required (Frater)
<table>
<thead>
<tr>
<th>Role of immune responses in cure: Deng et al Nature 2014</th>
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</thead>
<tbody>
<tr>
<td><strong>ART at Acute HIV n=10</strong></td>
</tr>
<tr>
<td>Sequence latent virus</td>
</tr>
<tr>
<td>CTL response against released latent virus</td>
</tr>
<tr>
<td>CTL response against released latent virus After pre-treating/activation with gag peptides</td>
</tr>
<tr>
<td>Humanized mouse with pt PBMCs and bone marrow cells</td>
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</table>
Conclusion

- Using CTL responses to cure HIV will require pre-activation but may be possible in those treated in acute and chronic infection.

- Good as had been increasingly thought that only acute HIV had a role in cure programmes.

- This strategy could be used in conjunction with other strategies e.g. ART + HDAC etc.

- A cure is a long way away: early days.
Overall conclusion

• Summarized: recent research may inform clinical practice
• NHS and BHIVA must respond to key research and does:
  • Treatment guidelines updated frequently
  • Position statements respond to immediate issues
• We must all support and carry out research

• 2015/2016 exciting year for primary and secondary HIV prevention
• With increased diagnoses and normal life expectancy, costs are unsustainable
  • Research shown generics will help
  • Need for a vaccine and cure as great as ever
Acknowledgments

Patients and volunteers who take part in research

Sheena McCormack, Sarah Fidler, Caroline Sabin, Andrew Phillips, Nicky Mackie, Gus Cairns, Simon Collins, Mike Malim, Kholoud Porter, Frank Post, Anton Pozniak, Mark Nelson, Martin Fisher, David Back, Saye Khoo, Marta Boffito, John Frater, Duncan Churchill, Anna Marie Gerretti, Alison Rodger, Sabine Kinloche, Annemeik de Ruiter, Graham Taylor, Alan Winston, Margaret Johnson, Andrew Hill, Anatole Menon-Johansson, David Asboe, Juan Tiraboschi

Apologies for missing crucial papers!