

# Update on Antiretroviral-Based HIV Prevention

Prof. Janneke van de Wijgert  
University of Liverpool, Institute of  
Infection and Global Health

12th European Meeting on HIV & Hepatitis –  
Treatment Strategies and Drug Resistance  
26-28 March 2014, Barcelona, Spain

# Outline of presentation

- Efficacy and safety of oral and topical PrEP thus far
- Oral and topical PrEP product/research pipeline
- Key challenges for the future
- Conclusions

## Not discussing:

- (Antiretroviral) Treatment as Prevention (TasP)
- Non-ARV prevention

# Efficacy in oral/topical PrEP trials

| Trial                          | Population  | Drugs*                           | 1 year Efficacy                                    |
|--------------------------------|---|----------------------------------|--|
| iPrEx [2010]                   | 2,499 MSM in 6 countries; 1.2 years**                   | Truvada                          | <b>44%</b> [15, 63]                                |
| CAPRISA 004 [2010]             | 889 women in South Africa; 2.5 years                    | TDF gel coital                   | <b>39%</b> [6, 60]                                 |
| FemPrEP [2011]                 | 3,900 women in 3 African countries                      | Truvada                          | Stopped: futility                                  |
| Partners PrEP [2011]           | 4,758 discordant couples in Uganda and Kenya; 1.9 years | Truvada<br>TDF                   | <b>75%</b> [55, 87]<br><b>67%</b> [44, 81]         |
| CDC TDF2 [2011]                | 1,219 women + men in Botswana; 1.1 years                | Truvada                          | <b>63%</b> [22, 83]<br>(M: 80%; W: 49%)            |
| VOICE [2013]                   | 5,021 women in 3 African countries                      | Truvada,<br>TDF<br>TDF gel daily | 0% [-50, 30]<br>Stopped: futility<br>15% [-21, 40] |
| Bangkok TDF Study (CDC) [2013] | 2,413 IDU in Bangkok; 4 years                           | TDF                              | <b>49%</b> [10,72]                                 |

\*Daily oral unless otherwise specified. \*\* Median follow up time

# High level adherence = protection

|                                     | % of blood samples with tenofovir detected | HIV protection efficacy in randomized comparison | HIV protection estimate with high adherence    |
|-------------------------------------|--|--|--|
| <b>Partners PrEP</b><br>FTC/TDF arm | 81%  | 75%  | 90%<br>(tenofovir in blood)                    |
| <b>TDF2</b>                         | 79%  | 62%  | 78%<br>(prescription refill)                   |
| <b>BTS</b>                          | 67%  | 49%  | 70% - 84%<br>(tenofovir in blood / pill count) |
| <b>iPrEx</b>                        | 51%  | 44%  | 92%<br>(tenofovir in blood)                    |
| <b>FEM-PrEP &amp; VOICE</b>         | <30%                                       | No HIV protection                                | N/A  |

Or could there also be biological or behavioural factors (other than poor adherence) that explain lack of efficacy in young women?

# Correlates of low adherence

- Low adherence in first month = low adherence throughout (Partner's PrEP)
- Adherence dropped over time (CAPRISA 004)
- Not attending appointments (Partner's PrEP, VOICE, others?)
- Younger age (Partner's PrEP, VOICE)
- Not partnered (FemPrEP, VOICE)
- Low perception of risk/stigma? (FemPrEP, others?)
- Less sex (Partner's PrEP, iPrEx)
- Alcohol use (Partner's PrEP)



# Safety in oral/topical PrEP trials

- HIV drug resistance: So far only in study participants with unrecognized, acute HIV infection. The true magnitude of HIVDR incidence will not be known until roll-out on a larger scale.
- Side effects: No product-related SAEs but modest decreases in renal function and bone mineral density in oral PrEP trials (not vaginal or rectal); and gastro-intestinal side effects in rectal PrEP trials.
- No safety data for adolescent, pregnant, and breastfeeding women for oral PrEP.

# FDA approval Truvada for oral PrEP

## FDA NEWS RELEASE

**For Immediate Release:** July 16, 2012

**Media Inquiries:** Erica Jefferson, 301-796-4900

[erica.jefferson@fda.hhs.gov](mailto:erica.jefferson@fda.hhs.gov)

**Consumer Inquiries:** 888-INFO-FDA

**FDA approves first drug for reducing  
the risk of sexually acquired HIV infection**

*Evidence-based approach enhances existing prevention strategies*

Today, the U.S. Food and Drug Administration approved Truvada (emtricitabine/tenofovir disoproxil fumarate), the first drug approved to reduce the risk of HIV infection in uninfected individuals who are at high risk of HIV infection and who may engage in sexual activity with HIV-infected partners ...



# WHO guidance on oral PrEP, July 2012

- [www.who.int/hiv/pub/guidance\\_prep/en/index.html](http://www.who.int/hiv/pub/guidance_prep/en/index.html)
- For use in the context of demonstration projects
- Initial focus on discordant couples and MSM
- Key points to be addressed at country level:
  - How to ensure HIV-negative status at initiation and regular retesting? (Note: best retesting interval unknown)
  - Only provide PrEP in addition to condoms and STI treatment
  - How to assess clinical contraindications (e.g. renal/bone disease)?
  - How to monitor safety (AEs) and adherence?
  - How to deliver/resupply drugs, and terminate if needed?
  - How to link clients who become infected to HIV care?
  - Address ethical issues where universal access to ART for HIV-positives has not yet been achieved



# Ongoing oral Truvada studies

- iPrEx OLE and Partners PrEP open-label continuations
- PROUD study UK: Truvada now vs. Truvada in 12 months (N=500 HIV-negative men)
- Numerous other demonstration projects
- Intermittent oral PrEP:
  - HPTN 066 US: PK/PD of different Truvada dosing schedules
  - ANRS iPerGay trial France/Quebec: RCT of Truvada compared to placebo (both arms access to PEP):
    - Two Truvada within 24 hours of sex
    - One as soon as possible afterwards and daily thereafter if sex continues until at least one day after the last act

# Truvada oral PrEP in real world

- So far, governments do not seem willing to include oral PrEP in publicly funded programs and/or are reluctant to allow roll-out
- Uptake by both physicians and individuals at risk (who mostly have to pay out of pocket) seems rather low

PrEP  
IN THE  
**REAL  
WORLD**



# Ongoing oral PrEP studies with other ARVs

- NEXT-PREP (HPTN 069): Placebo-controlled Phase II trial of maraviroc alone and in combination with tenofovir or with emtricitabine (FTC)
  - 400 MSM and 200 at risk women in the US

# Oral vs. topical

- Topical - advantages:
  - More rapidly achieves high levels in genital tissues (one NHP study showed that vaginal dosing also achieves high recal levels and vice versa)
  - Lower systemic levels suggests less toxicity
  - Potential to combine with contraception (e.g. multipurpose vaginal rings)
  - Less obvious competition with treatment
- Oral - advantages:
  - Familiarity and decades of adherence experience
  - High drug levels in local lymph nodes could be important



# Ongoing vaginal microbicide efficacy trials

- One tenofovir vaginal gel RCT, dosing before and after sex, compared to placebo:
  - FACTS 001: South Africa
- Two dapivirine vaginal ring RCTs of compared to placebo:
  - The Ring Study: South Africa, Uganda
  - ASPIRE: South Africa, Uganda, Zimbabwe, Malawi
- All due to report in 2015



# Rectal microbicide development

- Majority of MSM use lubricants during anal sex so acceptability of rectal gels is likely high
- About 40% of heterosexuals in US and UK have lifetime experience of anal sex
- Only Phase I safety trials to date
- Main early finding: Hyperosmolar gels (incl. OTC lubricants!) cause epithelial damage
- Original 1% TDF gel formulation is hypersosmolar – new reduced glycerin iso-osmolar gel developed for rectal use
- Phase II trial of iso-osmolar 1% TDF gel (MTN-017) started in October 2013
- Initiate Phase III in 2016?

# Multiple API

- Explant studies showed that combinations of 2-3 active pharmaceutical ingredients (API) are more effective than those with one API, including against HIV strains with drug resistance mutations.
- Field moving towards topical products containing multiple API.

# In development by delivery system

| Vaginal or rectal gel  | Vaginal ring  | Vaginal film/tablet                               | Injectables                    |
|--|---|---|--------------------------------|
| TDF alone (Conrad)<br>TDF-Maraviroc for rectal use (CHARM)           | TDF alone (Conrad)  | TDF –Maraviroc (Conrad/IPM)                       | TMC278 LA (Tibotec/HPTN)       |
| Dapivirine alone (IPM)<br>Maraviroc alone for rectal use (IPM)       | Dapivirine alone<br>Maraviroc alone<br>Dapivirine-Maraviroc (IPM/MTN) | Dapivirine alone<br>Dapivirine-Maraviroc (IPM)    | S/GSK '744 (GSK/Shionogi/ViiV) |
| Dapivirine-Darunavir (IPM/EU CHAARM)                                 | Dapivirine-Darunavir (IPM/EU CHAARM)                                  |   |                                |
| MIV150/Zn (Pop Council)  | MIV150/Zn (Pop Council)   |   |                                |
| IQP-0528 (ImQuest/NIH)<br>5P12-RANTES (MTN)<br>Griffithsin (NIH/MTN) | Dapivirine-Levonogestrel (IPM)<br>IQP-0528 (ImQuest/NIH)              | IQP-0528 film (ImQuest/NIH)<br>DS003 tablet (IPM) |                                |



# Long-acting injectables

- Rilpivirine (TMC278):

- NNRTI developed by Tibotec (Janssen) for treatment of HIV infection; oral formulation approved
- LA formulation administered IM every 2-3 months
- Explant, Phase I, and PK/PD studies promising
- Phase II in development with HPTN



- S/GSK 1265744:

- HIV-1 integrase inhibitor developed via joint venture between GSK/Shionogi/ViiV
- Evaluated clinically as an oral formulation but not approved
- Macaque rectal challenge studies, Phase I, and PK studies with nanoparticle version of the drug promising



## Next of Generation Delivery Systems In Development



Other gels

pH transition  
Subliming Solid matrix



Vaginal Films



Quick Dissolve Tablets



Pod Rings



Segmented Rings



Rings with other polymers



Devices +/- Gels

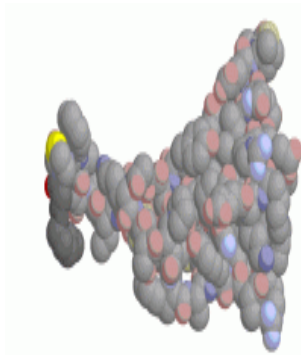
And in the distant future...



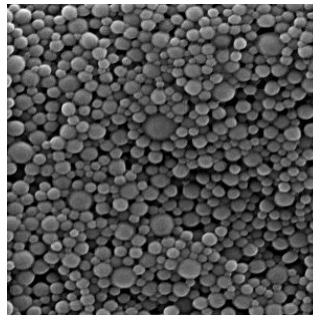
# Nanotechnology for Prevention

Increasing Delivery Options

Drug

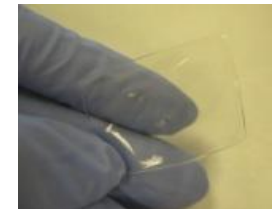


Drug  
in  
Nanoparticles



Drug-containing  
Nanoparticles in:

Vaginal Film

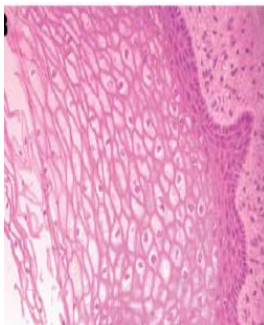


or

Vaginal Ring

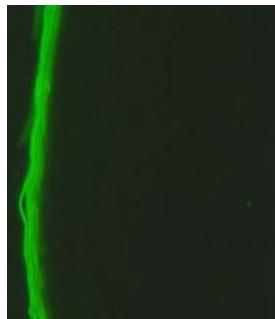


Normal Tissue

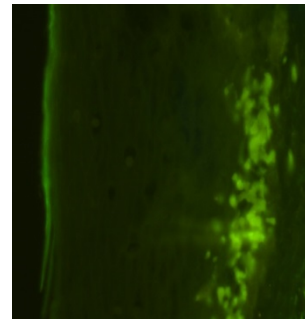


Vaginal  
Lumen

Drug alone



Drug  
in  
Nanoparticles



*Ham, et al. Pharm. Res. 2009 26:502*

# Which products will be available, realistically?

- Daily oral Truvada
- Daily oral TDF

Maybe in 3-6 years:

- Oral Truvada as needed before/after exposure
- Coital use of TDF gel vaginally
- Dapivirine vaginal ring (28 days per ring)



# Which RCTs are next, realistically?

- Large trials of rectal TDF gel for MSM
- Trials of other daily/intermittent/exposure-based oral ARV regimens
- Trials of injectables
- Depending on outcome of FACTS 001:
  - Single coital dose TDF gel instead of before/after
- Depending on outcome of dapivirine ring trials:
  - Other anti-HIV and multipurpose vaginal rings
  - Other anti-HIV vaginal gels/films/tablets

# Key challenges - political

- Moral dilemma: is it justified to give HIV-negative people ARVs when there are not enough ARVs to treat those who need them to stay alive?
- The widespread belief that making PrEP available will lead to reckless/condomless sex



# Key challenges - biological

- Not clear how much drug to deliver in which locations so that therapeutic concentrations persist beyond the period of viral exposure. PK/PD assessments throughout all phases of clinical development are still essential.
- Still doubts about long-term safety: unexpected safety endpoints may not be captured sufficiently in RCTs. Holistic systems biology approaches needed?



# Key challenge: How to improve adherence?

- Long-acting formulations that are less user-dependent (vaginal rings currently one month; injectables 2-3 months)
- Pay extra attention to those who are poor adherers early on, and to sex partners (if appropriate and feasible)
- ‘Real-time’ PK monitoring during trials
- Involve experts that have not yet been involved much in this type of research, e.g. social marketing (NIH meeting planned in May 2014)



# Key challenge: How to determine efficacy of new products while rolling out effective ones?

- Non-inferiority trials (large N and uncertain)
- Placebo-controlled, but offering all available effective interventions to all study arms (large N)
- Open-label designs like PROUD
- Build portfolio of evidence:
  - Studies with HIV endpoints but smaller than Phase III non-inferiority trials
  - Pharmacodynamic endpoints (but would need to know correlates of protection)

# Conclusions

- ARV-based prevention is now a reality
- Should be used in combination with other prevention strategies
- Will likely continue to be a niche strategy for those at high risk and/or no other prevention options
- Many challenges but that should not impede progress!