The changing landscape of biomedical HIV prevention research

MRC Clinical Trials Unit

UCL

EATG European AIDS Treatment Group

EATG Training Academy

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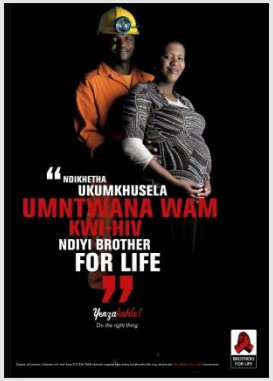
Behavioural Interventions
abstain,
be faithful

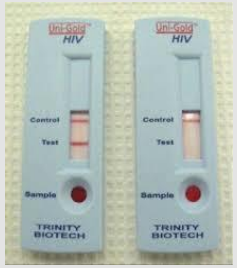
Male condoms

Female condoms



PMTCT

HIV Prevention 2010



HIV testing

Needle exchange

VMMC

Post Exposure Prophylaxis

STI treatment

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GAME
CHANGER
AHEAD

Oct 2009: RV144 HIV vaccine

Page last updated at 13:28 GMT, Tuesday, 20 October 2009 14:28 UK

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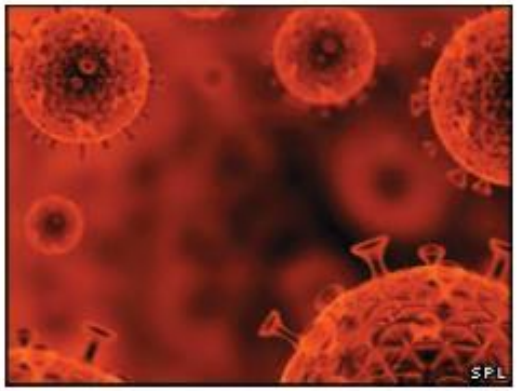
HIV vaccine trial was significant

By Matt McGrath
BBC News science and environment reporter

A review of a trial of an HIV vaccine in Thailand has concluded that it does show real signs of a protective effect.

Scientists announced last month that a combination of vaccines gave a 31% level of protection in trials among 16,000 heterosexuals aged 18-30.

Doubts had been raised about whether the finding was significant.



The search for an HIV vaccine has proved frustrating

July 2010: Tenofovir microbicide

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Home > *Science* Magazine > 3 September 2010 > Abdool Karim *et al.*, **329** (5996): 1168-1174

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- Abstract
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RESEARCH ARTICLE

Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women

Quarraisha Abdool Karim[1,2,*,†], Salim S. Abdool Karim[1,2,3,*], Janet A. Frohlich[1], Anneke C. Grobler[1], Cheryl Baxter[1], Leila E. Mansoor[1], Ayesha B. M. Kharsany[1], Sengeziwe Sibeko[1], Koleka P. Mlisana[1], Zaheen Omar[1], Tanuja N. Gengiah[1], Silvia Maarschalk[1], Natasha Arulappan[1], Mukelisiwe Mlotshwa[1], Lynn Morris[4], Douglas Taylor[5], on behalf of the CAPRISA 004 Trial Group

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Ongoing vaginal microbicide trials

- FACTS 001: Tenofovir gel (BAT24)
  - 8 sites in SA, enrolling 2060 women 18-30yrs
- IPM027 The Ring Study – dapivirine monthly ring
  - 7 sites in SA/Uganda, enrolling 1950 women 18-45yrs
- MTN 020 ASPIRE – dapivirine monthly ring
  - 15 sites in Malawi, SA, Uganda, Zim, enrolling 3476 women 18-45yrs

- Over a dozen other studies to support licensure:

http://data.avac.org/OngoingMicrobicideTrials.aspx

Oct 2013: First rectal microbicide trial

- MTN017:
  - Phase II trial
  - Reduced glycerine formulation of tenofovir gel
    - Daily
    - Before and after sex
  - Truvada oral daily
  - Enrolling 186 MSM/TSW in Peru, South Africa, Thailand and the United States

http://www.mtnstopshiv.org

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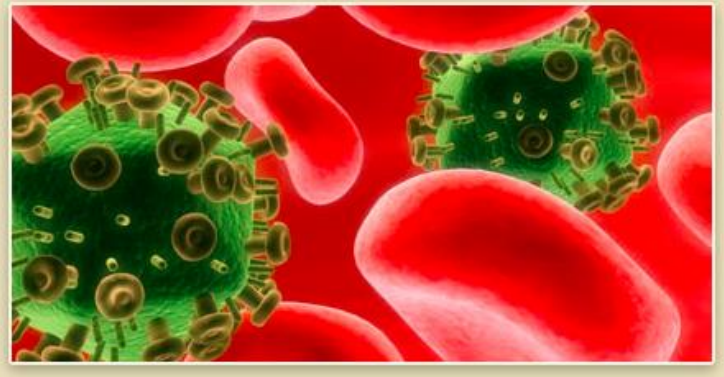

The Latest...

For those attending the 8th IAS Conference on HIV Pathogenesis, Treatment & Prevention (IAS 2015), July 19-22, in Vancouver, please join MTN & partners at two satellite sessions we are co-hosting at the meeting:

Creating Rectal Microbicides People Desire: How do we get there?, 12:30-14:30, Sunday, July 19

Minor Issues, Major Consequences: Ensuring adolescents' access to proven prevention methods, 18:30-20:30, Monday, July 20

Welcome

The **Microbicide Trials Network** is a U.S. National Institutes of Health-funded worldwide collaborative clinical trials network focused on preventing the sexual transmission of HIV. Read more...

Research Sites

Network

LOC
LC
SDMC

Enrolling Studies

MTN-015
MTN-016
MTN-023/IPM 030

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July 2011: Treatment as Prevention

OXFORD JOURNALS

Clinical Infectious Diseases

ABOUT THIS JOURNAL CONTACT THIS JOURNAL SUBSCRIPTIONS CURR

Oxford Journals › Medicine › Clinical Infectious Diseases › Volume 50 Issue Supplement 3 › P

Treatment to Prevent Transmission of HIV-1

Myron S. Cohen and Cynthia L. Gay

University of North Carolina at Chapel Hill, Chapel Hill

Reprints or correspondence: Dr Myron S. Cohen, 130 Mason Farm Rd, Bioinformatics Bldg, UNC Chapel Hill, Chapel Hill, NC 27599-7030 (mscohen{at}med.unc.edu).

Abstract

Antiretroviral therapy (ART) has the potential to prevent human immunodeficiency virus (HIV) transmission by reducing the concentration of HIV in blood and genital secretions. Indeed, mathematical models with favorable assumptions suggest the potential of ART to stop the spread of HIV infection. Empirical results from ecological and population-based

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Ongoing TasP trials

- PopART/HPTN 071: 24 villages, 60,000 people in South Africa & Zambia
  - SOC
  - Test and ARV for all positives
  - Test-linked ARV for all CD4 <350
- JHU USAID: 24 clusters, 12,000 people in Tanzania
  - SOC
  - Test-linked ARV for all CD4 <350
- Botswana Combination Prevention Project: 30 villages, 20,000 people
  - SOC
  - Test and ARV for all viral load above 10,000
- ANRS 12249 Trial: 32 clusters, 40,000 people in South Africa
  - SOC
  - Test and ARV for all positives

PrEP

Pre Exposure Prophylaxis

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Nov 2010: Pre-Exposure Prophylaxis

U.S. Department of Health & Human Services

a A A

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FDA NEWS RELEASE

For Immediate Release: July 16, 2012
Media Inquiries: Erica Jefferson, 301-796-4988, erica.jefferson@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

En Español

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. Truvada, taken daily, is to be used for pre-exposure prophylaxis (PrEP) in combination with safer sex practices to reduce the risk of sexually-acquired HIV infection in adults at high risk.

**Subsequent mathematical modelling based on drug levels observed in iPrEX estimate that daily Truvada use could reduce the risk of HIV infection by as much as 99%*

	Study	Drug	Population	Effect (95%CI)	Detectable
November 2010	iPrEX	Truvada	G/MSM/TSW: Braz, Eca Peru SA Thai USE	44% (15,63)	92% (40, 99)
April 2011	FemPrEP	Truvada	Women: Kenya, SA, Tanz	0%	
July 2011	Partners PrEP	Truvada	Discordant Kenya, Uganda	75% (55, 87)	86% (57,95)
July 2011	Partners PrEP	Tenofovir	Discordant Kenya, Uganda	67% (44, 81)	90% (56, 98)
July 2011	CDC TDF2	Truvada	Hetero Botswana	62% (22, 83)	78%
November 2011	VOICE	Tenofovir	Women: Malawi, SA, Uganda, Zim	0%	
March 2013	VOICE	Truvada	Women: Malawi, SA, Uganda, Zim	0%	
June 2013	CDC Bangkok	Tenofovir	IDU Thailand	49% (10, 72)	74% (17, 94)

Truvada demonstration studies

- Approx. 12 in USA & 12 in E/S/W Africa, South America, Thailand, India and Australia
  - All open-label without control groups
  - For more details of PrEP demonstration studies: http://data.avac.org/OngoingPrEPTrials.aspx
- UK and France
- PROUD and IPERGAY

Ongoing alternative PrEP trials

- **IPERGAY** (phase III) – France, Canada, Germany
  - Randomized to "on demand" (pre/post sex) Truvada versus placebo

Stopped

- **ADAPT** (HPTN 067) (phase II) - SA, Thailand, US
  - Randomized to daily, time-driven (twice week/post), and event-driven (BAT24) dosing
- **NEXT-PrEP** (HPTN 069/ACTG 5305) (phase II) - USA
  - Randomized to different combinations: **Maraviroc, M+ FTC , M+TFV, FTC+TFV**
- **HPTN 076** (Tibotec) **& HPTN 077** (GSK)
  - 3 month long acting slow release products

PROUD study

500 MSM reporting UAI last/next 90dy, 18+, Willing to take a pill

Randomize HIV negative MSM (exclude if on treatment for hepB/Truvada contra-indicated)

Truvada **NOW** and MI+

Truvada **IN 12M** and MI+

Follow **3 monthly** for up to 24 months

Main endpoints: recruitment and retention

Aims of Pilot

- Feasibility of larger clinical trial
  - Level of interest in PrEP in clinic populations (R&R)
  - Acceptability of randomisation
- Characteristics of men who take up offer of PrEP
- Risk behaviour, impact of PrEP on risk mitigation/compensation (self-report, STIs)
- Adherence behaviour over time (self-report, pill count, subset of PK, MEMS Cap)
- Facilitators and barriers related to adhering to a daily pill and related to risk behavior (risk-adherence matrix IDIs)

PROUD Cohort

- 35 median age
- 79% white; 58% UK born
- 60% university educated, 82% employed
- 96% self identify as gay
- 47% in a relationship
- Median of 10 partners in last 90 days (baseline)
- Median of 5 as receptive; 5 as insertive partner
- Median of 2 partners for condomless sex as receptive and 3 as insertive partners
- 40% used PEP in last yr – 21% more than once

www.bhiva.org/documents/Conferences/2014Liverpool/Presentations/140404/MonicaDesai.pdf

Results

Group	NO. of infections	Follow up	Incidence per 100	90& CI
OVERALL	22	453	4.9	3.4 – 6.8
Immediate	3	239	1.3	0.4 – 3.0
Deferred	19	214	8.9	6.0 – 12.7
Efficacy 86% (90% CI); 58 – 96%				

Trial stopped and ALL men recruited now offered PrEP

Table adapted from
http://www.proud.mrc.ac.uk/pdf/PROUD_CROI%202015_Final.pdf

Healthcare providers' knowledge of, attitudes to and practice of PrEP

- **Design:** anonymous cross-sectional survey of sexual health care providers
- **Recruitment:** Sept-Nov 2013 from professional societies, conferences and social media
- **Sample:**
  - Doctor (59%), Health adviser (19%), sexual health nurse (16%), other (6%)
  - Female 64% and male 36%
  - 35% under 39yrs old, 35% aged 40-49, 31% aged 50 or above
  - 27% involved in PROUD; 73% not

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KAP findings

- 28% report high knowledge – highest among doctors (39%)
- 58% felt able to discuss with patients – highest among doctors (73%)
- 43% not involved with PROUD had been asked about PrEP in last year
- 54% supported availability of PrEP – lowest for doctors (41%)
- 78% supported targeted provision to higher risk groups

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KAP findings

- 53% question if effective prevention tool in real world
- 80% reluctant to prescribe without UK specific guidance
- 42% concerned that PrEP may result in increase of STI
- 29% concerned about impact of PrEP on ART resistance
- 67% confident Truvada safe as PrEP
- 56% believe PrEP better option than PEP for frequent PEP users

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"If something comes along that's better than condoms,
I'm all for it, but Truvada is not that,"
said Michael Weinstein, president of the AIDS Healthcare Foundation.
"Let's be honest: It's a party drug."

USA approves widespread use of Truvada

Centre's for Disease Control and Prevention issue statement of use of PrEP and guidelines for its use.

- PrEP is recommended as one prevention option for sexually-active adult MSM (men who have sex with men) at substantial risk of HIV acquisition (IA)1
- PrEP is recommended as one prevention option for adult heterosexually active men and women who are at substantial risk of HIV acquisition. (IA)
- PrEP is recommended as one prevention option for adult injection drug users (IDU) at substantial risk of HIV acquisition. (IA)
- PrEP should be discussed with heterosexually-active women and men whose partners are known to have HIV infection (i.e., HIV-discordant couples) as one of several options to protect the uninfected partner during conception and pregnancy so that an informed decision can be made in awareness of what is known and unknown about benefits and risks of PrEP for mother and foetus (IIB)

http://www.cdc.gov/hiv/pdf/PrEPguidelines2014.pdf

PrEP in USA

- FDA approved Truvada July 2012
- Prescribers survey (01/11 – 03/13)
- 55% of all US pharmacies responded
- 1,774 individuals: 150 in 2011, 1,274 in 2012 and 350 in Q1 2013
- 37% prescribers have not prescribed ARV before
- 12% Infectious Diseases
- 48% scripts for women

PrEP in Europe

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The black hole

- NO EMA approval for PrEP
- NO reimbursement
- NO wide knowledge of how to use PrEP
- NO European Guidelines for its use
- REAL risk of internet buying

However…

- Industry is moving forward with regulators to license drugs for prevention
- Payers are starting to talk about the cost savings of PrEP
- Communities want to know more about it
- Stigma decreasing???
- The old pill arguments seem to be fading but….are still there

PrEP demonstration studies (10)

Project	Country	Pop.	Design/key questions	Status
iPrEx OLE	Br, Pe, Eq, SA, Th, US	MSM/TGW	Open Label extension	Enrolled; Nov13
TDF2 FU	Bots	Hetero	Open Label extension	Nov 12; Nov 13
Bangkok FU	Thailand	People who inject drugs	Open Label extension	Q4 13; Q4 14
Partners PrEP	Kenya & Uganda	SD	PrEP as "bridge" to ART	Aug 13; June 15
CHAMPS	South Africa	Hetero abdol	Prevention 'menu' for adolescents	July 11; June 15
WRHI	South Africa	FSW	PrEP and TasP as combined prevention and care	Feb 14; Sep 16
LVCT and SWOP	Kenya	Women, FSW, MSM	Introduce PrEP into combination prevention	Feasibility results Dec 2013
National Agency	Nigeria	SD	PrEP and TasP as combined prevention and care	Formative
Durbar & Ashodaya Samithi	India	FSW&T	PrEP intro	Feasibility results Oct 2013
Victorian PrEP Demo Project	Australia	At-risk populations	PrEP effectiveness of PrEP	Funded; to run 3 years

But how to take it?

- **Optimal** dosage is one tablet (Truvada) **daily** (gives up to 96% protection)
- Full protection gained after 30 days (for rectal protection it's 7 days, vaginal 21 days)
- Studies looking at different dosage including the "disco dose"
  - 3 days prior + 2 days after potential exposure
  - 2 hrs pre and 3 days post potential exposure
  - LAA 1 / 4 weeks
  - LAA 1 / 12 weeks
  - Gels and lubes containing the drug (but incredibly hard to formulate)

Questions going forward

- Guidance: in absence of clinical guidelines?
- Equity: access to who and where?
- Control: future trials: are they needed?
- Terminology: ‘unprotected’ vs. condomless sex
- Messages: complication in what we are saying?
- Stigma: “Why are you taking that poison?” OR “I want to protect myself” OR “I’m on PrEP yippee – I don’t need to worry about anything”

What issues does PrEP raise?

- For the Eastern Europe and Western Europe discussion after the break!

A massive thank you to…

- **Mitzy Gafos**
- **Sheena McCormack**
- MRC Clinical Trials Unit at University College London
- And all whose slides have been used by EATG and MRC
- All volunteers who took part in the trials to prove PrEP worked

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