Strategic use of antiretroviral drugs to prevent HIV transmission

22th Tunisian Congress of Infectious Diseases

2nd Congress of Federation of Arab Societies of Clinical Microbiology and Infectious Diseases

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overview

1. Introduction
2. WHO's guidance on treatment as prevention (TasP)
3. Ongoing research on TasP
4. Pre-exposure prophylaxis (PrEP)
4. Next steps

1. Introduction

Access to antiretroviral therapy (ART)

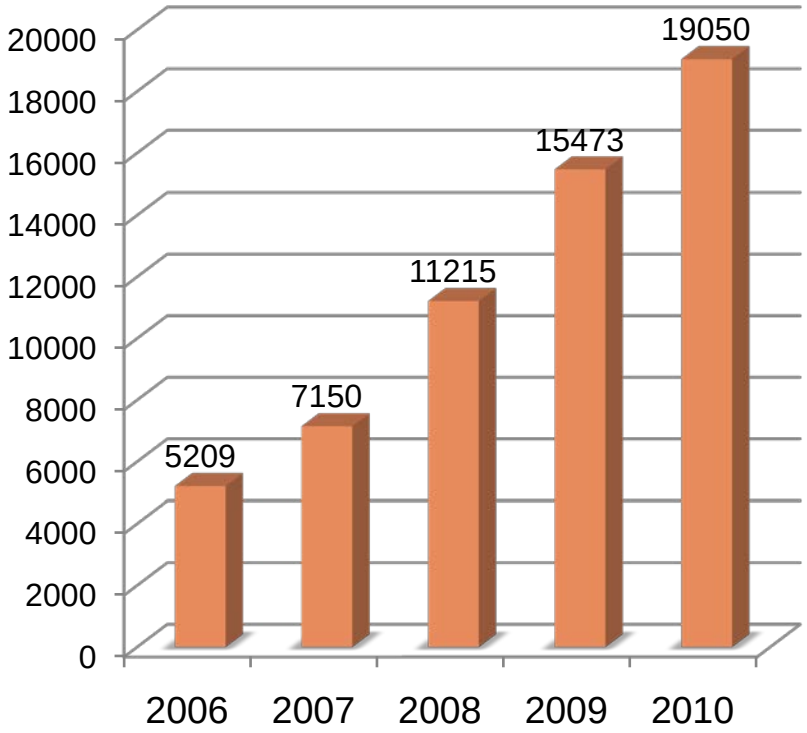
- **There has been progress in HIV treatment, at the end of 2010**
  - **6.6 million people were receiving ART in LMIC, overall coverage 47%**
  - **10 LMIC had achieved universal access**
  - **globally AIDS death decreasing**

- **There are still many challenges**
  - **Est. 9 million people in need of ART not accessing treatment yet**
  - **<u>New infections still outpace treatment</u>, for every person started on ART, 2 are newly infected**

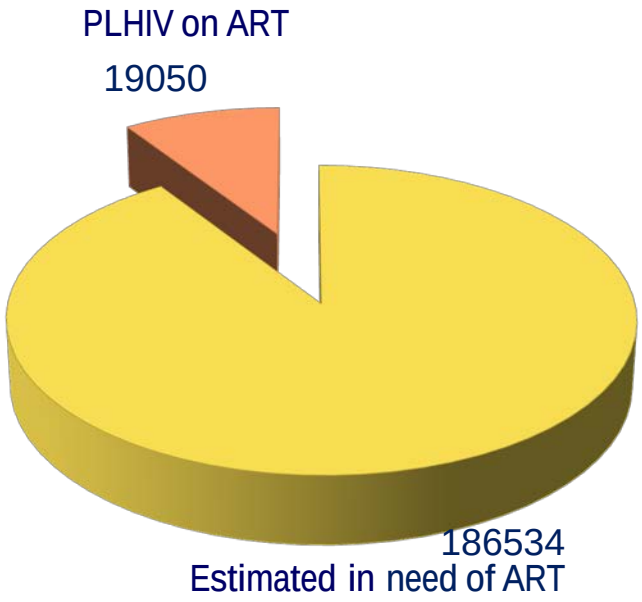
Progress report 2011: Global HIV/AIDS response, WHO 2011.
http://www.who.int/hiv/pub/progress_report2011/en/index.html

ART coverage in EM region

Number of PLHIV on ART, 2006–2010



Regional ART coverage in 2010: 10 %



Source:
Towards universal access: progress report. WHO, UNAIDS, UNICEF (2007, 2008, 2009, 2010, 2011)

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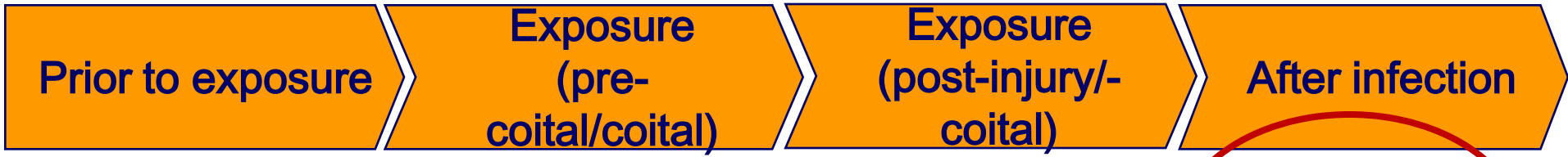
How to sustain the response

- **Currently**
  - **We need to retain people on ART and continuously add new ones - cost of treatment increase**
  - **Funding landscape is uncertain**
- **We cannot achieve Universal Access to treatment unless there is a dramatic reduction in new infections**

Many opportunities for biomedical prevention interventions



Prior to exposure	Exposure (pre-coital/coital)	Exposure (post-injury/-coital)	After infection
Male circumcision Oral pre exposure prophylaxis (PrEP) Microbicide	Intermittent PrEP Microbicide	Oral post exposure prophylaxis (PEP) Microbicide	ART irrespective of CD4 count

All in combination with condom use and/or use of clean needles and syringes and opioid substitution therapy

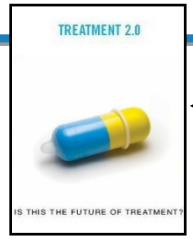
Adapted from M Cohen and Robin Shattock 20

2.WHO guidance on treatment as prevention (TasP)

WHO guidance for ART in resource limited settings

UNIVERSAL ACCESS

Intl AIDS Conference
Vancouver



"Treatment 2.0"

Radical simplification and optimization of quality treatment to increase ART access
Adding the benefits of treatment in prevention of new infections

1996 – ART in industrialized settings
The Dawn of HAART potent ART combination becomes available.

2002/2003 – WHO guidelines
Treatment costs high, ART toxicity is a concern, health systems are weak
"Treat those with greatest need".
(Treat at CD4 < 200)
"The 3 by 5 Initiative"

2006 – WHO guidelines
Access improves,
Rx costs lower but late diagnosis as a major barrier.
Treat if CD4 < 200, but consider if < 350
"Commitment to Universal Access"

2010 – WHO guidelines
Evidence mounting to treat earlier and with less toxic regimens. Do no harm and equity as key principles.
"Treat at CD4 <350"

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Use of ARVs for HIV prevention

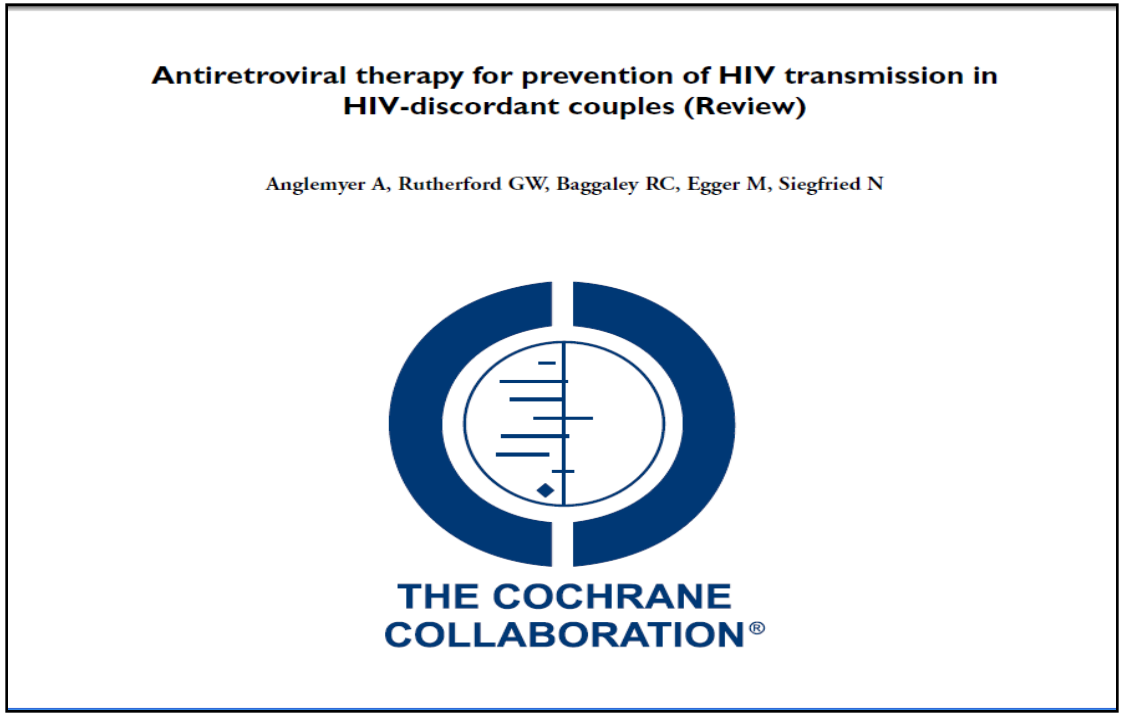
- ARVs have been used to prevent HIV transmission for over 10 years
  - use of ARVs to prevent transmission of HIV as part of prevention of mother to child transmission (PMTCT),
  - the use of ARVs for post exposure prophylaxis (PEP) after needle stick and/or sexual exposure

- There is now increasing evidence of the benefit of ART in those infected to prevent onward transmission of HIV

Formulating guidance on TasP

- WHO convened expert meetings to help inform the process of translating the latest evidence into new guidance.
- Reviewed the evidence
- Formulated recommendations
- Conducting further studies to inform remaining knowledge gaps

Review of ART for prevention of HIV in serodiscordant couples

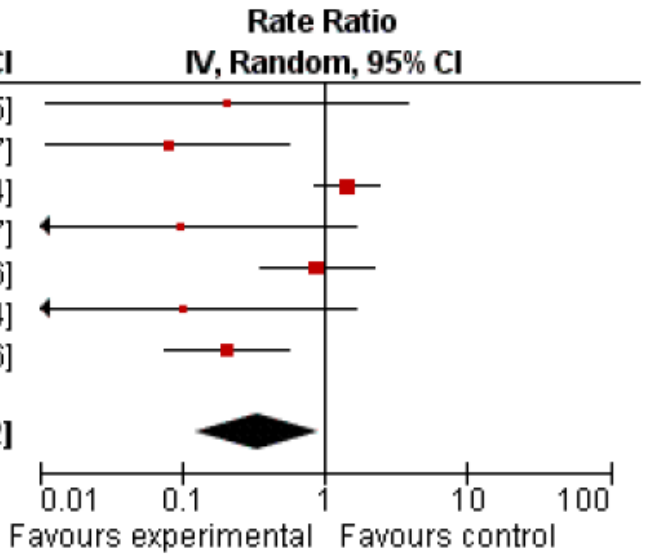


To determine if ART use in an HIV-infected member of an HIV-discordant couple is associated with lower risk of HIV transmission to the uninfected partner compared to untreated discordant couples.

Systematic review (7 observational studies) showed 66% less incident HIV infections in partners of infected spouses receiving ART

Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Random, 95% CI
Del Romero 2010	-1.58	1.48	7.9%	0.21 [0.01, 3.75]
Donnell 2010	-2.53	1	12.5%	0.08 [0.01, 0.57]
Lu 2010 (1)	0.363	0.27	23.0%	1.44 [0.85, 2.44]
Melo 2008	-2.33	1.45	8.1%	0.10 [0.01, 1.67]
Musicco 1994	-0.13	0.46	20.4%	0.88 [0.36, 2.16]
Reynolds 2011	-2.29	1.42	8.4%	0.10 [0.01, 1.64]
Sullivan 2009	-1.58	0.51	19.7%	0.21 [0.08, 0.56]
Total (95% CI)			**100.0%**	**0.34 [0.13, 0.92]**

Heterogeneity: $Tau^2 = 1.04$; $Chi^2 = 22.11$, $df = 6$ ($P = 0.001$); $I^2 = 73\%$
Test for overall effect: $Z = 2.13$ ($P = 0.03$)

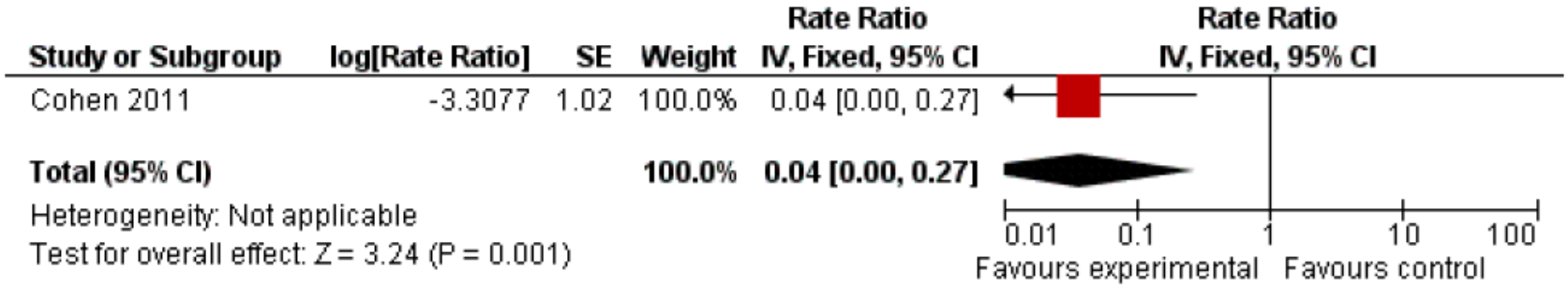


(1) Estimated from median follow-up time.

Forest plot of comparison: 2 Treated with ART vs Not Treated with ART (Observational Studies), outcome: 2.1 Incident HIV Infection.

Anglemyer A, et al 2011

Systematic review (1 RTC) showed 96% less incident HIV infections in couples where the HIV-infected index patient received ART



Forest plot of comparison: 1 Delayed vs Immediate ART (RCTs), outcome: 1.1 Linked Incident HIV Infection.

Anglemyer A, et al 2011

HPTN 052: Immediate vs Delayed ART in Serodiscordant Couples

HIV-infected, sexually active serodiscordant couples; CD4+ cell count of the infected partner: 350-550 cells/mm^3

(N = 1763 couples)

Immediate ART
Initiate ART at CD4+ cell count 350-550 cells/mm^3
(n = 886 couples)

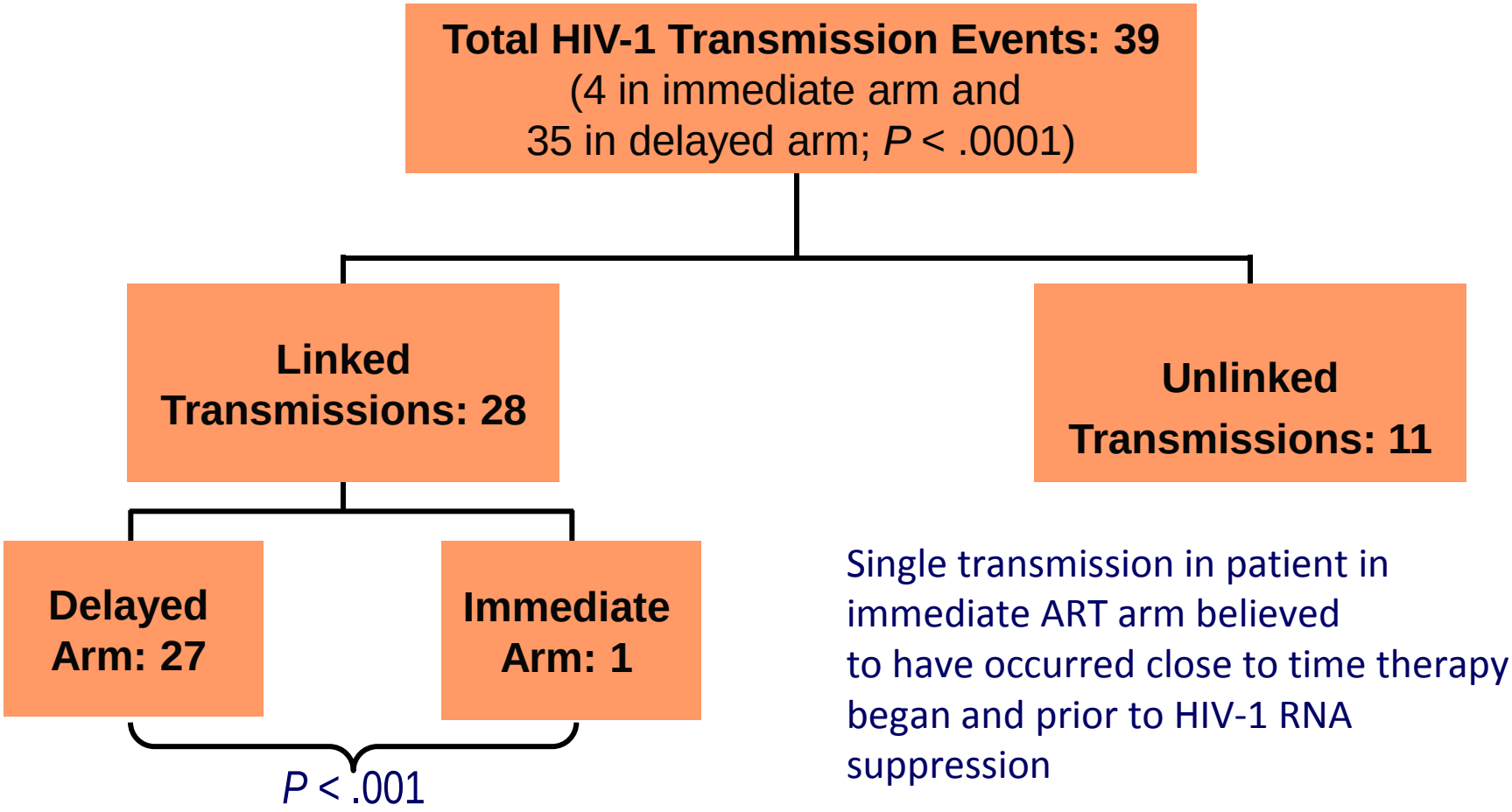
Delayed ART
Initiate ART at CD4+ cell count ≤ 250 cells/mm^3*
(n = 877 couples)

*Based on 2 consecutive values ≤ 250 cells/mm^3.

- Primary efficacy endpoint: virologically linked HIV transmission
- Primary clinical endpoints: WHO stage 4 events, pulmonary TB, severe bacterial infection and/or death
- Couples received intensive counseling on risk reduction and use of condoms

Cohen MS, et al. IAS 2011. Abstract MOAX0102.
Cohen MS, et al. N Engl J Med. 2011;[Epub ahead of print].

HPTN 052: HIV Transmission Reduced by 96% in Serodiscordant Couples



Single transmission in patient in immediate ART arm believed to have occurred close to time therapy began and prior to HIV-1 RNA suppression

Cohen MS, et al. IAS 2011. Abstract MOAX0102.
Cohen MS, et al. N Engl J Med. 2011;[Epub ahead of print].

Recent WHO recommendations

Guidance on couples counseling and testing
including antiretroviral therapy for treatment and prevention in serodiscordant couples

- First formal WHO TasP Guidance
- Strongly recommends couples testing & counseling
- HIV-positive partners with >350 CD4 cells/μL in serodiscordant couples should be offered ART to reduce HIV transmission to uninfected partners.

Programmatic update: Use of Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants

Recommendation for **Option B+** : lifelong ART treatment for all HIV-infected pregnant women, regardless of CD4 count, leading to;

- further simplification of regimen , service delivery and harmonization with ART programmes,
- protection against mother-to-child transmission in future pregnancies,
- a continuing **prevention benefit against sexual transmission to serodiscordant partners**,
- avoiding stopping and starting of ARV drugs

There many questions….

- Can we extrapolate from HPTN 052 to other populations and modes of transmission?
- Does ART as prevention work in populations other than serodiscordant couples?
- What is the individual clinical benefit of initiating ART >350?

3. Ongoing research to inform knowledge gaps on ART as prevention

TasP - current research

- Currently being investigated:
  - Absolute risk in SDC if PLHIV on ART (PARTNER, n=1650 SDC) in Europe
  - Absolute risk in SDC gay male relationships (Opposites Attract) in Australia
  - Benefit to PLHIV from early initiation of ART (START, n=4000)
  - Community benefit from ”test and treat” (PopART (HPTN 071), ANRS 12249,

- Outstanding:
  - How to diagnose HIV early, link-to-care & ensure adherence to ART
  - External validity of HPTN 052 – people who inject drugs
  - Behavioral impact: e.g. harm from more condom-less sex?

WHO-NIH consultation in Asia: Planned implementation research

	Thailand	Indonesia	Cambodia	Vietnam	China
Population	MSM	MSM FSW	All SD couples FSW ++	All SD couples IDU++	All SD couples MSM
Goal	To guide future national policy & strategy		To guide future national policy & strategy		Improve existing policy & strategy
Primary objective	Feasibility of universal testing and immediate ART	New HTC approaches & uptake, adherence immediate ART	Feasibility of identifying partner (network approach), early ART	Feasibility improved implementation cascade	Programme strengthening
ART criteria	Irrespective CD4 TDF-based	Irrespective CD4 TDF-based	Irrespective CD4	Irrespective CD4 TDF-based (possibly FDC)	Irrespective CD4 TDF
Enrolment	Outreach Internet, peers & health services	NGO's and public health services for MSM and FSW	VCT/TI sites Pre ART	HTC Methadone sites Pre ART	HTC Pre ART

4. Pre exposure prophylaxis (PrEP)

Pre exposure prophylaxis (PrEP)

- Pre-exposure prophylaxis (PrEP) is the use of antiretroviral drugs by a person who is HIV-negative to avoid HIV infection.
- Prior evidence use of ARV for PMTCT, PEP
- Proof of concept
  - CAPRISA 004, iPrEx, Partners PrEP and TDF2 clinical trials.

PrEP *(cont.)*

- The **iPrEx trial** among **MSM** and transgender women (Grant et al.,2010)
  - 44% reduction in HIV transmission, and 73% among those who took pills on 90% of days or more.
- The **Partners PrEP** trial of daily TDF alone and TDF/FTC among **serodiscordant couples** in Uganda.
  - a 67% reduction in HIV transmission in those on TDF alone and 75% reduction on TDF/FTC. (Donnell et al 2012).
- The **TDF2 trial** of daily TDF/FTC among **heterosexual men** and **women** in Botswana (CDC, 2011)
  - a 63% reduction in HIV transmission

PrEP *(cont.)*

The FDA's Antiviral Drugs Advisory Committee (ADAC) voted in favour of recommending *Truvada (TDF/FTC)* as PrEP (pre-exposure prophylaxis) for men who have sex with men, and for use by the HIV-negative partner in serodiscordant couples.

- no serious concerns about either safety or resistance were found
- Studies constitute proof of concept of the safety and partial effectiveness of oral PrEP.
- Studies also showed the potential effects of combination prevention approaches

5. What Next …

Key questions for decision makers:

1. What is the magnitude of the ART prevention benefit in the local epidemiological context?
2. How can results be translated into effective programs - at scale and at what additional cost?
3. In which settings and for what populations should ART be used to have the greatest impact?
4. What is the best mix of prevention interventions to optimize impact?
5. What are best ways to deliver care and achieve retention?

WHO Focus related to TasP – 3 Priority areas

1. Develop norms and standards
2. Inform programmatic and operational decisions
3. Define metrics for monitoring and evaluating impact of TasP

WHO TasP Guidance Focus: 2012/13

- 2012 – Guidance on couples HIV testing and counselling and ART as prevention in sero-discordant couples
- 2012 HIV/TB Collaborative Policy (discusses TasP and TB)
- 2012 – Programmatic update on operational aspects of PMTCT ARV (Options A, B, B+)
- **2012 – Treatment as Prevention technical/programmatic update**
- **2012 – PrEP rapid advice (June)**
- **2013 WHO Consolidated guidance will combine all ARV related guidance**

Conclusion

- **For ART as prevention to be successful**
  - Need to diagnose HIV infection early, treat and retain people in treatment and care services
  - We have to ensure that
    - ART that is capable of maximally and durably suppressing viremia;
    - adherence to an effective ARV regimen is high
    - there is absence of a concomitant STI.
- **The priority always for those in need of treatment for their own health**
- **TasP, PrEP, additional tools in combination prevention**

Acknowledgement

Dr Ying-Ru Lo, WHO HQ