Quelles stratégies de prévention ?

TasP : Possible réalité pour les pays en développement ?

Pr François DABIS
When to start ART: Consequences of the evolving recommendations

Estimated millions of people eligible for ART in lower & middle-income countries in 2011

- **CD4 ≤ 200**
  - Recommended Since 2002

- **CD4 ≤ 350**
  - + TB/HIV
  - + HBV/HIV

- **CD4 ≤ 350**
  - + Expanded CD4 independent conditions

- **CD4 ≤ 500**
  - "Test and treat"
  - All HIV+

ART regardless of CD4 count for:
- HIV-SD couples
- Pregnant women
2013 WHO guidelines
Consolidation along the continuum of care
From 2013 WHO guidelines to Treatment as Prevention (TasP)
Consolidation along the continuum of care will remain the cornerstone

Effectiveness = reduction in HIV transmission
Treatment as Prevention (TasP)

Consolidation along the continuum of care is the cornerstone
Treatment as Prevention (TasP)
Consolidation along the continuum of care is the cornerstone
- **Provider-initiated C&T** systematic review: wide variation and mixed results in identifying previously undiagnosed individuals (Roura M. AIDS, 2013)
HIV counselling & testing (C&T): How?

- **Provider-initiated C&T** systematic review: wide variation and mixed results in identifying previously undiagnosed individuals (Roura M. AIDS, 2013)

- **Home-based C&T** systematic review: High uptake of testing (88%) and of delivery of test result (77%) (Sabapathy K. PLoS Med, 2012)
HIV counselling & testing (C&T): How?

- **Provider-initiated C&T** systematic review: wide variation and mixed results in identifying previously undiagnosed individuals (Roura M. AIDS, 2013)

- **Home-based C&T** systematic review: High uptake of testing (88%) and of delivery of test result (77%) (Sabapathy K. PLoS Med, 2012)

- **Community-based C&T** (outside health facilities) works in all sorts of settings, with various approaches and for different target groups including those with high CD4 counts (Suthar AB. PLoS Med, 2013)
C&T effects

- C&T improves HIV-related risk behavior (Fonner VA. Cochrane Database Syst Rev, 2012)

- C&T « modestly » reduces acquisition of HIV (ACCEPT HPTN 043. CROI, 2013)
C&T effects

- C&T improves HIV-related risk behavior (Fonner VA. Cochrane Database Database Syst Rev, 2012)
- C&T « modestly » reduces acquisition of HIV (ACCEPT HPTN 043. CROI, 2013)
- C&T is a pre-requisite to ARV-based biomedical prevention such as TasP +++
Treatment as Prevention (TasP)

Consolidation along the continuum of care is the cornerstone
Prevention of HIV-1 Infection with Early Antiretroviral Therapy

ART reduces sexual transmission: effectiveness (1)

Systematic Review of HIV Transmission between Heterosexual Serodiscordant Couples where the HIV-Positive Partner Is Fully Suppressed on Antiretroviral Therapy

Mona R. Loutfy¹,²,³,⁴*, Wei Wu¹, Michelle Letchumanan¹,³, Lise Bondy², Tony Antoniou³,⁴, Shari Margolese¹, Yimeng Zhang², Sergio Rueda⁵,¹⁰, Frank McGee⁶, Ryan Peck⁷, Louise Binder⁸, Patricia Allard⁹, Sean B. Rourke⁴,⁵,¹⁰, Paula A. Rochon¹,²,³

Rate of transmission
0.0 to 0.14 per 100 person-years
(upper limit of 95% CI: 0.31)
ART reduces sexual transmission: effectiveness (2)


- Behavioral study nested within a RCT of early ART (ANRS 12 136 Temprano)
- Estimated protective effect of early ART: 90% (95% CI: 81 - 95%)
High Coverage of ART Associated with Decline in Risk of HIV Acquisition in Rural KwaZulu-Natal, South Africa

Frank Tanser,1* Till Bärnighausen,1,2 Erofili Grapsa,1 Jaffer Zaidi,1 Marie-Louise Newell1,3

www.sciencemag.org  SCIENCE  VOL 339  22 FEBRUARY 2013
ART coverage, 2004-2011
Tanser F. Science, 2013

- **ART coverage** = proportion of the total HIV-infected population receiving ART at <200 then <350 CD4 cells/µl
- → >20 000 patients
- Spatial analysis using a standard Gaussian kernel of radius 3km
Adjusted HIV acquisition hazard by ART coverage category adjusted for age and sex (A) and for all variables (B)

Tanser F. Science, 2013
Treatment as Prevention (TasP)
Consolidation along the continuum of care is the cornerstone
Health care seeking is largely motivated by symptoms: how to increase treatment uptake in early disease stages?
Health care seeking is largely motivated by symptoms: how to increase treatment uptake in early disease stages?

- Home treatment initiation
  (MacPherson P. Malawi. CROI, 2013)

- Social marketing campaigns
- Financial incentives to register in care
- Build proximity health posts
- Mobile health teams
- Free transportation to health facilities
- Retention in care and treatment could be motivated by symptoms: **how to maintain retention and adherence in early disease stages?**
Retention in care and treatment could be motivated by symptoms: how to maintain retention and adherence in early disease stages?

- Define loss to follow-up
- Monitor closely program retention (early detection)

- Document interventions of validated effectiveness, e.g. text messaging
  Horvath T. Cochrane Database Syst Rev, 2012 (2 RCTs in Kenya – improved adherence: 22%)
- Will there be risk compensation with early ART?

- The overall evidence in sub-Saharan Africa has been limited so far (Venkatesh KK. AIDS, 2011) and did not favor this hypothesis
Will there be risk compensation with early ART?

- The overall evidence in sub-Saharan Africa has been limited (Venkatesh KK. AIDS, 2011) and did not favor this hypothesis.

- In rural KwaZulu Natal, South Africa, no evidence of increased sexual risk-taking in the general population during ART scale up; condom use with regular sexual partner increased and proportion with multiple sexual partners decreased. (McGrath N. AIDS, 2013.)
Will there be risk compensation with early ART?

- The overall evidence in sub-Saharan Africa has been limited (Venkatesh KK. AIDS, 2011) and did not favor this hypothesis.

- In rural KwaZulu Natal, South Africa, no evidence of increased sexual risk-taking in the general population during ART scale up (McGrath N. AIDS, 2013).

- In Abidjan, Côte d’Ivoire, risky sex was reported by 10% of those on early ART vs 12.8% in those on standard ART (p=0.17) - Jean K. J Infect Dis, in press.
- Is there a risk of undesirable resource allocation (« crowding out »)?

  This is not an argument against TasP but against TasP without sufficient resources
Resource constraints (2)

- Task-shifting is efficient (Stretch, South Africa. Lancet, 2012)

- Other sources of efficiency gains can be sought

... but will this be sufficient??

Human resources capacity may simply be lacking without major training efforts of qualified health workers
Resource constraints (3)

- Universal programs, vertically structured or fully integrated? versus highly specialized programs targeting key populations?

The need for implementation studies documenting where and how efficiency is maximized
Treatment as Prevention (TasP)

The need for high-level evidence of effectiveness

- HIV Testing
- General HIV Care and Prevention
- Initiating ART
- Monitoring (toxicity & ART response)
- 2nd Line
- 3rd Line
- Operational and service delivery

Effectiveness
TasP RCTs (as of September 2013)

- 4 in Africa:
  - ANRS 12 249 TasP (South Africa)
  - HPTN 071 PopART (South Africa & Zambia)
  - CDC BCPP (Botswana)
  - SEARCH (Uganda & Kenya)

1 in the US:
- HPTN 065 TLC-Plus (Washington DC & Bronx NY)
ANRS 122 249

Treatment as Prevention (TasP)

Update

Paris, 19 septembre 2013
Ukuphila kwami, ukuphila kwethu*
* My Health for Your Health

ANRS 12 249 TasP
A cluster randomised trial in Hlabisa sub-district, KwaZulu-Natal, South Africa

http://mereva.net/tasp

TasP **overall primary objective**

• To directly estimate the effect of ART initiated immediately after the diagnosis of infection and irrespective of CD4 count criteria in people not yet eligible for ART on the incidence of new HIV infections in the general population in the same setting
TasP Phase 1 aims

- Provide sufficient guarantees in terms of acceptability and feasibility of the TasP intervention at individual and community level as well as on the parameters used to estimate the trial sample size to continue the trial and decide how to do so
TasP trial design (1/2)

• Cluster-randomised controlled trial

• **Component 1**: Full prevention and HIV testing strategy in both the intervention and control arms
  
  – Current range of community and clinic HIV testing options **AND**
  
  – Implementation of **regular** (6 months, then 4 months) rounds of **home-based** HIV testing
  
  – Comprehensive set of preventive services:
    
    IEC, condom distribution, circumcision services, syndromic management of STIs and post-exposure prophylaxis, family planning
TasP trial design (2/2)

Component 2: For all HIV-infected adult individuals identified:

Control Arm
• Offer ART according to national guidelines (currently)
  All patients with CD4 <350 cells/mm³, WHO clinical stage 3 or 4 or MDR/XDR Tb

Intervention Arm
• Offer universal immediate ART initiation
TasP Phase 1 specific objectives

• Among all participants:
  – To estimate the acceptability and feasibility three times over a 14-month period of providing repeat HIV testing to all adult members of a community

• Among HIV-infected participants:
  – To estimate entry into care and ART, retention, morbidity/mortality, TB, virological failure, quality of life, etc. over a 7 to 19-month follow-up period

• Within the health system:
  – To appreciate the challenges faced by the health care system and health care professionals in providing the trial intervention
TasP setting: Hlabisa subdistrict (KZN, SA)

- 1 430 km²
- Approx. 220 000 Zulu-speaking people
- 24% overall HIV prevalence
**TasP clusters**

- 34 communities/clusters
- Stratified on the basis of predicted HIV prevalence
- Randomly allocated in equal measure to control and intervention communities (17:17)
  - Phase 1: in 4 (striped on map) then 10 clusters
  - 1 000 participants per cluster, 800 HIV-neg
Phase 1 is ongoing

• Clusters # 1 & 2 opened: March 2012

• Clusters # 3 & 4 opened: July 2012

• Clusters # 5 to 10 opened: January to August 2013
## Progress - Feasibility (September 2013)
### Round 1 – Ten clusters

<table>
<thead>
<tr>
<th>Status within trial, n(%)</th>
<th>Sample size/model assumptions, n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Registered</td>
<td>11,537</td>
</tr>
<tr>
<td>Contacted</td>
<td>8,347 (72)</td>
</tr>
<tr>
<td>Participation</td>
<td>7,865 (94)</td>
</tr>
<tr>
<td>HIV status ascertained</td>
<td>6,465 (82)</td>
</tr>
<tr>
<td>HIV positive</td>
<td>1,965 (30)</td>
</tr>
<tr>
<td>Seen in TasP clinic</td>
<td>912</td>
</tr>
<tr>
<td>Seen in DoH clinic</td>
<td>510</td>
</tr>
<tr>
<td>Total linked to care</td>
<td>1422 (72)</td>
</tr>
</tbody>
</table>
Pour conclure

TasP : Possible réalité pour les pays en développement ?

- Continuum de prévention et de soins :
  **Universal Test & Treat (UTT) / TTU**

- Une évolution quasi inéluctable, mais
  
  **Quand ? Comment ? Qui paiera ?**
TasP : Possible réalité pour les pays en développement ?


2015-2017 : Effectiveness

Comment la mesurer ?
Remerciements

Francois.dabis@isped.u-bordeaux2.fr
TasP timeline - protocol

- Project developed since September 2009
- Submitted to ANRS in March 2010, funding approved November 2010 (+ additional GIZ funding)
  - **Pilot phase: 2011 - 2013**
  - **Focusses on the acceptability and feasibility of the TasP intervention at individual and community level**
- TasP registration:
  - South African Trial Register: DOH-27-0512-3974
- **Expansion phase: 2014 - 2015**
TasP Phase 1 primary objective

- To validate and update the parameters of the model used to estimate the trial sample size and HIV incidence in terms of:
  - age distribution and HIV prevalence in the study population,
  - uptake of HIV testing,
  - linkage to care upon HIV diagnosis,
  - internal migration
  - and ART initiation over 14 months
TasP Phase 1 other objectives

• To better define the *trial procedures* as the acceptability of HIV testing and entry into care may present unexpected challenges.

• To *revise the protocol*, if necessary, and in light of changes in the international and national ART guidelines.
TasP organization

- Principals investigators: François Dabis & Marie-Louise Newell
- Scientific Advisory Board (Chair: B. Hirschel)
- Data Safety Monitoring Board (Chair: P. Yeni)
- Coordinators: Collins Iwuji & Joanna Orne-Gliemann
- ANRS: Brigitte Bazin, Claire Rekacewicz, Jean-François Delfraissy
## TasP Working Group

### At the Africa Centre

- **Social sciences**  
  J. Imrie, J. Larmarange
- **Health economics**  
  T. Bärnighausen
- **Epidemiology and Biostatistics**  
  F. Tanser
- **Clinical science**  
  R. Bland, R. Lessells
- **Bioinformatics**  
  T. de Oliveira
- **Virology Lab Head**  
  J. Viljoen
- **Data management**  
  C. Newell
- **Treatment programme liaison**  
  K. Naidu
- **Nurse manager**  
  N. Okesola

### In France, Switzerland, USA

- **Social sciences**  
  F. Lert, R Dray-Spira
- **Health economics**  
  B. Spire, S. Boyer
- **Adult Medicine**  
  A. Calmy
- **Virology**  
  M-L. Chaix
- **Data management**  
  S. Karcher
- **Statistician**  
  R. Thiébaut
- **Modelling**  
  K. Freedberg
Homestead identification

Homestead identification using GPS and GIS
Trial registration / HIV status

• Complete Household Registration form - electronically on net book

• Complete Household Information / Asset questionnaire; paper-based

• Complete individual questionnaire

Offer rapid HIV testing and counselling to all adults
Trial clinics

- HIV-infected participants have option of attending the TasP or Department of Health (DoH) clinic

- Africa Centre maintains database on those accessing HIV treatment and care in the sub-district

Ethics approval to link DoH & TasP databases

Hlabisa DoH Clinic

Includes PoC CD4
Clinic manager

Patient registration at a clinic visit

Patient fingerprint recording

Documents and specimens being captured on clinic visit conclusion
Phase 1 is ongoing (b)

SAB 1\textsuperscript{st} meeting: 
November 2012 (Paris)

DSMB 1\textsuperscript{st} meeting: 
May 8, 2013 (Paris)

SAB 2\textsuperscript{nd} meeting: 
May 17-18, 2013 (Hlabisa)