anRS
French National Agency for Research on AIDS and Viral Hepatitis
An autonomous agency at Inserm

UNIVERSITÉ BORDEAUX SEGALEN

Inserm

Quelles stratégies de prévention ?

TasP : Possible réalité

pour les pays en développement ?

Pr François DABIS

Bordeaux School of public health
ISPED
Institut de Santé Publique d'Epidémiologie et de Développement

Abstinence

Be faithful

Condom

(male) Circumcision

Counselling & Testing

Microbicides

Post-exposure prophylaxis

Pre-exposure prophylaxis

Sexually transmitted infections control

(antiretroviral) Treatment (TasP)

Vaccine

When to start ART: Consequences of the evolving recommendations

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

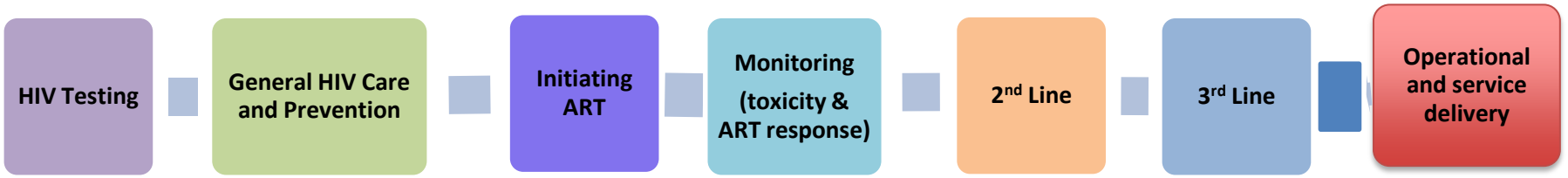
11	15	23	25	32
CD4 ≤ 200 Recommended Since 2002	CD4 ≤ 350 + TB/HIV HBV/HIV	CD4 ≤ 350 + Expanded CD4 independent conditions	CD4 ≤ 500	"Test and treat" All HIV+

ART regardless of CD4 count for:

- HIV-SD couples
- Pregnant women

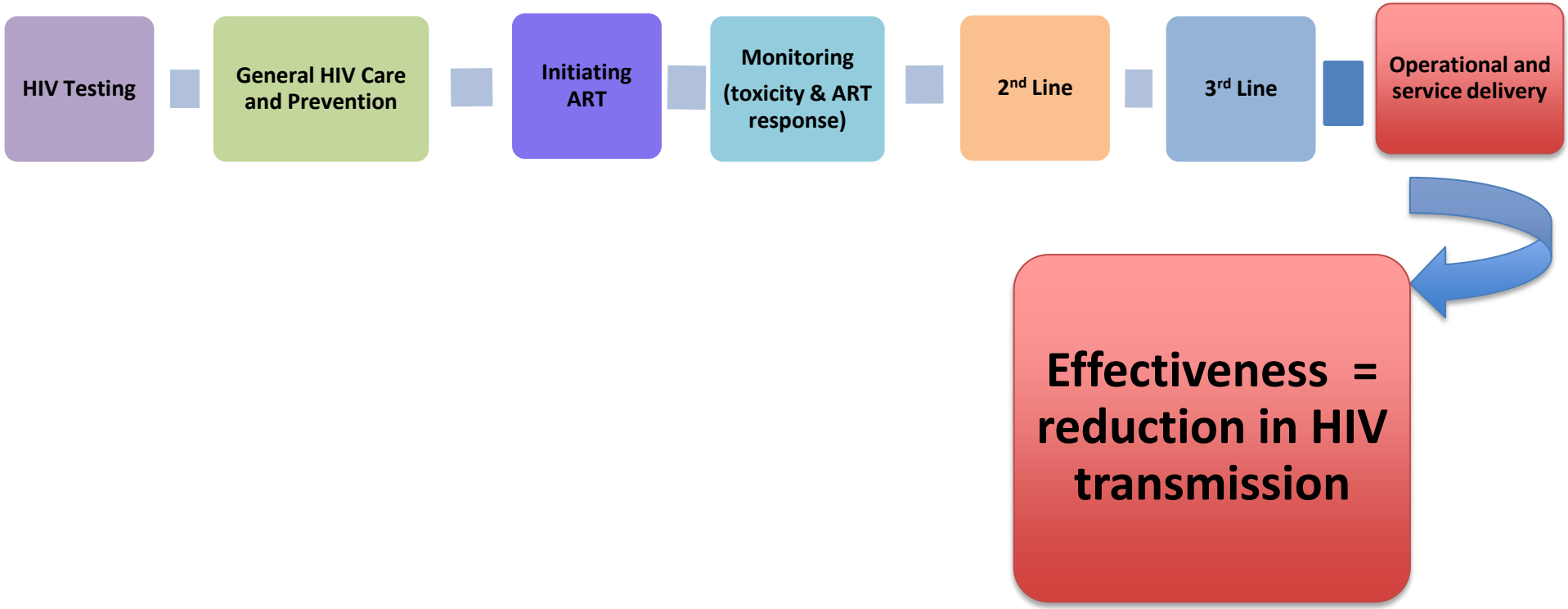
World Health Organization

2013 WHO guidelines
Consolidation along the continuum of care



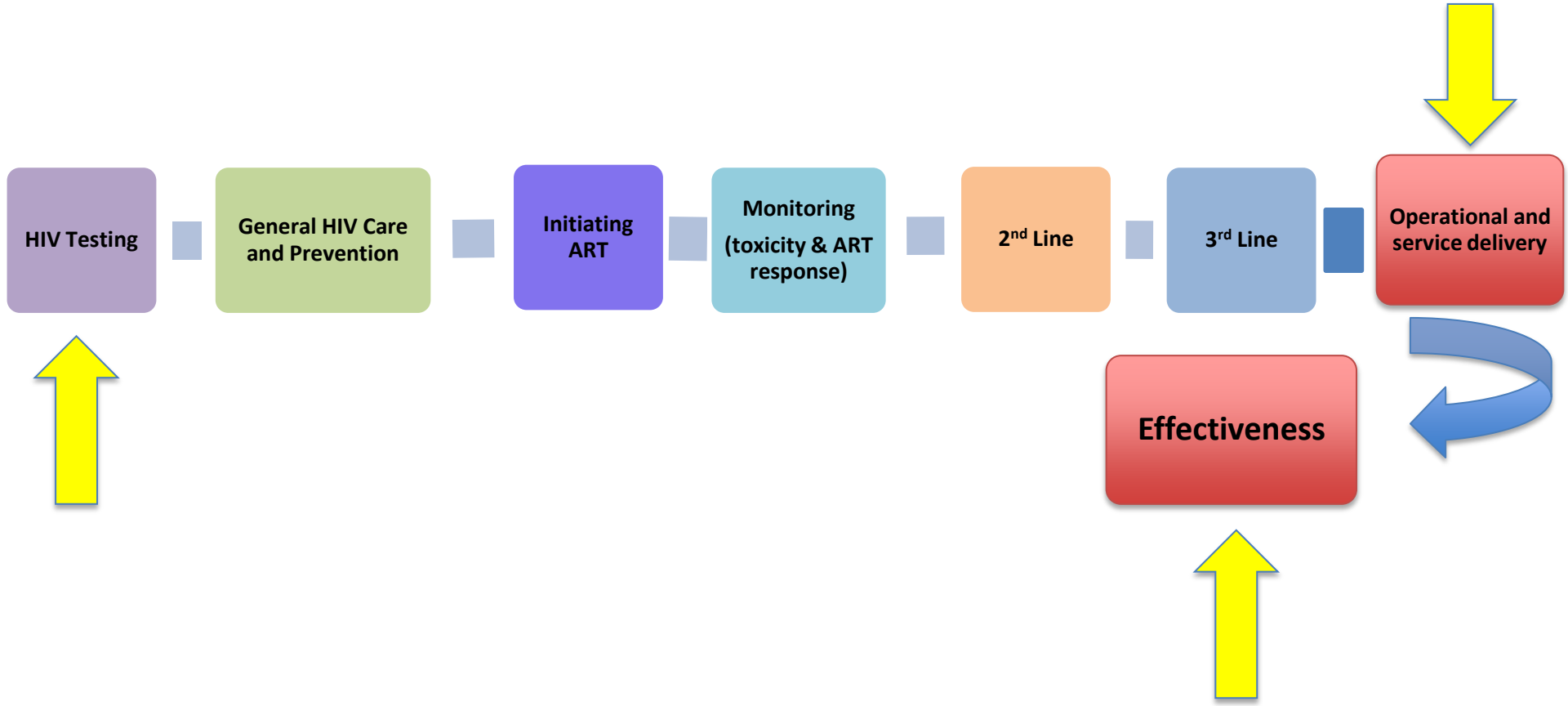
From 2013 WHO guidelines to Treatment as Prevention (TasP)

Consolidation along the continuum of care will remain the cornerstone



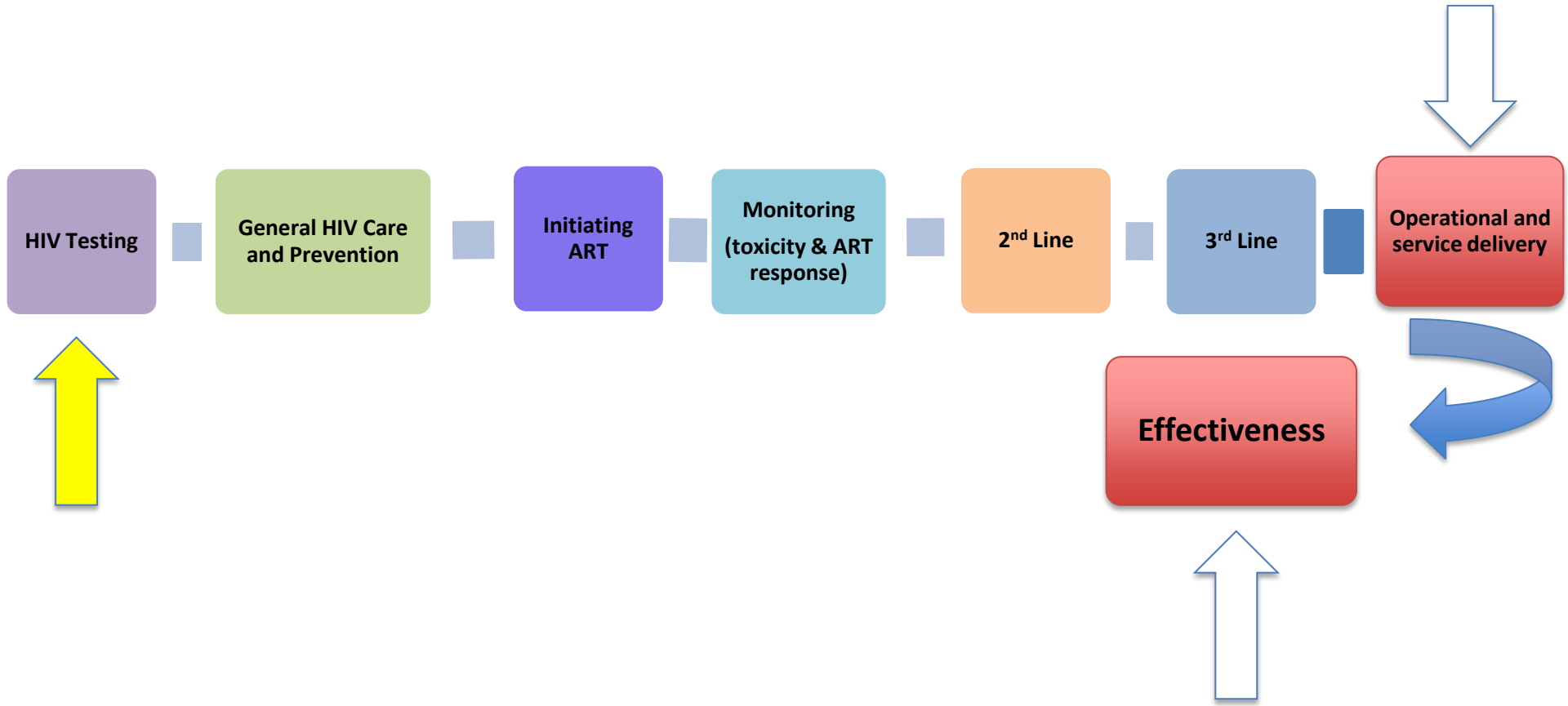
Treatment as Prevention (TasP)

Consolidation along the continuum of care is the cornerstone



Treatment as Prevention (TasP)

Consolidation along the continuum of care is the cornerstone



HIV counselling & testing (C&T): How?

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

HIV counselling & testing (C&T): How?

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- **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)

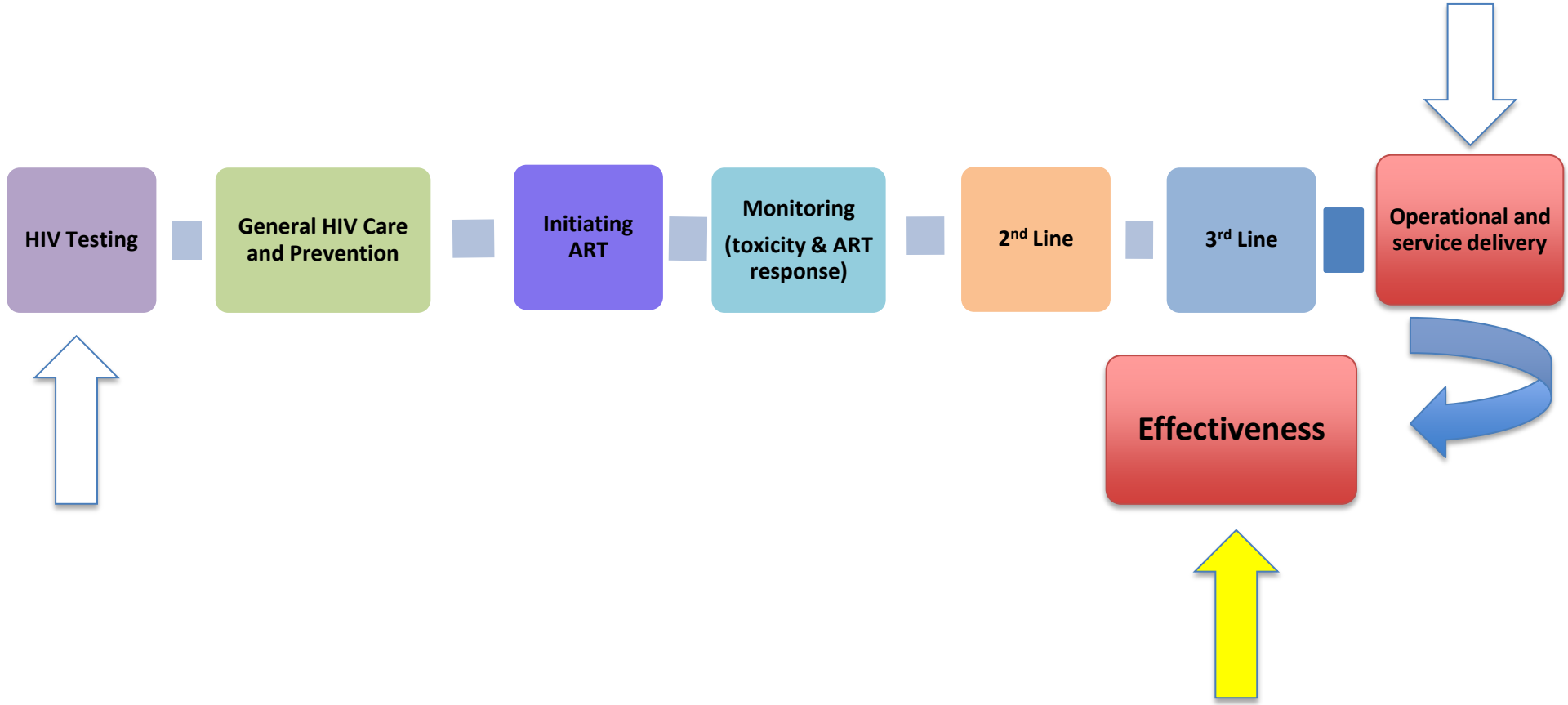
C&T effects

- C&T improves HIV-related risk behavior (Fonner VA. Cochrane Database 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



ART reduces sexual transmission: 96% efficacy

The NEW ENGLAND JOURNAL of MEDICINE
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ORIGINAL ARTICLE

Prevention of HIV-1 Infection with Early Antiretroviral Therapy

Myron S. Cohen, M.D., Ying Q. Chen, Ph.D., Marybeth McCauley, M.P.H., Theresa Gamble, Ph.D., Mina C. Hosseinipour, M.D., Nagalingeswaran Kumarasamy, M.B., B.S., James G. Hakim, M.D., Johnstone Kumwenda, F.R.C.P., Beatriz Grinsztejn, M.D., Jose H.S. Pilotto, M.D., Sheela V. Godbole, M.D., Sanjay Mehendale, M.D., Suwat Chariyalertsak, M.D., Breno R. Santos, M.D., Kenneth H. Mayer, M.D., Irving F. Hoffman, P.A., Susan H. Eshleman, M.D., Estelle Piwowar-Manning, M.T., Lei Wang, Ph.D., Joseph Makhema, F.R.C.P., Lisa A. Mills, M.D., Guy de Bruyn, M.B., B.Ch., Ian Sanne, M.B., B.Ch., Joseph Eron, M.D., Joel Gallant, M.D., Diane Havlir, M.D., Susan Swindells, M.B., B.S., Heather Ribaudo, Ph.D., Vanessa Elharrar, M.D., David Burns, M.D., Taha E. Taha, M.B., B.S., Karin Nielsen-Saines, M.D., David Celentano, Sc.D., Max Essex, D.V.M., and Thomas R. Fleming, Ph.D., for the HPTN 052 Study Team*

ART reduces sexual transmission: effectiveness (1)

February 2013 | Volume 8 | Issue 2 | e55747

OPEN ACCESS Freely available online

PLOS | ONE

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

Mona R. Loutfy[1,2,3,4*], Wei Wu[1], Michelle Letchumanan[1,3], Lise Bondy[2], Tony Antoniou[3,4], Shari Margolese[1], Yimeng Zhang[2], Sergio Rueda[5,10], Frank McGee[6], Ryan Peck[7], Louise Binder[8], Patricia Allard[9], Sean B. Rourke[4,5,10], Paula A. Rochon[1,2,3]

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)

Jean K. et al. Effect of early antiretroviral therapy on sexual behaviors and HIV-1 transmission risk in adults with diverse heterosexual partnership status in Côte d'Ivoire. J Infect Dis *in press.*

- **Behavioral study nested within a RCT of early ART (ANRS 12 136 Temprano)**

- **Estimated protective effect of early ART: 90% (95% CI: 81 - 95%)**

The population impact of ART: HIV incidence

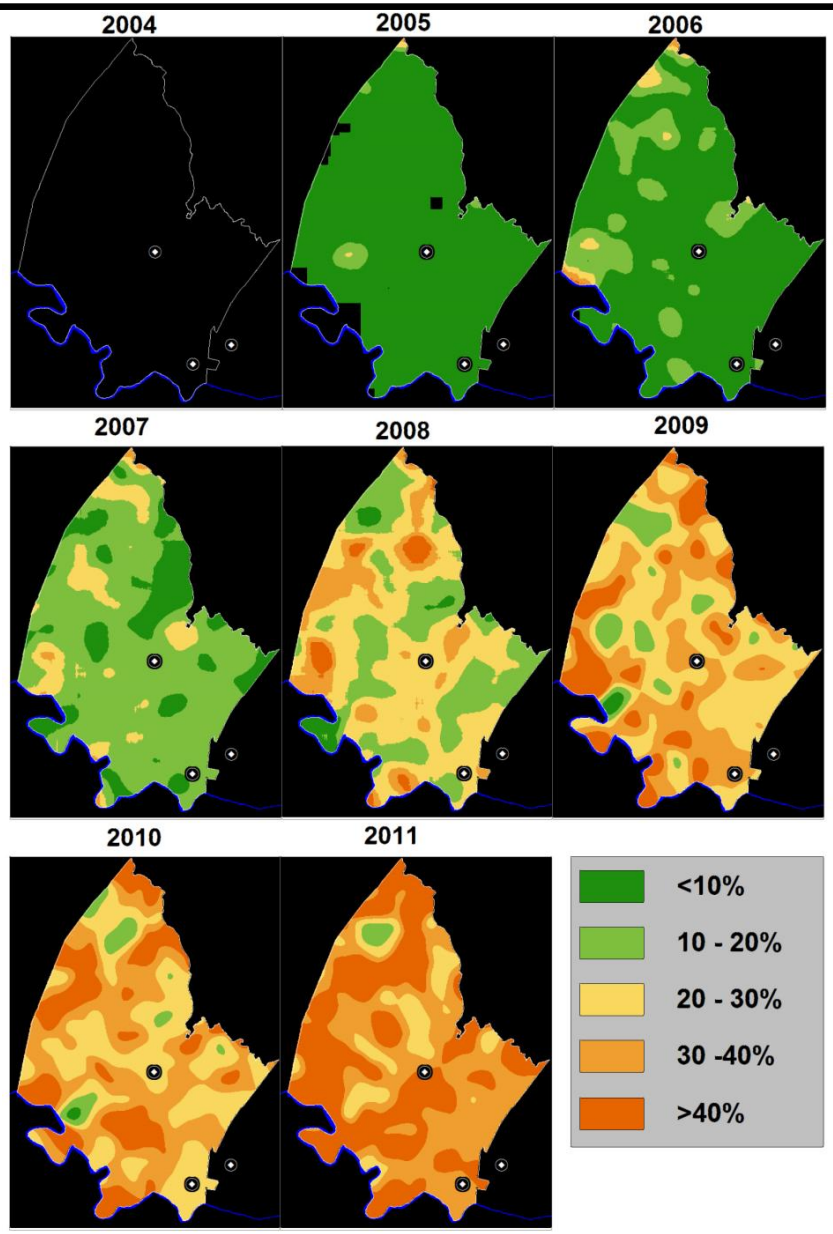
REPORTS

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 Newell[1,3]

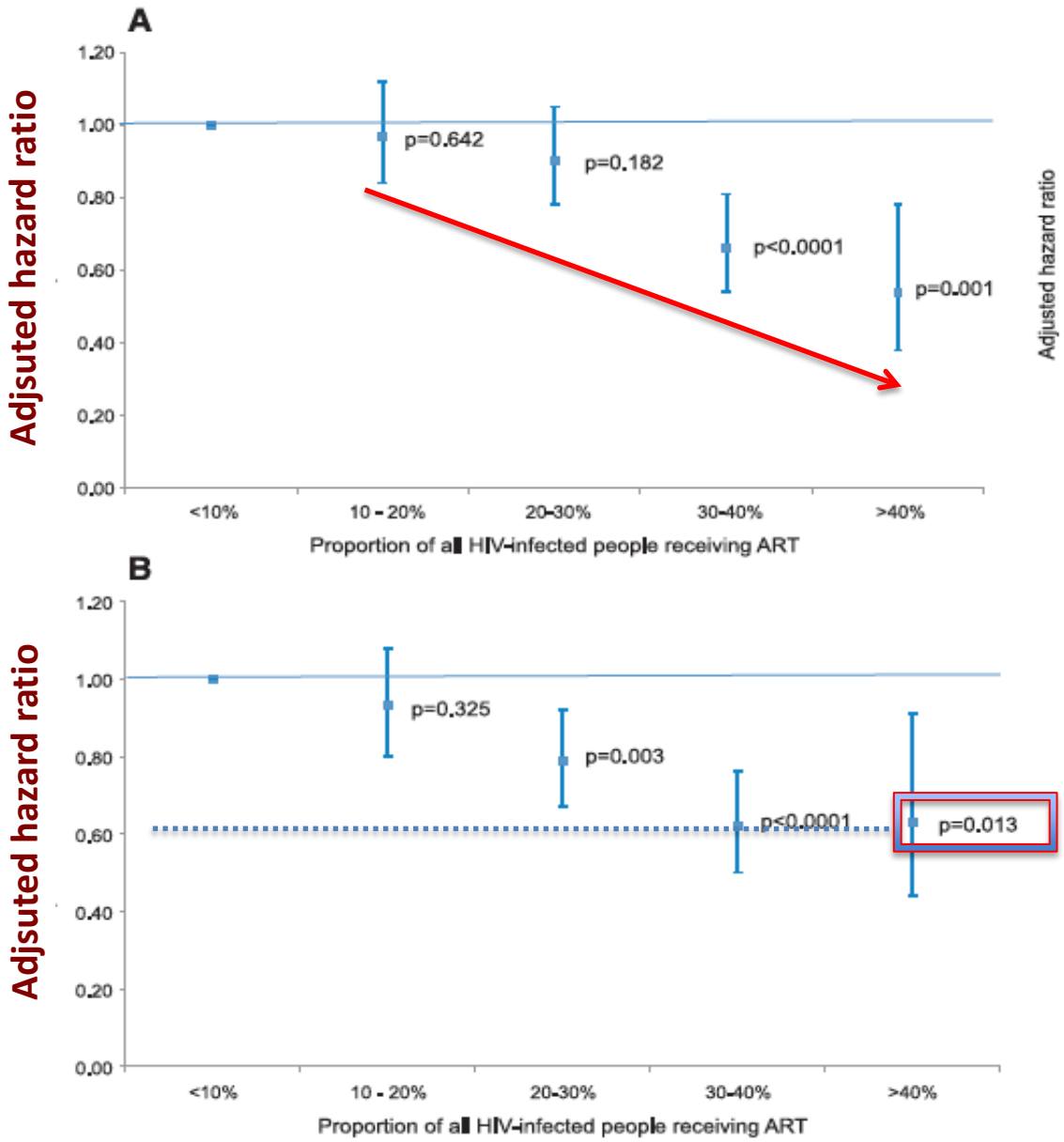
www.sciencemag.org SCIENCE VOL 339 22 FEBRUARY 2013

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

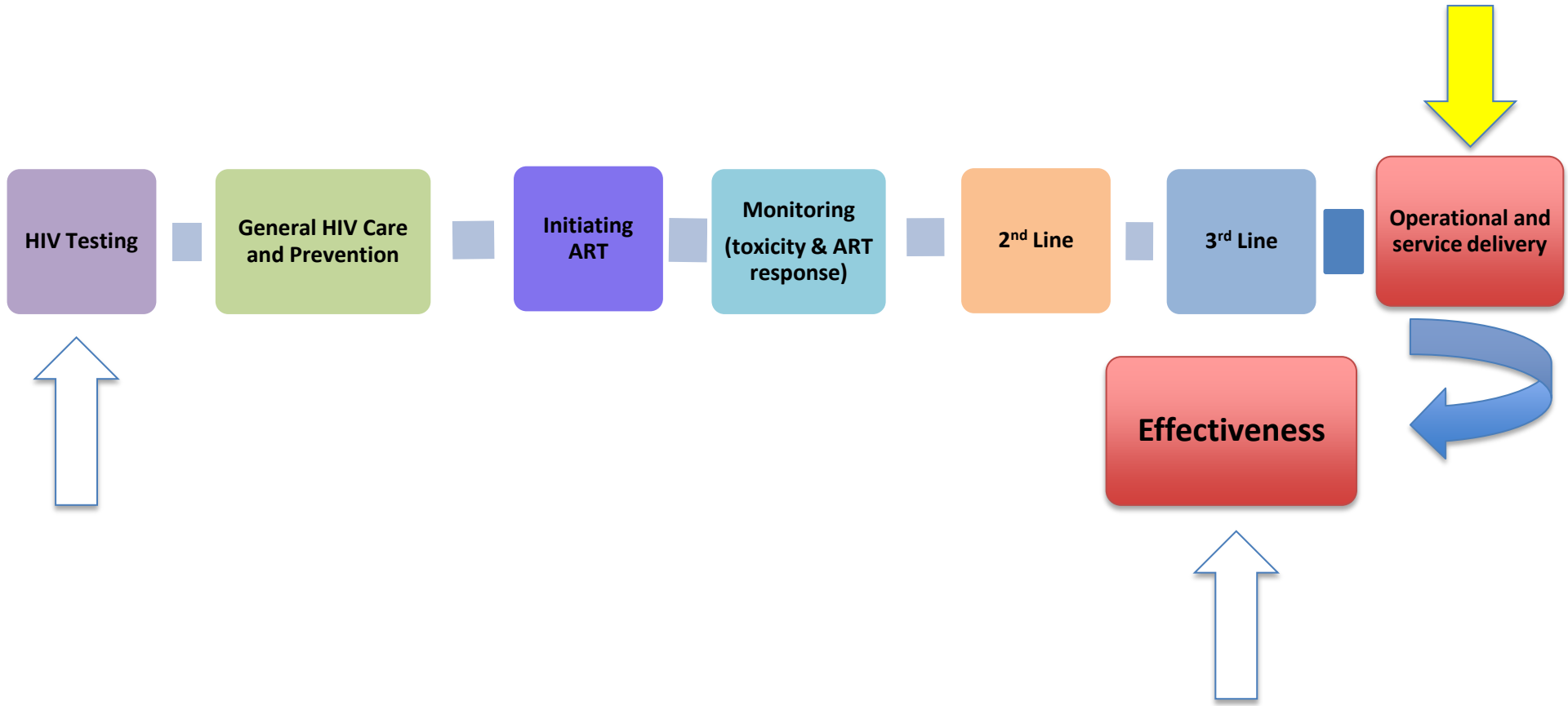
Adjusted HIV acquisition hazard by ART coverage category adjusted for age and sex (A) and for all variables (B)



Tanser F. Science, 2013

Treatment as Prevention (TasP)

Consolidation along the continuum of care is the cornerstone



Health system concerns (1)

- **Health care seeking is largely motivated by symptoms: how to increase treatment uptake in early disease stages?**

Health system concerns (1)

- **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

Health system concerns (2)

- Retention in care and treatment could be motivated by symptoms: how to maintain retention and adherence in early disease stages?

Health system concerns (2)

- **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

  Chi BH. Proposed universal definition. PLoS Med, 2011.

  - Monitor closely program retention (early detection)

  Egger M. Nomogram. PLoS Med, 2011.

  - Document interventions of validated effectiveness, e.g. text messaging

  Horvath T. Cochrane Database Syst Rev, 2012 (2 RCTs in Kenya – improved adherence: 22%)

  Cameroon, Kenya protocoles. BMJ Open, 2013

Behavioural concerns

- **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?

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- 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?

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- 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*.

Resource constraints (1)

- **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)

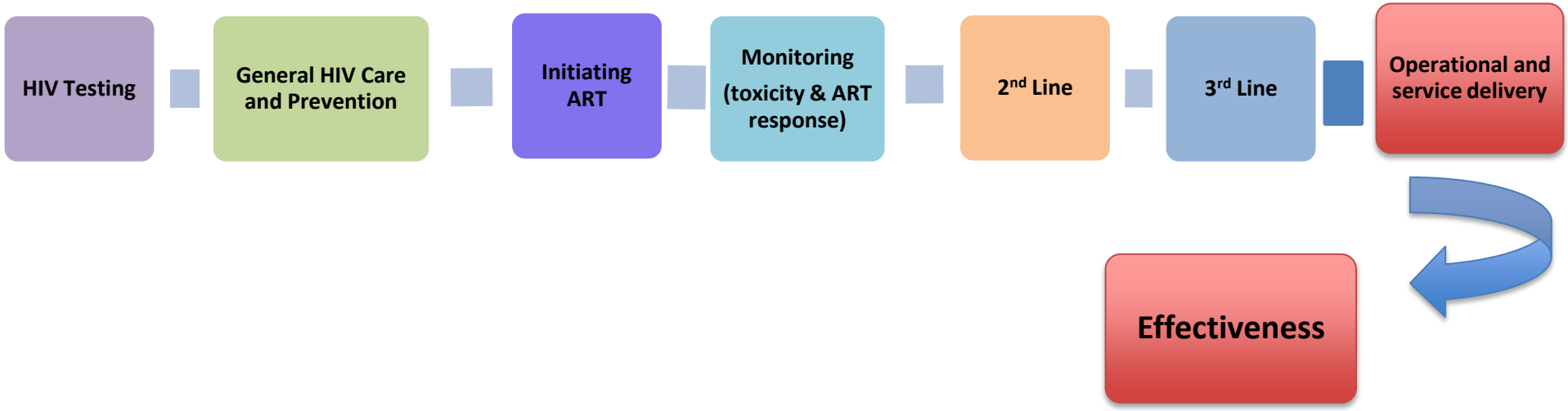
- Universal programs, vertically structured or fully integrated?

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



TasP RCTs (as of September 2013)

- **4 in Africa:**

ANRS 12 249 TasP (South Africa)

HPTN 071 PopART (South Africa & Zambia)

CDC BCPP (Bostwana)

SEARCH (Uganda & Kenya)

---

1 in the US:

HPTN 065 TLC-Plus (Washington DC & Bronx NY)

French National Agency for Research on AIDS and Viral Hepatitis

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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

Iwuji C et al. Trials. 2013; 14: 230. (Open Access)

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**
- **<u>Component 1</u>: Full prevention and HIV testing strategy in both the intervention and control arms**
  - Current range of community and clinic HIV testing options **<u>AND</u>**
  - 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/mm^3, WHO clinical stage 3 or 4 or MDR/XDR Tb

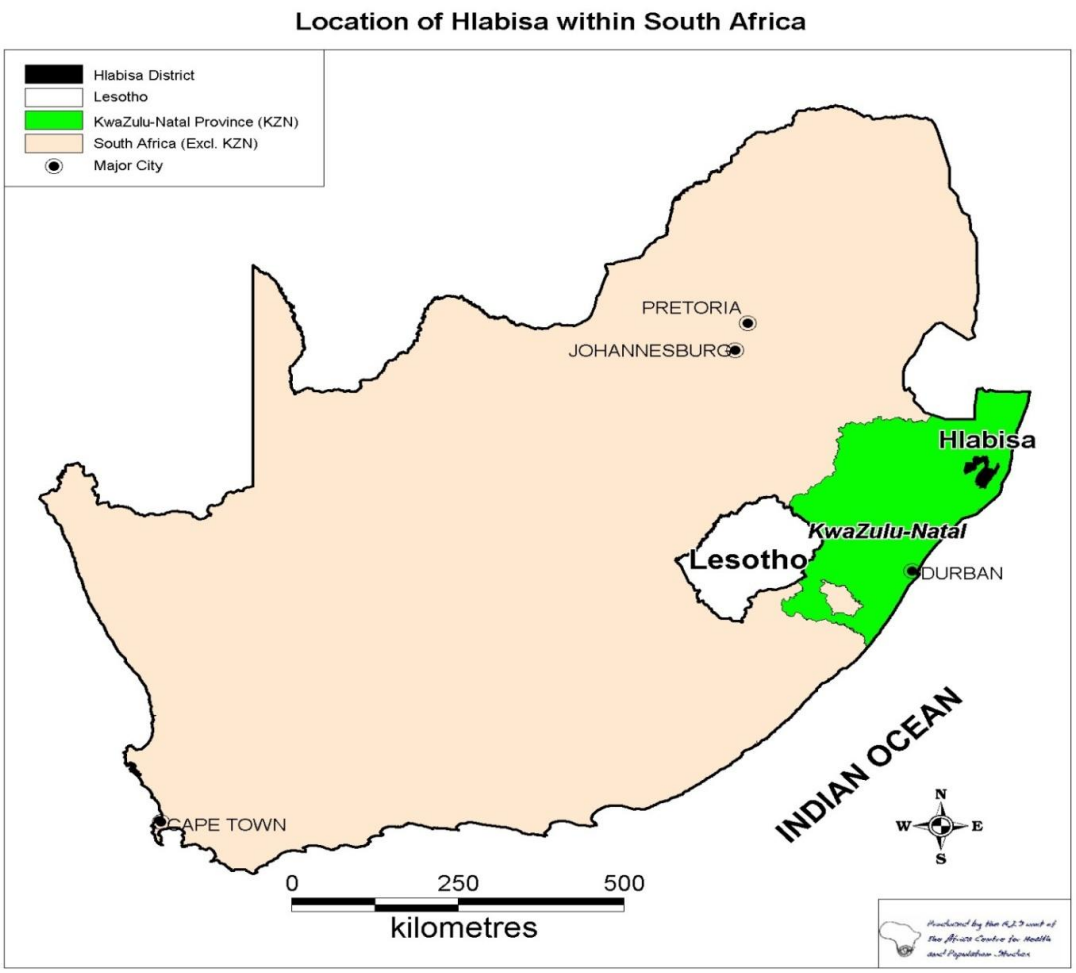
Intervention Arm

- Offer **universal immediate ART** initiation

TasP Phase 1 specific objectives

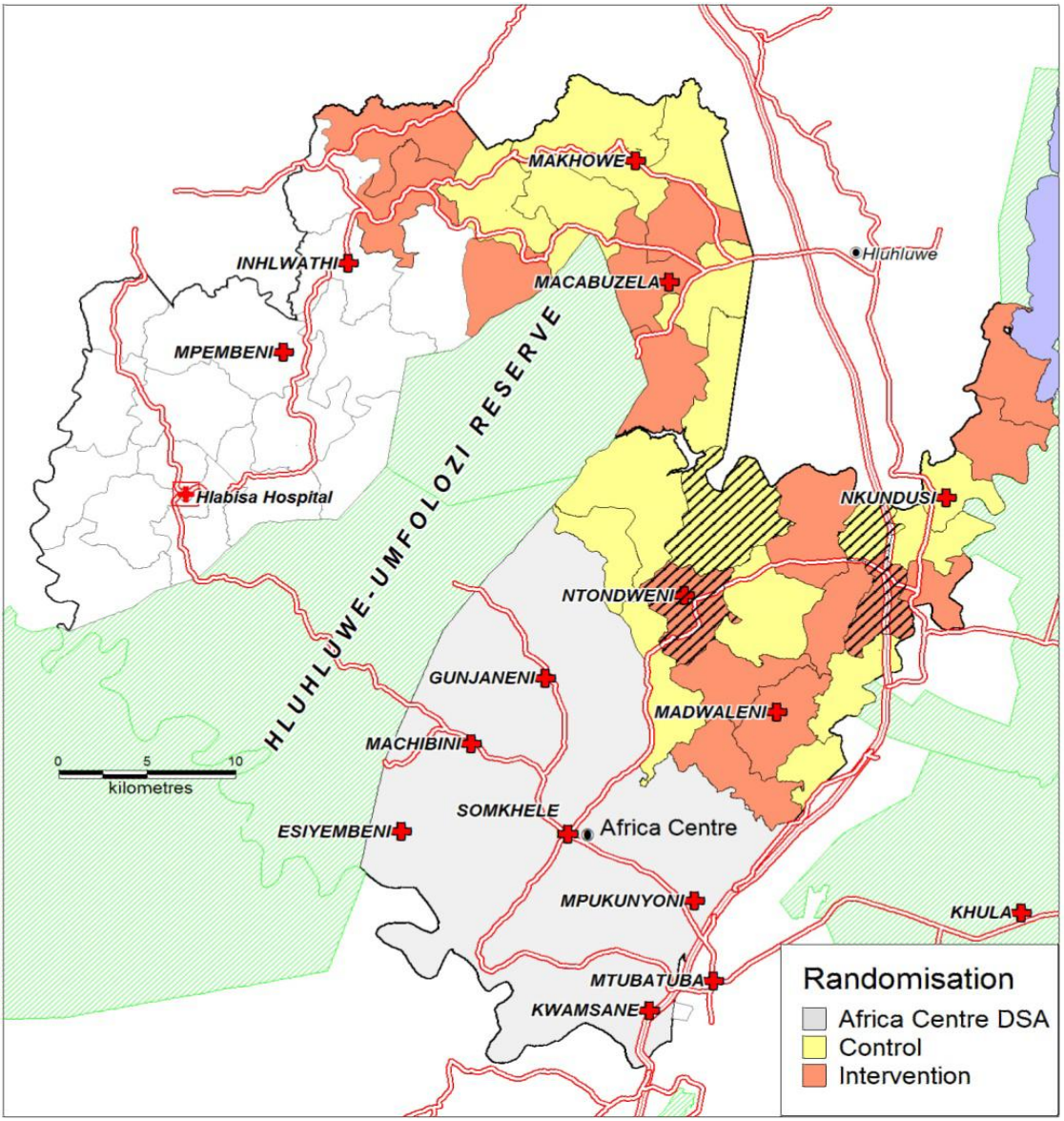
- Among all participants:
  - To estimate the acceptability and feasibility three times over a 14-month period of providing repeat HIV testing to all adult members of a community
- Among HIV-infected participants:
  - To estimate entry into care and ART, retention, morbidity/mortality, TB, virological 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 km^2
- 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

	Status within trial, n(%)	Sample size/model assumptions, n(%)
Registered	11 537	10 000
Contacted	8 347 (72)	9 000 (90)
Participation	7 865 (94)	-
HIV status ascertained	6 465 (82)	7 200 (80)
HIV positive	1 965 (30)	1 440 (20)
Seen in TasP clinic	912	-
Seen in DoH clinic	510	-
Total linked to care	1422 (72)	1 008 (70)

TasP

Antiretroviral Treatment as Prevention
(Ukuphila kwami, ukuphila kwethu (my health for our health)

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 ?

2014-2015 : Eléments tangibles sur la faisabilité et l'acceptabilité en Afrique

2015-2017 : Effectiveness

Comment la mesurer ?

Remerciements

T. Bärnighausen, B. Bazin, R. Dray-Spira, G. Hirnschall, C. Iwuji, K. Jean, J. Larmarange, F. Lert, ML. Newell, J. Orne-Gliemann, C. Rekacewicz, F. Tanser

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An autonomous agency at Inserm

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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:
  - http://clinicaltrials.gov/: NCT01509508
  - 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

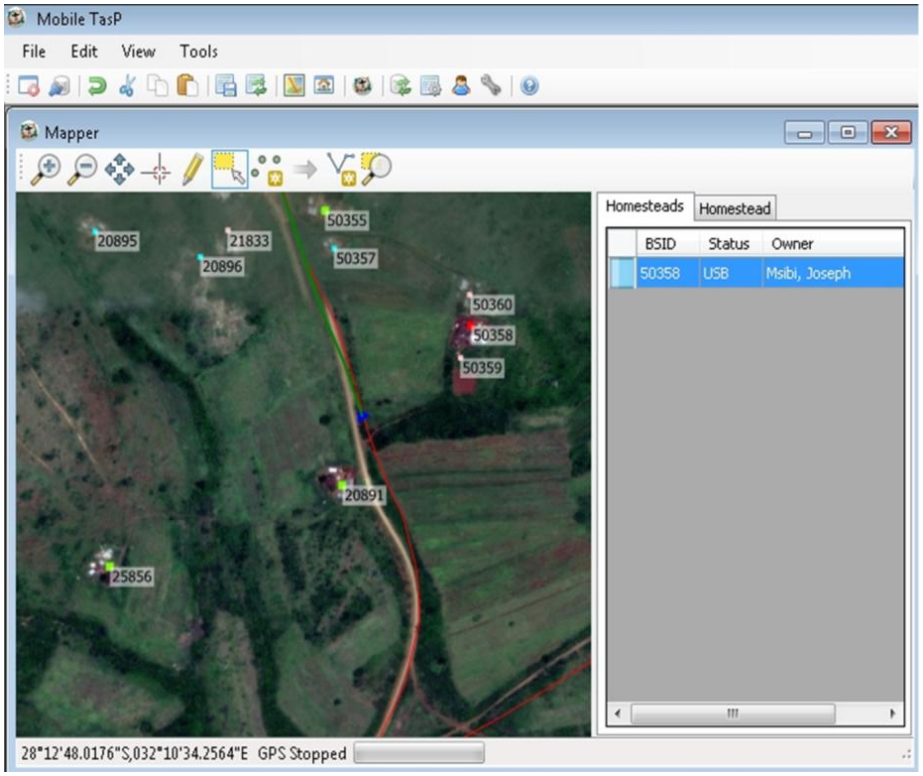
TasP organization

- 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

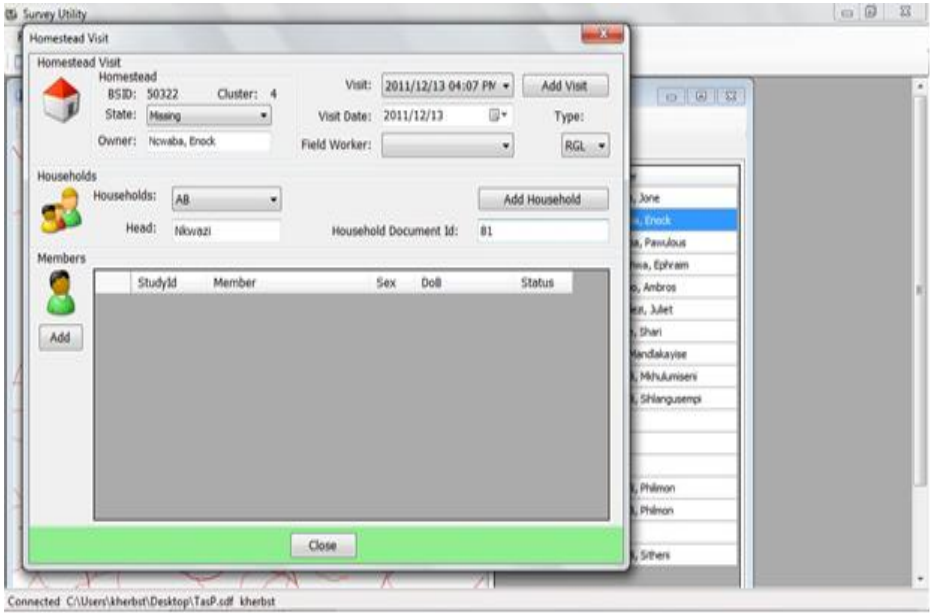


Homestead identification using GPS and GIS

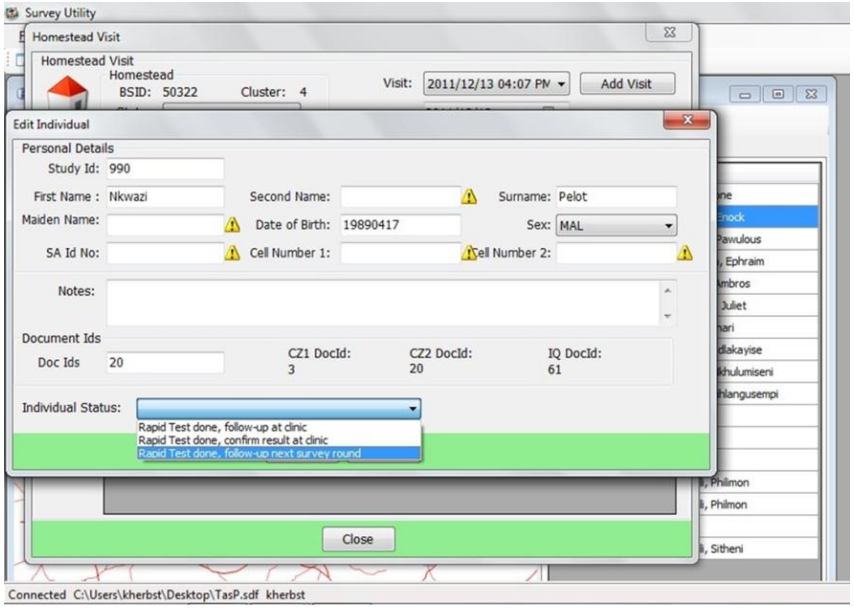
TasP

Antiretroviral Treatment as Prevention
(Ukuphila kwami, ukuphila kwethu (my health for our health)

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

TasP

Antiretroviral Treatment as Prevention

(Ukuphila kwami, ukuphila kwethu (my health for our health)

Trial clinics

TasP Clin

- 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

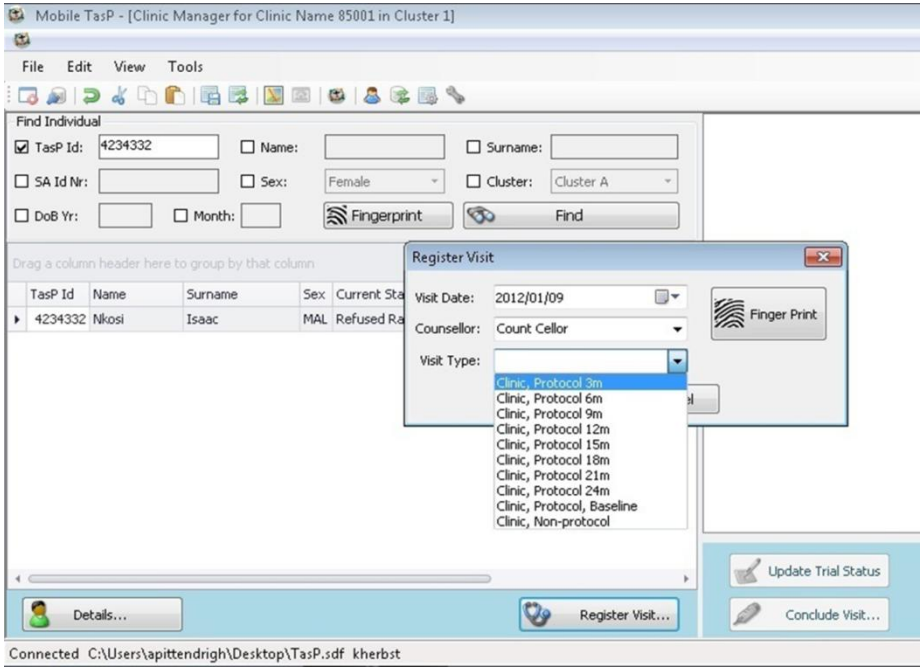
Ethics approval
to link DoH & TasP databases

Hlabisa DoH Clinic

Includes PoC CD4

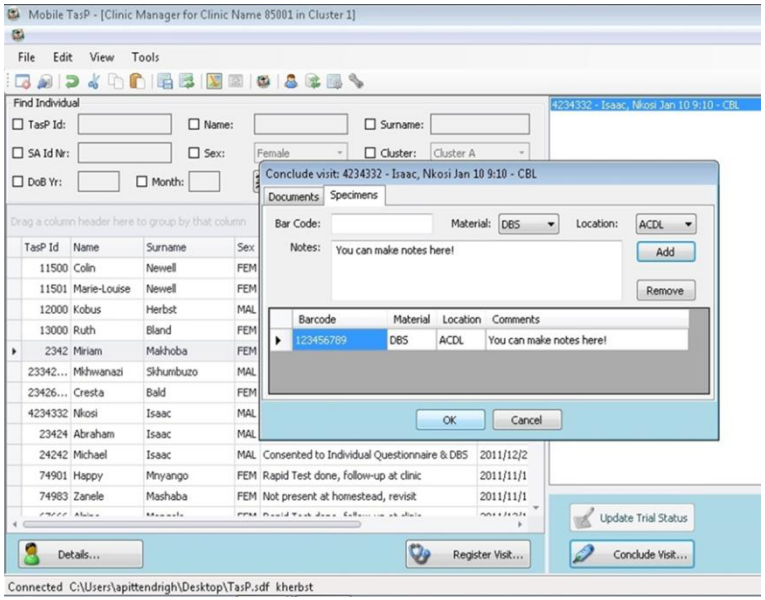
TasP
Antiretroviral Treatment as Prevention
(Ukuphila kwami, ukuphila kwethu (my health for our hea

Clinic manager



Patient registration at a clinic visit

Patient fingerprint recording



Documents and specimens being captured on clinic visit conclusion

TasP

Antiretroviral Treatment as Prevention

(Ukuphila kwami, ukuphila kwethu (my health for our health)

Phase 1 is ongoing (b)

SAB 1st meeting:

November 2012 (Paris)

DSMB 1st meeting:

May 8, 2013 (Paris)

SAB 2nd meeting:

May 17-18, 2013 (Hlabisa)