9° WORKSHOP NAZIONALE CISAI

PREVENZIONE
E GESTIONE
DELLE CO-MORBIDITÀ
ASSOCIATE
ALL'INFEZIONE DA HIV

9° workshop nazionale CISAI

Bari, 21 e 22 Marzo 2019

Le infezioni sessualmente trasmissibili: quali implicazioni nel paziente HIV-positivo

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FONDAZIONE ASIA

CISAI Coordinamento Italiano Studio Allergie e Infezione da HIV

BARI | 21-22 MARZO 2019
CENTRO CONGRESSI PALACE HOTEL BARI

Institute of Infectious and Tropical Diseases - University of Brescia

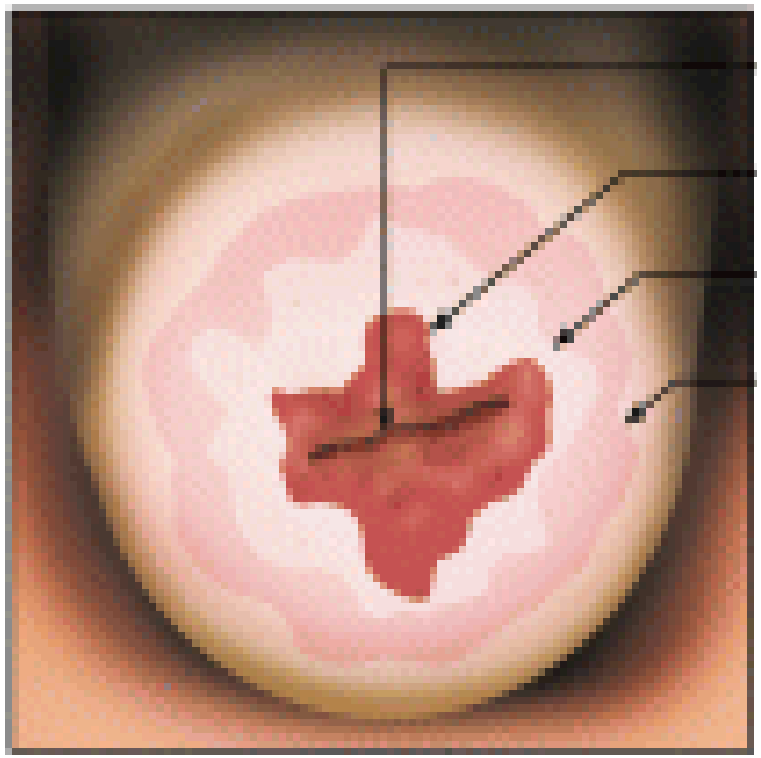
WHO Collaborating Centre for TB/HIV collaborative activities and for TB elimination

Sommario

- HIV si trasmette efficacemente per via sessuale
- STI come cofattore di trasmissione
- Le implicazioni per la prevenzione della trasmissione sessuale di HIV
- (Patomorfosi delle STI in soggetti con infezione da HIV)

Source of HIV shedding in the female genital tract

Genital associated lymphoid tissue consisting of cervical stroma lymphocytes



Parous adolescent cervix showing the squamocellular junction and the cervical transformation zone

Coombs RW, AIDS, 2003; 17:455

Source of HIV shedding in the male genital tract

Sperms considered to be virus free

Virus vehiculated by polinuclear cells, lymphocyte and macrophages, present also in seminal plasma

Very large between and within subject variations in semen composition

Main source seems to be the urethra

Timing of HIV shedding at genital sites

Longitudinal studies ranging from 8 to 10 weeks:

Men

Continuously detected	28 – 37%
Intermittently detected	39 – 44%
Never detected	24 – 28%

Coombs RW, JID, 1998; 177:320
Gupta P, JID 2000; 182: 79

Women

Continuously detected	29%
Intermittently detected	58%
Never detected	13%

Coombs RW, JID, 2001; 184:1187

Probability of sexual transmission of HIV

- Risk of transmission is low after a single sexual contact
  - Receptive anal intercourse**: 0.8 - 3%**
  - Penile-vaginal intercourse:

    M to F = **0.05 - 0.15%**, F to M = **0.03 - 0.09%**
  - Oral intercourse: unclear, but **~ 10x lower** than vaginal intercourse
- Cofactors important in transmission

Metanalysis of 43 publications of observational studies of the risk of HIV-1 transmission per heterosexual contact

In **high income countries** (and absence of antiretrovirals) **risk is low**:

- female-to-male: 0.04% per act (0.01-0.14)
- male-to-female: 0.08% per act (0.06-0.11)

In **low income countries risk is higher** even in absence of commercial sex:

- female-to-male: 0.38% per act (0.13-1.10)
- male-to-female: 0.30% per act (0.14-0.63)

Boily MC, Lancet Infect Dis 2009; 9:118

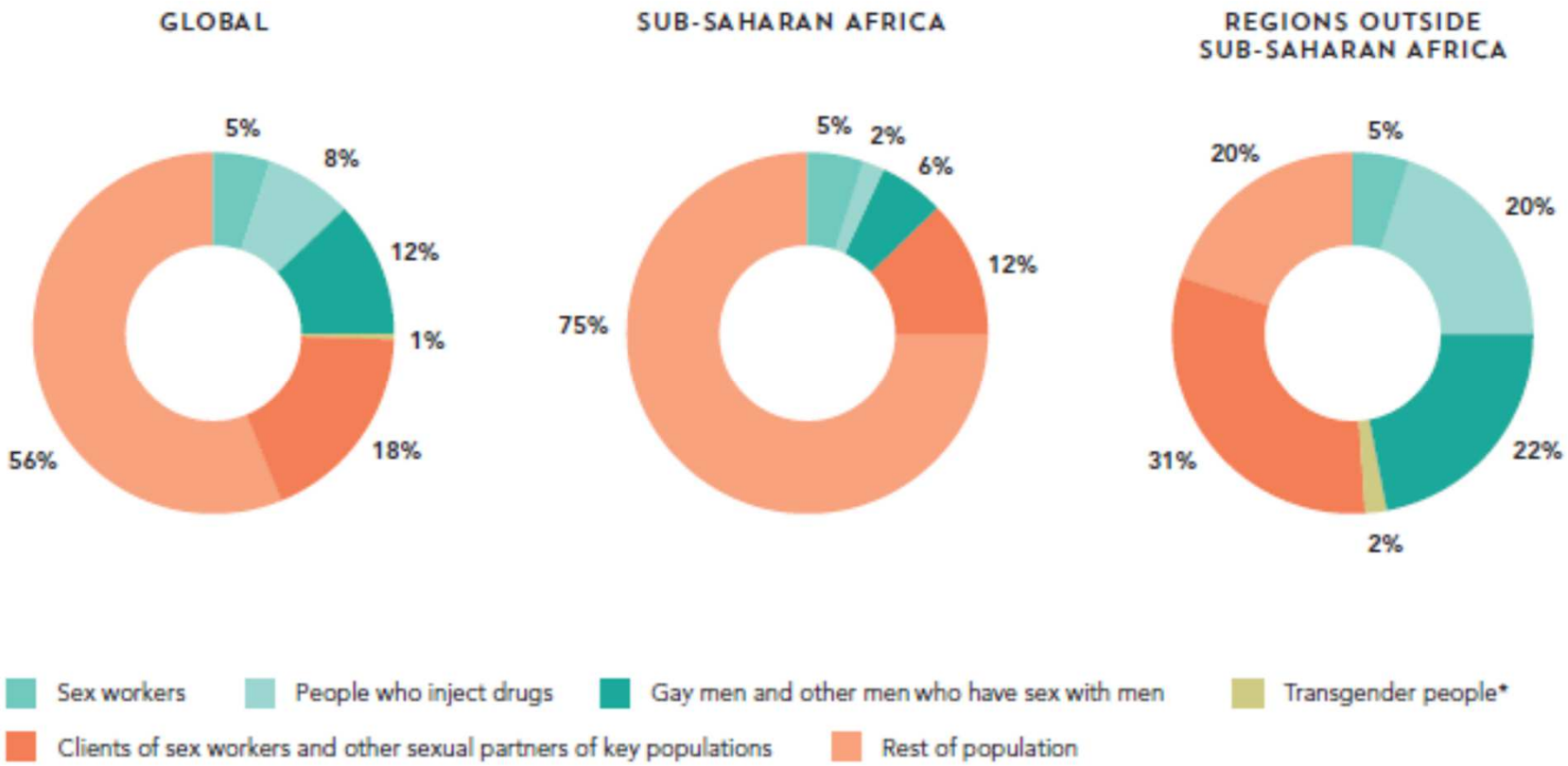
Determinants of HIV load in genital secretions

Serum HIV viral load

Plasma RNA concentrations, both qualitatively and quantitatively were the most important factor (the only one at significancy level) predicting genital HIV-1 shedding in women

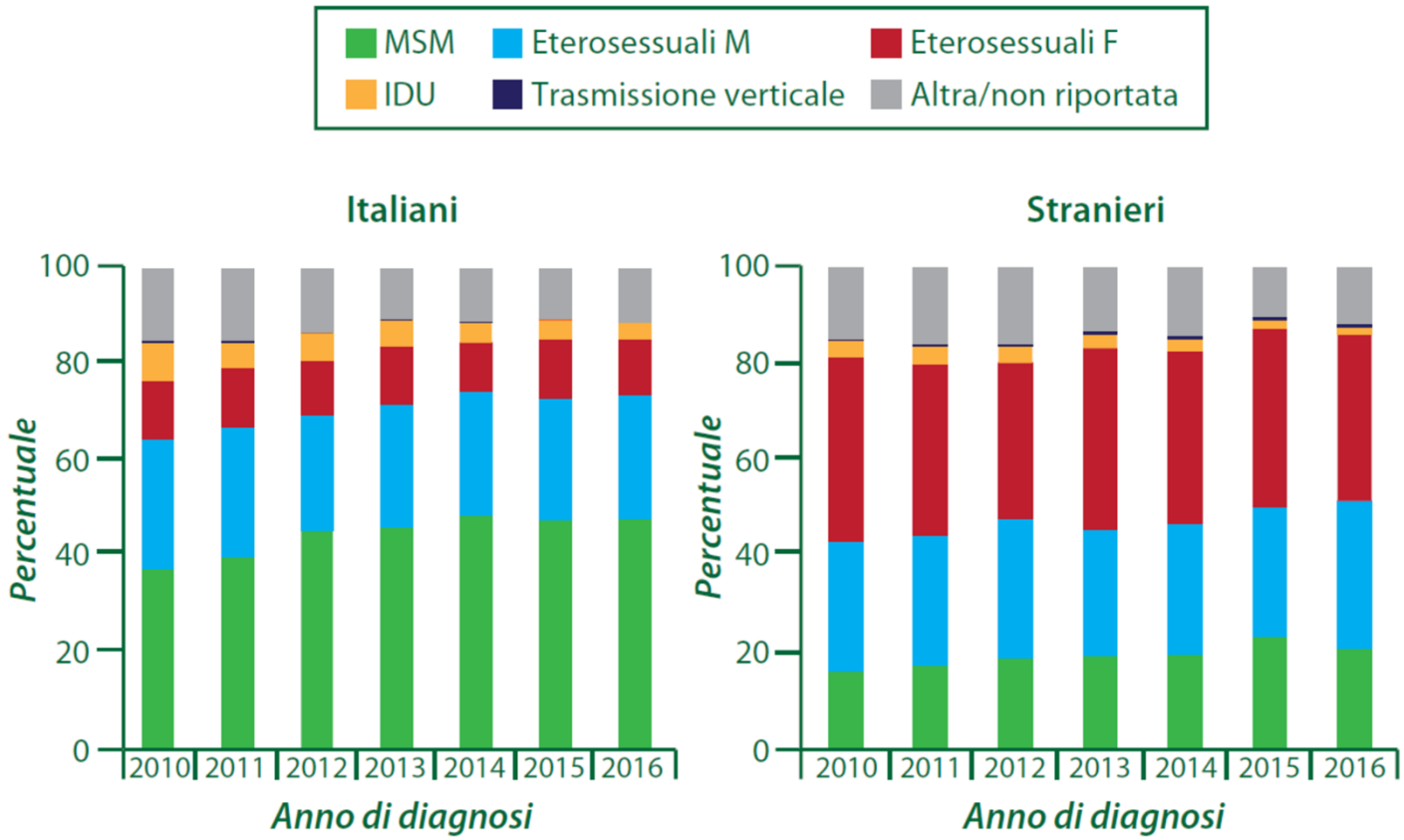
Kovacs A, Lancet 2001; 358: 1593

Distribution of new HIV infections, by population, global, sub-Saharan Africa and countries outside of sub-Saharan Africa, 2015



Source: UNAIDS - Global HIV report 2017

Way of transmission of new HIV infections, Italy – 2010-2016



Notiziario dell'ISS – 2017

STIs and risk of sexual transmission of HIV

Similar behavious transmit both HIV and STIs ➔ STIs are an indicator of HIV risk

AND

STIs are a risk factor for HIV acquisition / transmission

Biological Mechanisms for the STD Cofactor

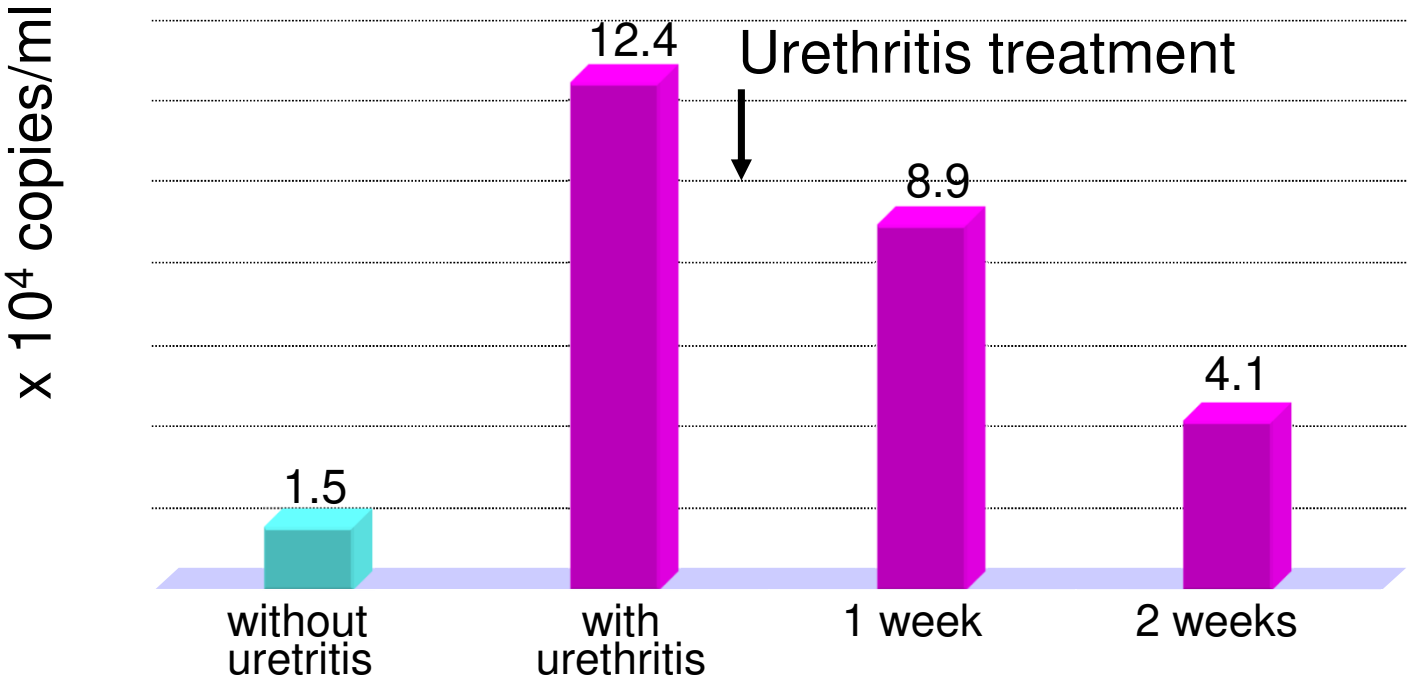
Infectiousness:

- Inflammation increases HIV viral load in genital secretions
- HIV can be cultured from genital lesions such as ulcers of syphilis

Susceptibility:

- Breaks in epithelial barrier allow viral access
- Inflammation increases number and/or receptivity of target cells
- Enhancement of viral survival

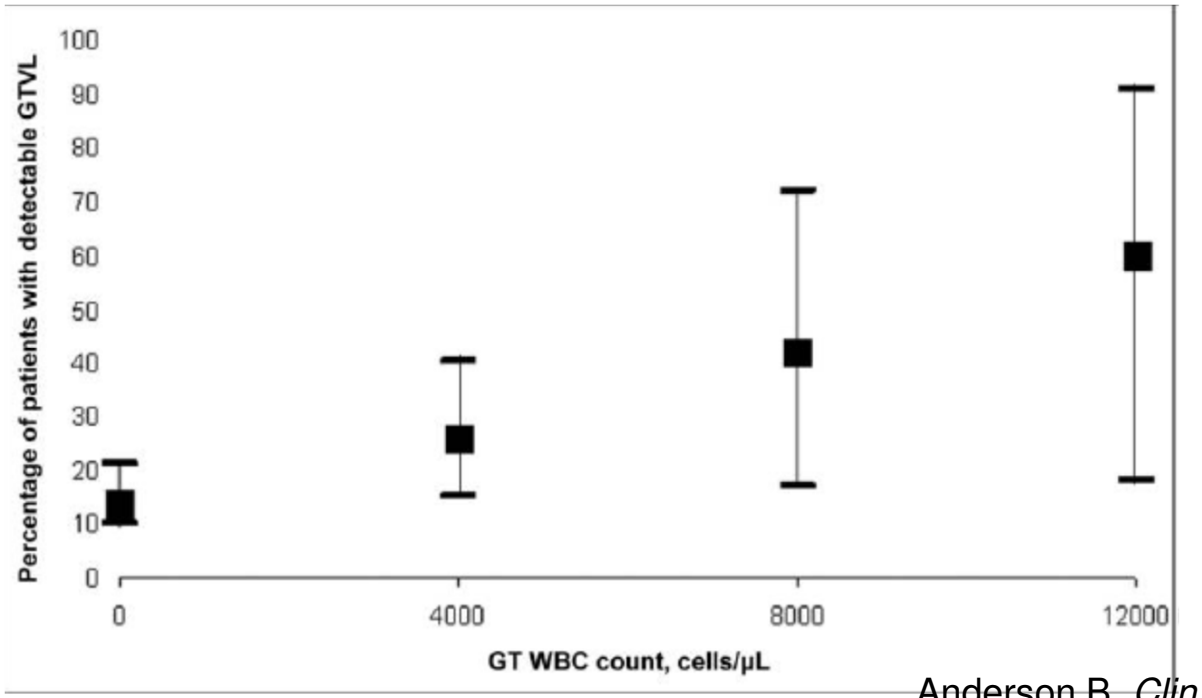
Median concentration of HIV-1 RNA in semen among 104 men with and without urethritis in Malawi



Cohen *et al., Lancet,* 1997

Genital tract leucocytes and shedding of genital HIV type 1 RNA

- The presence of GT WBCs in vaginal secretions predicts viral shedding independent of the presence of infections
- GT WBCs may be a surrogate marker for HIV infectiousness



Anderson B, *Clin Infect Dis* 2008; 47:1216-21

Cofactor magnitude used in a simulation analysis

Ulcerative STD		Non-Ulcerative STD	
Chancroid	25	Gonorrhoea	3
HSV-2 Primary	25	Chlamydia	3
HSV-2 Recurrent	15	Trichomoniasis	2
Syphilis Primary	7.5		

Metanalysis of 43 publications of observational studies of the risk of HIV-1 transmission per heterosexual contact

The higher risk of transmission in low-income countries may be justified by the **higher prevalence of STI**

The effect of **gender** is largely counterbalanced by the **geographical setting** (male-to-female risk equal to female-to-male in low-income coutries)

Boily MC, Lancet Infect Dis 2009; 9:118

Metanalysis of 43 publications of observational studies of the risk of HIV-1 transmission per heterosexual contact

Effect of genital ulcers and circumcision on Relative Risk:

RR for the presence of **ulcers** 5.3 (1.4 – 19.5)

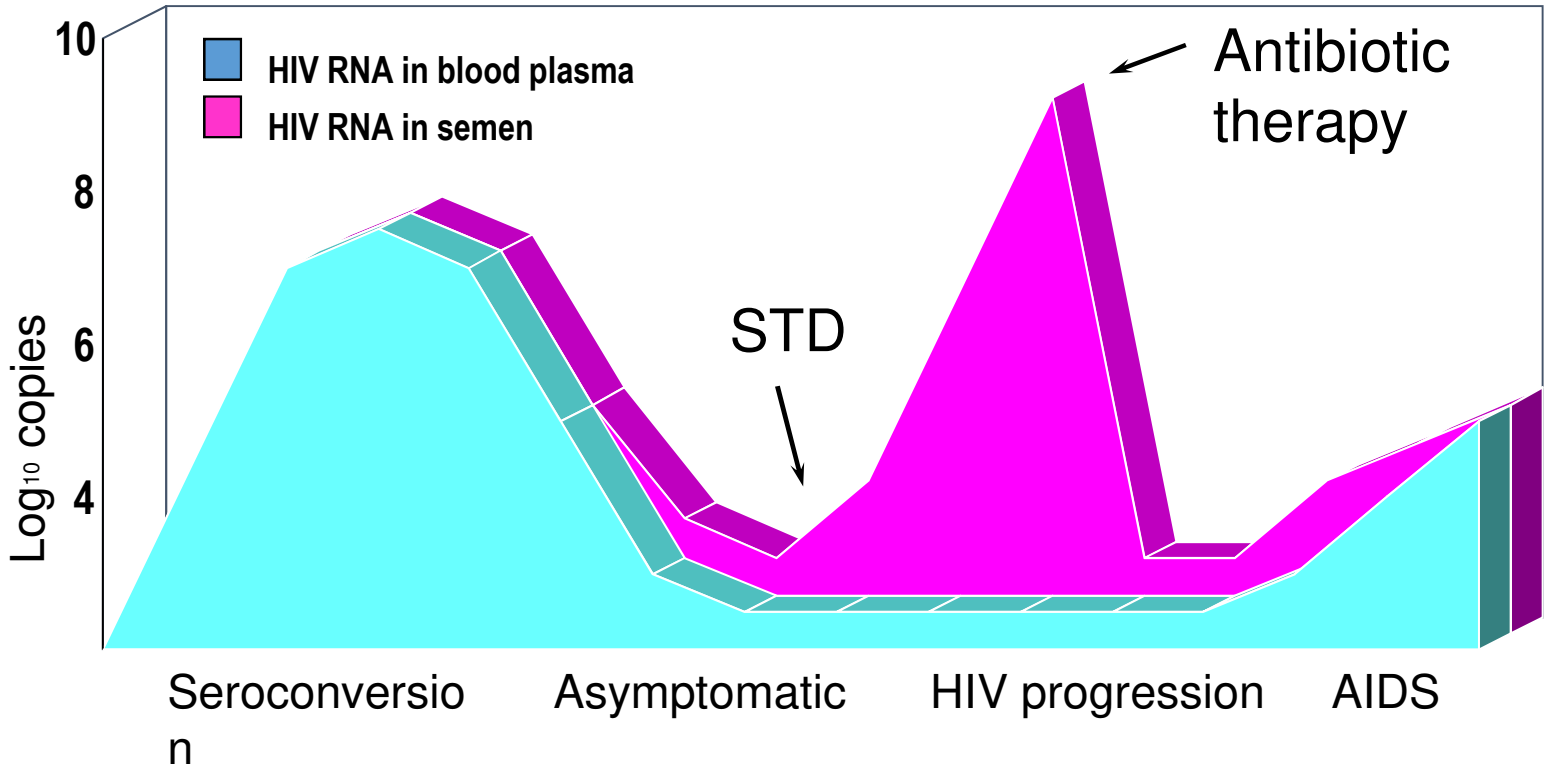
Circumcision reduces by two-fold the risk of infection

Boily MC, Lancet Infect Dis 2009; 9:118

What are the implications of the interactions ?

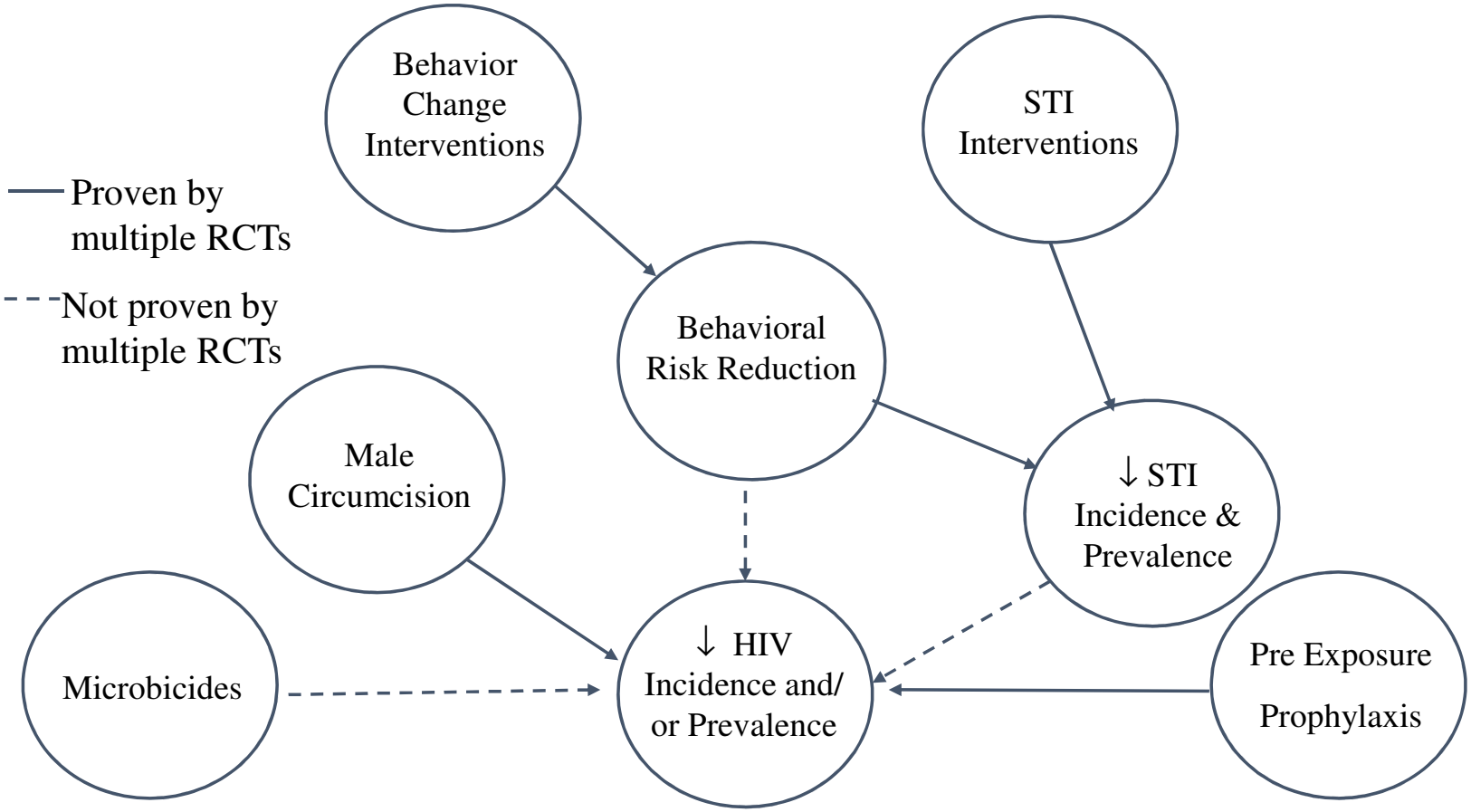
Interventions to control other STIs will reduce the incidence of HIV in the intervention population

Hypothetical model of impact of STD on HIV genital shedding in men



From ISSTDR, Seville 1997; M. Cohen, plenary presentation

Impact on HIV Incidence & Prevalence of Preventive Interventions and of HIV/AIDS Morbidity & Mortality



The role of sexually transmitted infections in the evolution of the South African HIV epidemic

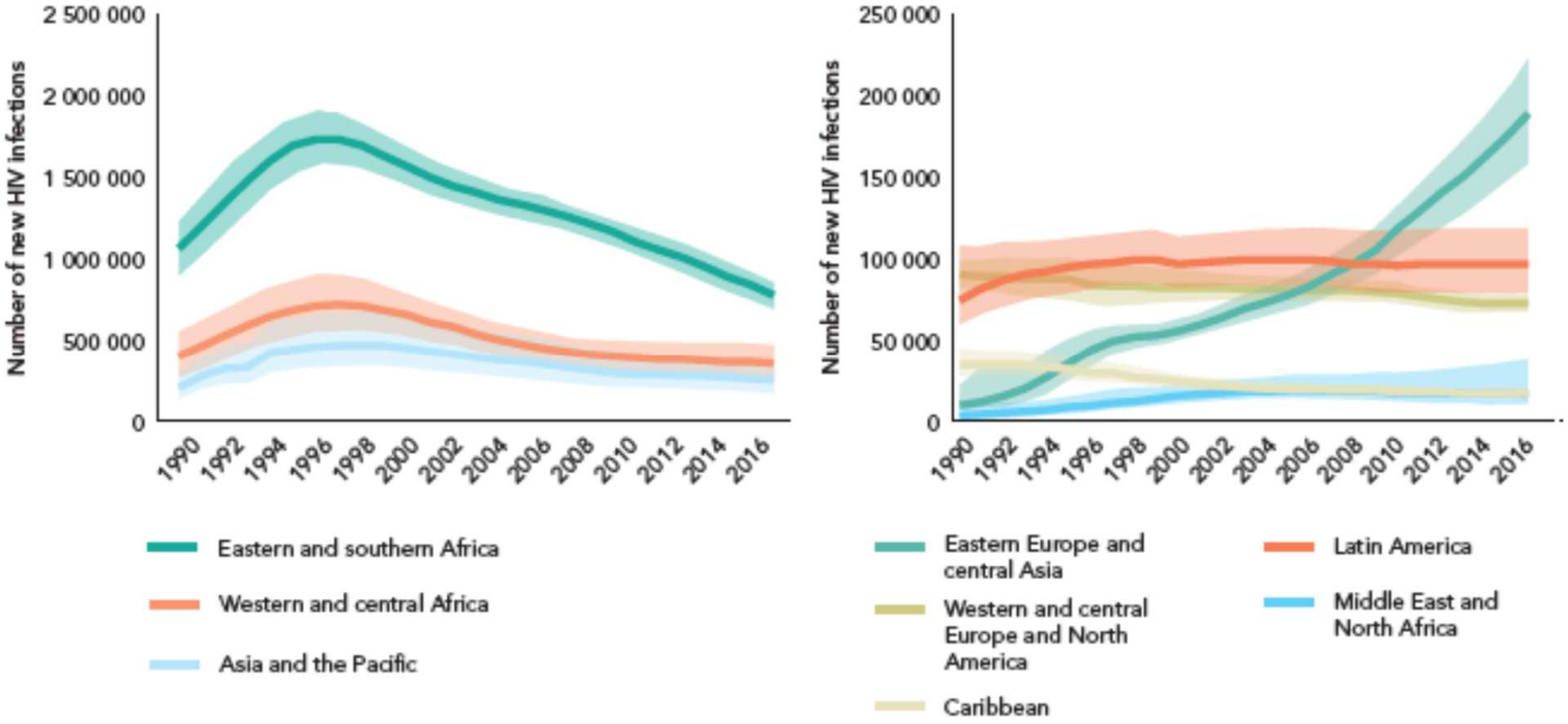
Leigh F. Johnson[1], Rob E. Dorrington[2], Debbie Bradshaw[3] and David J. Coetzee[1]

RESULTS The proportion of new HIV infections in adults that were attributable to curable STIs reduced from 39% (uncertainty range: 24–50%) in 1990 to 14% (8–18%) in 2010, while the proportion of new infections attributable to genital herpes increased. Syndromic management programmes are estimated to have reduced adult HIV incidence by 6.6% (3.3–10.3%) between 1994 and 2004, by which time syndromic management coverage was 52%. Had syndromic management been introduced in 1986, with immediate achievement of 100% coverage and a doubling of the rate of health seeking, HIV incidence would have reduced by 64% (36–82%) over the next decade, but had the same intervention been delayed until 2004, HIV incidence would have reduced by only 5.5% (2.8–9.0%).

CONCLUSIONS Sexually transmitted infections have contributed significantly to the spread of HIV in South Africa, but STI control efforts have had limited impact on HIV incidence because of their late introduction and suboptimal coverage.

Johnson et al Trop Med Int Health 2012

New HIV infections, all ages, by region, 1990–2016

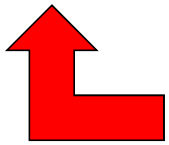


Source: UNAIDS - Global HIV report 2017

Basic reproductive rate of HIV

$$R_o = \beta c D$$

β		c		D
Probability of transmission of infection	X	Rate of sex partner change	X	Duration of infectiousness



STI as an enhancing co-factor

Transmission reduced or potentially eliminated?

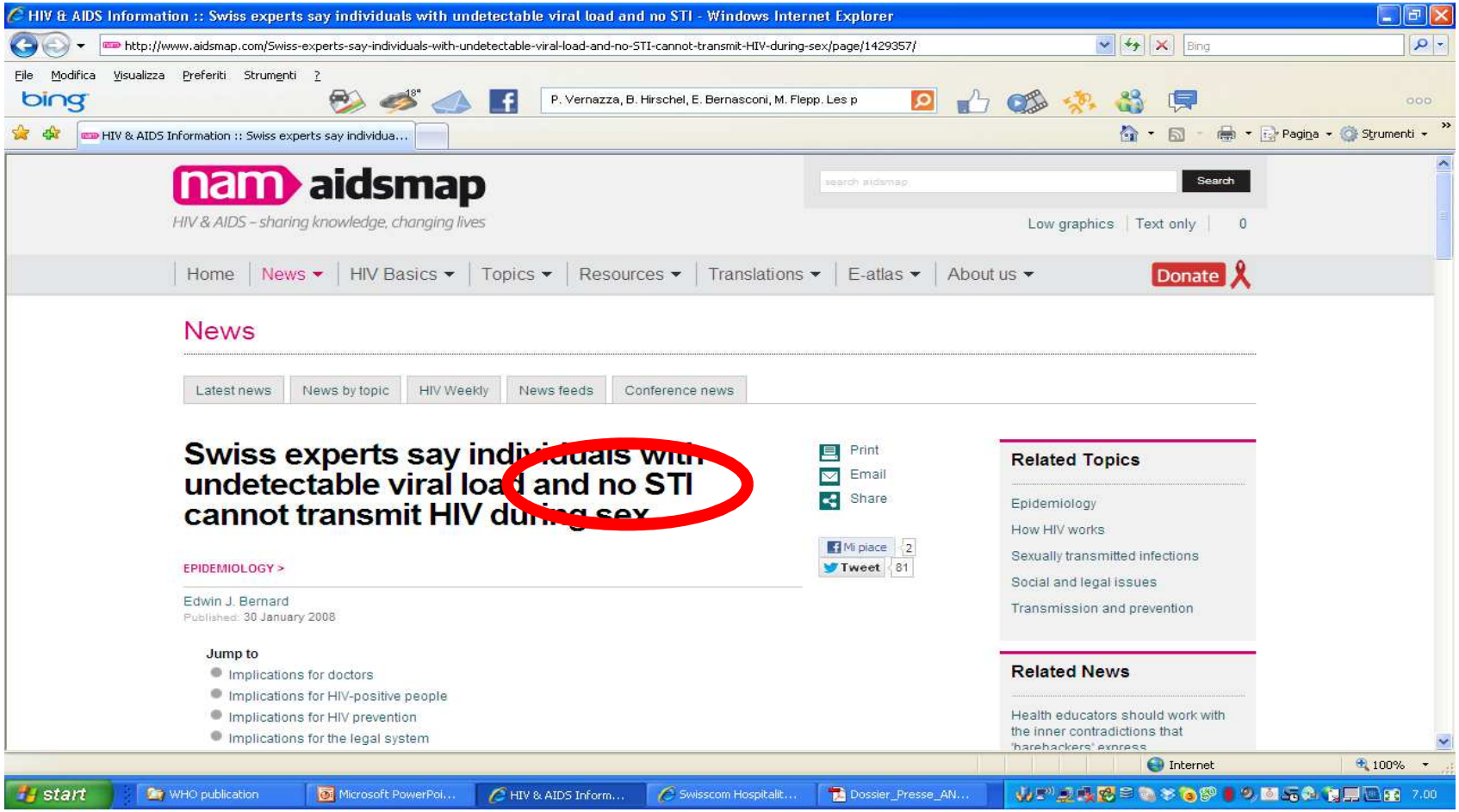
Table 1. Probability of transmitting HIV in a single act used in modelling expected transmission, by type of sex, ART status of infected participant and condom use

	No ART		ART
	Unprotected	Protected	All
MSM insertive	0.014	0.0028	0.0005
MSM receptive	0.007	0.0014	0.0005
Heterosexual	0.001	0.0002	0.00005

MSM = men who have sex with men; ART = antiretroviral therapy.

Safren SA et al. Journal of the International AIDS Society 2016, 19:21096

The Swiss statemen to safe sex without condom



The way forward for STI control as an HIV prevention tool

1. Integrated planning of HIV and STI elimination strategies

2. Target the population at risk for STI (to reduce acquisition of HIV)

3. Target the population with HIV infection (to reduce transmission of HIV)

Services for sexually transmitted infections

- Address issues specific to STI.
- Provide an opportunity to offer provider-initiated testing and counselling for HIV.
- Serve as entry points for HIV care and treatment interventions.
- Assist in identifying changes in risk behaviour associated with HIV transmission (syphilis prevalence)
- Serve as biomarkers of HIV and the effectiveness of programmes to prevent sexually transmitted infections (incidence of gonorrhoea and primary and secondary syphilis)

UNAIDS annual report 2011

STI clinic network

- Accredited network to ensure:
  - client-appropriate services (accessible and acceptable)
  - comprehensive list of interventions (from partner treatment to vaccination)
  - standardized diagnostic procedures and treatment regimens (within syndromic approach)
  - Surveillance, monitoring and evaluation

Organizzazione dei servizi (1)

1. Attività continuativa con orario di apertura settimanale di almeno **10 ore** per ciascuno dei due poli
2. **Accesso libero**, oltre ad accesso con appuntamento, garantito a tutte le persone che per anamnesi o sospetto clinico siano a rischio per una IST
3. **Accettazione dell'utente sia diretta che telefonica** a cura di personale amministrativo che opera secondo procedure prestabilite; l'accesso **non richiede impegnativa del medico di medicina generale**. La prestazione medica e le indagini diagnostiche sono **gratuite**, in relazione agli standard delle prestazioni diagnostiche e terapeutiche pattuite con la regione
4. **Visita** medico-specialistica per le IST (infettivologia, dermatologia, ginecologia, etc); è garantita la confidenzialità assoluta per tutto il percorso con esecuzione dei necessari accertamenti in anonimato, se richiesto
5. Esecuzione diretta di **prelievi** di campioni biologici (fluidi genitali, sangue) per esecuzione di test laboratoristici di screening

Organizzazione dei servizi (2)

6. **Somministrazione diretta di terapia** per le IST (inclusa la terapia dell'infezione da HIV ed epatiti grazie alla co-locazione del servizio presso una sede infettivologica);
7. Offerta dello **screening** per HIV e per le altre IST secondo quanto previsto dalla direttiva regionale
8. Ricerca e trattamento dei **contatti** sessuali
9. Notifica dei casi al **sistema di sorveglianza regionale** delle IST (esteso a condilomatosi, infezione da Clamydia, Uretriti/cervico-vaginiti NG-NC e Trichomonas, infezione da Herpes genitale)
10. Offerta delle **vaccinazioni** previste dalla direttiva regionale per soggetti a rischio di IST
11. attività di **collaborazione** in tema di IST dedicata in particolare alla medicina di base, alle strutture del territorio e alle strutture di Pronto Soccorso

Procedure diagnostico-terapeutiche

- Viene adottato l'**approccio sindromico** per l'impostazione di un approccio terapeutico empirico
- L'offerta immediata del trattamento è tuttavia abbinata all'esecuzione di **test diagnostici di laboratorio** diretti a confermare il sospetto diagnostico e, ove possibile, la definizione della sensibilità ai farmaci.
- Le indagini diagnostiche per le IST incluse nella tabella 2 non prevedono costi per il paziente, applicando il codice di **esenzione D98**.
- Sono adottati **standard di trattamento** sia sindromico che eziologico
- I **farmaci per il trattamento**, sindromico o eziologico, dei casi di IST identificati, sia per il paziente che per gli eventuali contatti, sono dispensati dall'ambulatorio stesso e somministrati in modo supervisionato. La rendicontazione del consumo dei farmaci avviene tramite il file F. La somministrazione di farmaci per via intramuscolare prestazione non prevedono costi per l'utente, ma si avvale dell'esenzione B01.

STI Treatment Pocket European Guidelines 2018

IUSTI

STI TREATMENT GUIDELINES IUSTI 2018

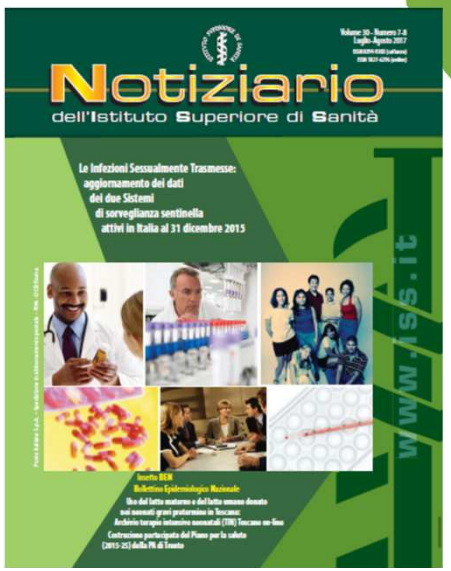
Patologia	Trattamento prima scelta	Alternativa
Sifilide	**EARLY**: Benzathine penicillin G 2.4 million units IM as single dose (one injection of 2.4 million units or 1.2 million units in each buttock). **LATE**: Benzathine penicillin G 2.4 million units IM (one injection 2.4 million units single dose or 1.2 million units in each buttock) weekly on days 1, 8 and 15. **NEURO**: Benzyl penicillin 18–24 million units IV daily, as 3–4 million units every 4 h during 10–14 days.	Doxycycline 200 mg oral daily (either 100 mg twice daily or as a single 200 mg dose) for 14 days. OR Azithromycin 2 g oral as single dose. Doxycycline 200 mg oral daily (either 100 mg twice daily or as a single 200 mg dose) during 21–28 days. Ceftriaxone 1–2 g IV daily during 10–14 days. OR Procaine penicillin 1.2–2.4 million units IM daily and probenecid 500 mg four times daily, both during 10–14 days.
Infezione da Neisseria Gonorrhoeae	Ceftriaxone 500 mg IM as a single dose together with azithromycin 2 g oral as a single dose.	Cefixime 400 mg oral as a single dose together with azithromycin 2 g as a single oral dose. OR Ceftriaxone 500 mg IM as a single dose. OR Spectinomycin 2 g IM as a single dose together with azithromycin 2 g oral as a single dose.

Testing coverage and prevalence of HIV infection among STI clients

(Italian national STI Surveillance System 1991-2015, 115.207 subjects)

34,696 non tested
30.1%

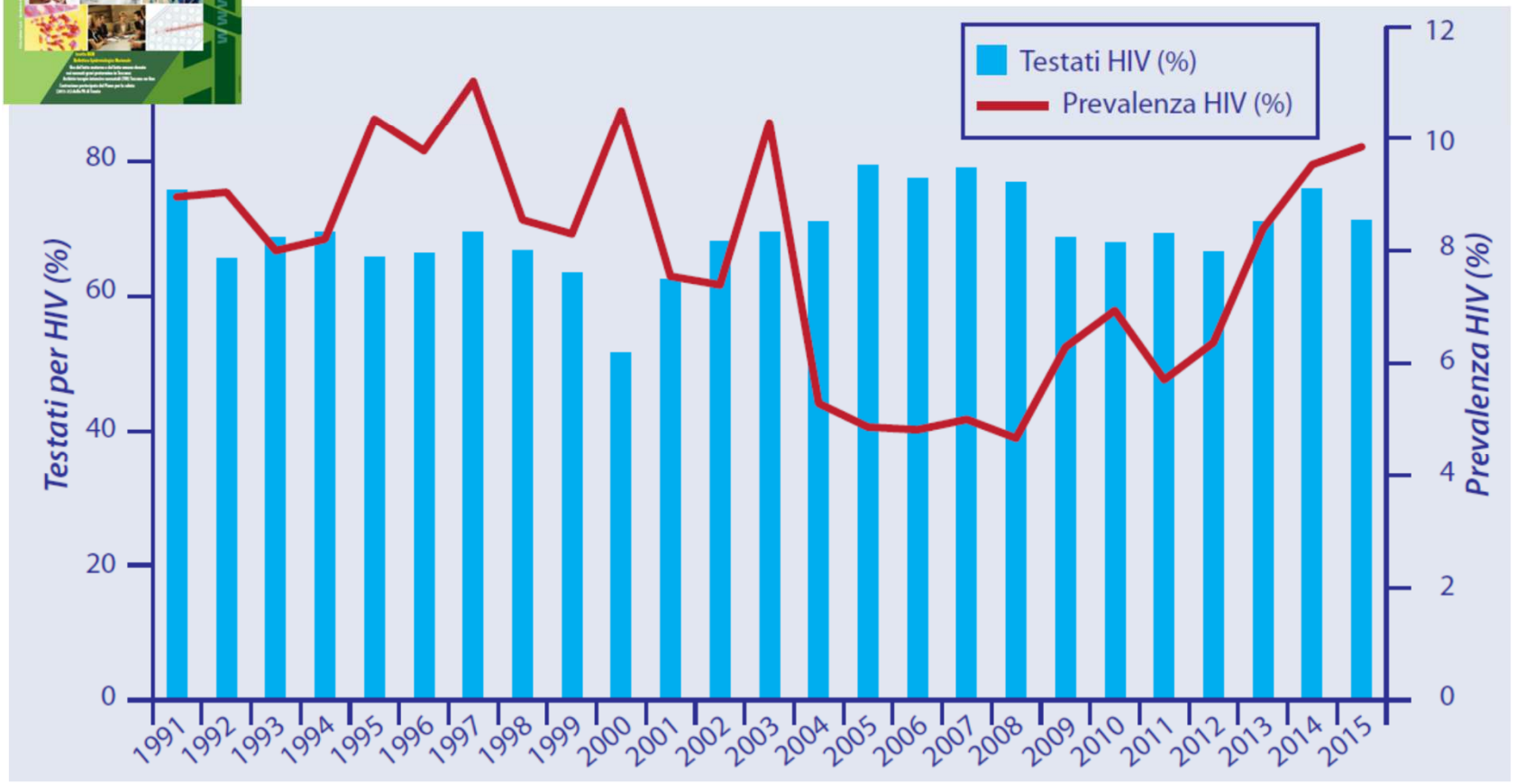
80,511 tested
69.9%



6.162 HIV positive

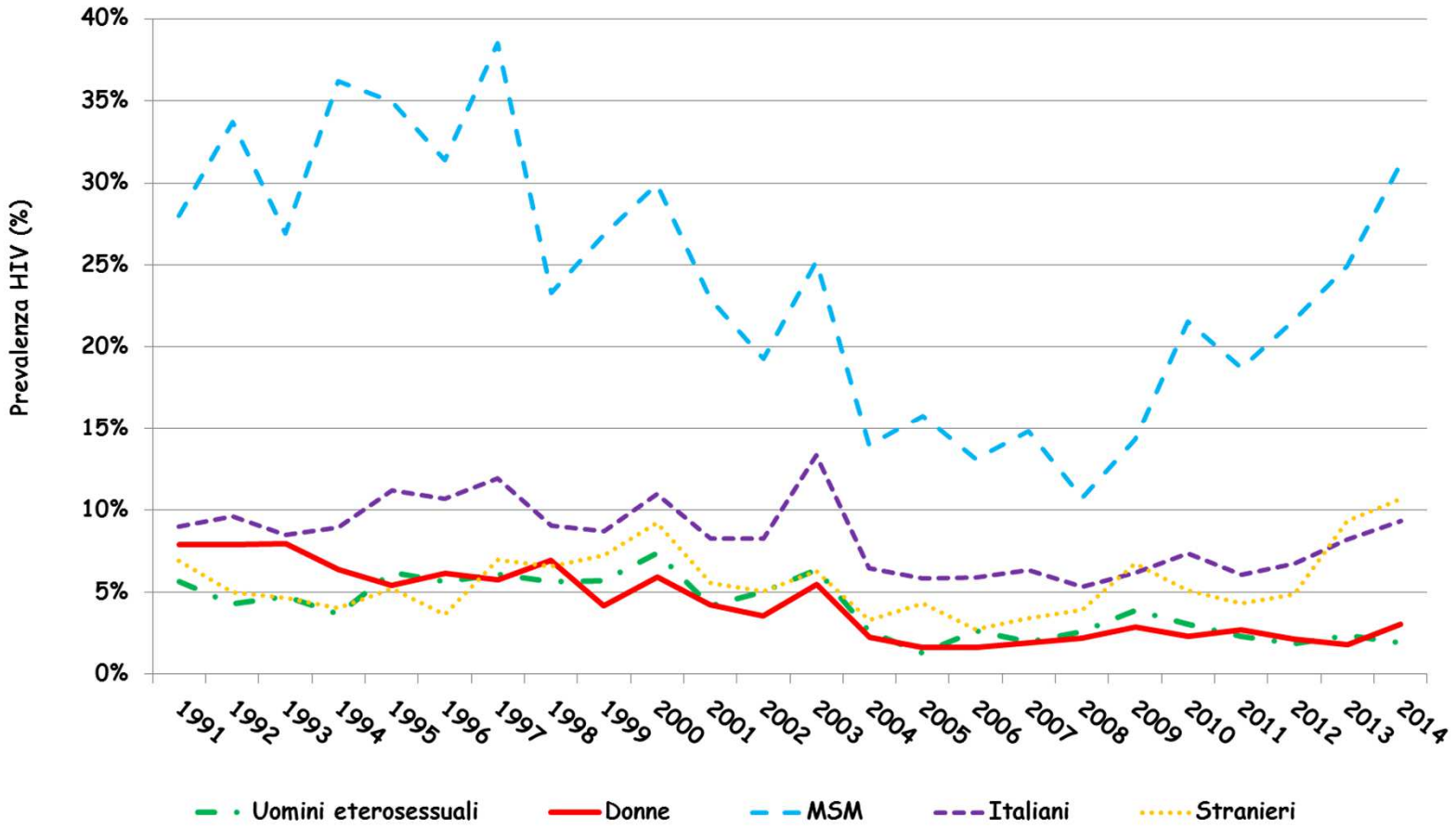
7,7% (IC 95%: 7,5-7,8)

Trend in testing coverage and prevalence of HIV infection among STI clients - (Italian national STI Surveillance System 1991-2015, 115.207 subjects)



Prevalenza di HIV in diversi sottogruppi di soggetti con IST

(Sistema di Sorveglianza Sentinella delle IST basato su centri clinici, 1991-2014)



HIV tests and HIV prevalence according to risk factors and type of STI

Fattore di rischio*	N. soggetti testati per HIV	Prevalenza HIV (%)
Omosessuali tossicodipendenti iniettivi	374	65,5
Eterosessuali tossicodipendenti iniettivi	1.563	55,7
Omosessuali non tossicodipendenti iniettivi	6.933	21,7
Eterosessuali non tossicodipendenti iniettivi	37.537	2,5
MST diagnosticata	**N. soggetti testati per HIV**	**Prevalenza HIV (%)**
Sifilide I-II	3.751	14,9
Pediculosi del pube	1.283	10,5
Herpes genitale	4.616	9,2
Condilomi ano-genitali	20.811	8,6
Uretrite/Cervicite da *Neisseria gonorrhoeae*	4.059	7,4
Sifilide latente	5.675	6,8
Mollusco contagioso	3.086	5,6
Uretrite/Cervicovaginite NG-NC	8.126	2,9
Uretrite/Cervicite da *Chlamydia trachomatis*	3.619	2,0

Notiziario dell'ISS – Febbraio 2012

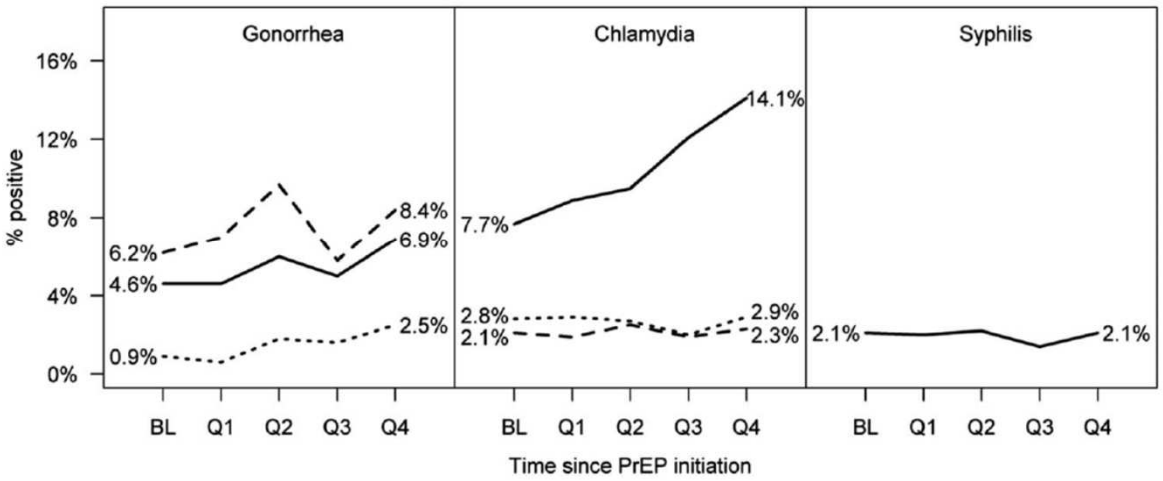
Efficacy of PrEP

- The biological efficacy of daily oral tenofovir-based regimens used as PrEP to reduce HIV acquisition has been established through randomised placebo-controlled trials in
  - men who have sex with men
  - heterosexual individuals
  - intravenous drug users

Incidence of STIs during PrEP

Quarterly STI positivity was high and increased over time for rectal chlamydia (P , 0.001) and urethral gonorrhea (P = 0.012). No HIV seroconversions occurred during PrEP use; however, 2 occurred in individuals who discontinued PrEP after losing insurance coverage.

FIGURE 2. STIs at baseline (BL) and during the first year of preexposure prophylaxis use. For gonorrhea and chlamydia, solid, dashed, and dotted lines represent rectal, pharyngeal, and urethral infections, respectively, among those tested. For syphilis, the line represents treatment with benzathine penicillin among individuals at baseline and with any follow-up during each quarter. Increases were statistically significant for urethral gonorrhea ($P = 0.012$) and rectal chlamydia ($P < 0.001$).



Marcus JL et al. J Acquir Immune Defic Syndr. 2016 Dec 15;73(5):540-546

World Health Organization

JUNE 2016

GLOBAL HEALTH SECTOR STRATEGY ON

SEXUALLY TRANSMITTED INFECTIONS 2016–2021

TOWARDS ENDING STIs

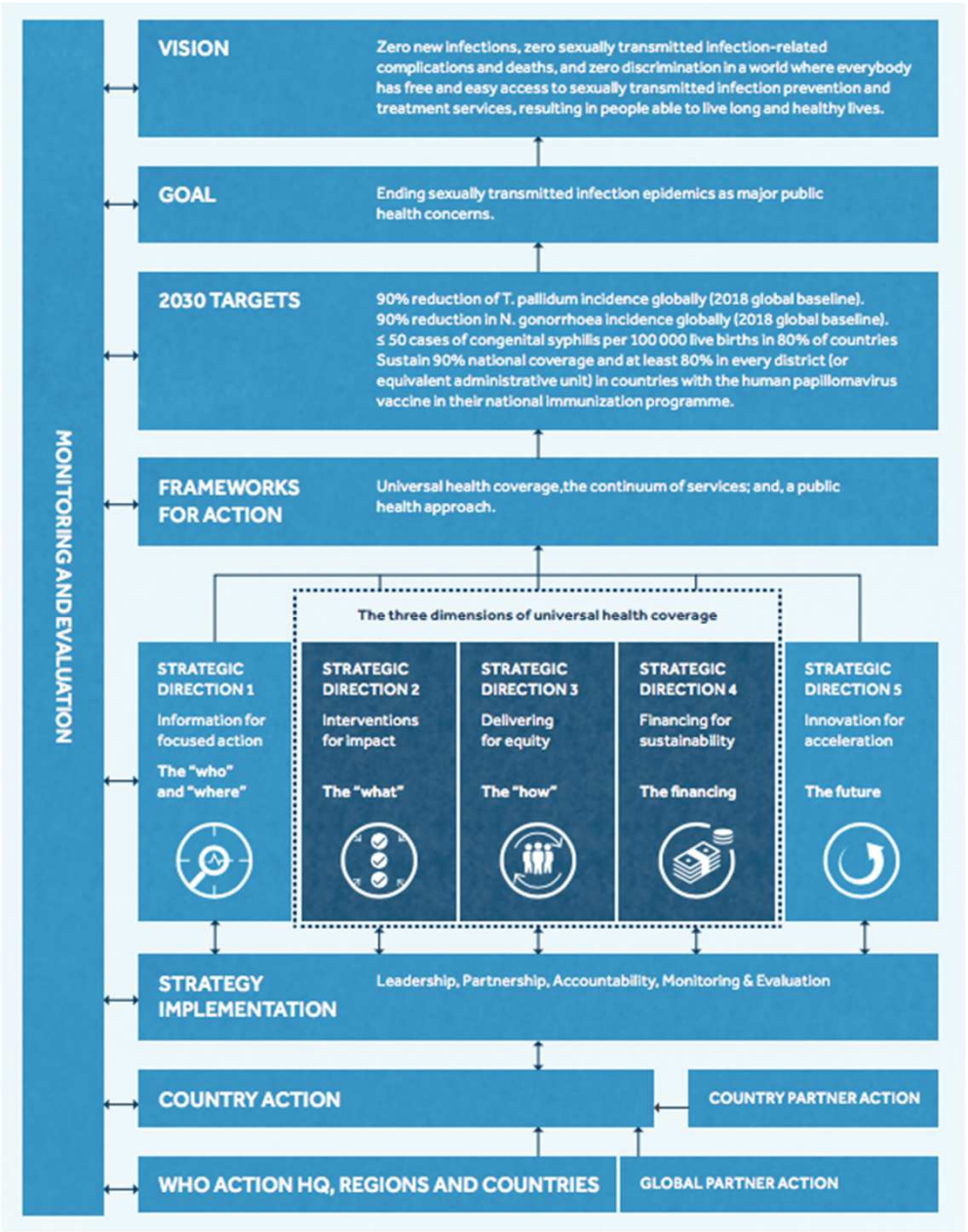


Figure 4. The three dimensions of universal health coverage: All people receive the services they need of sufficient quality to make a difference without incurring financial hardship

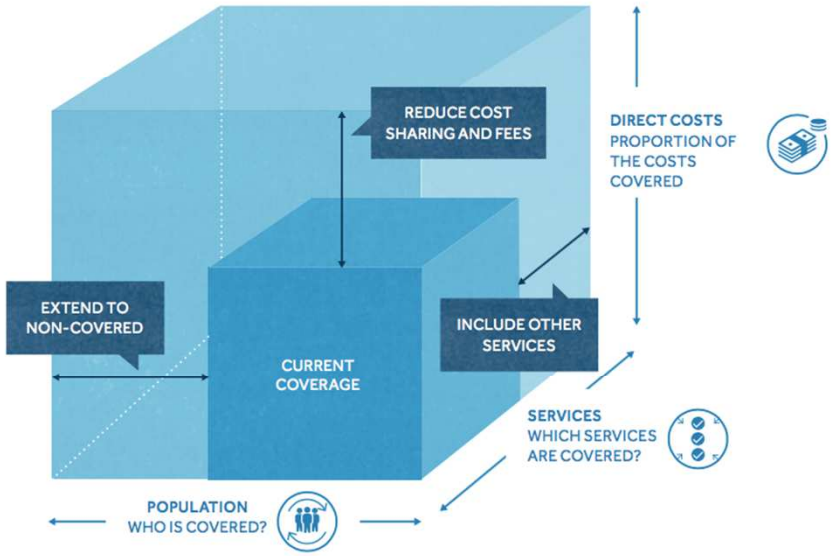
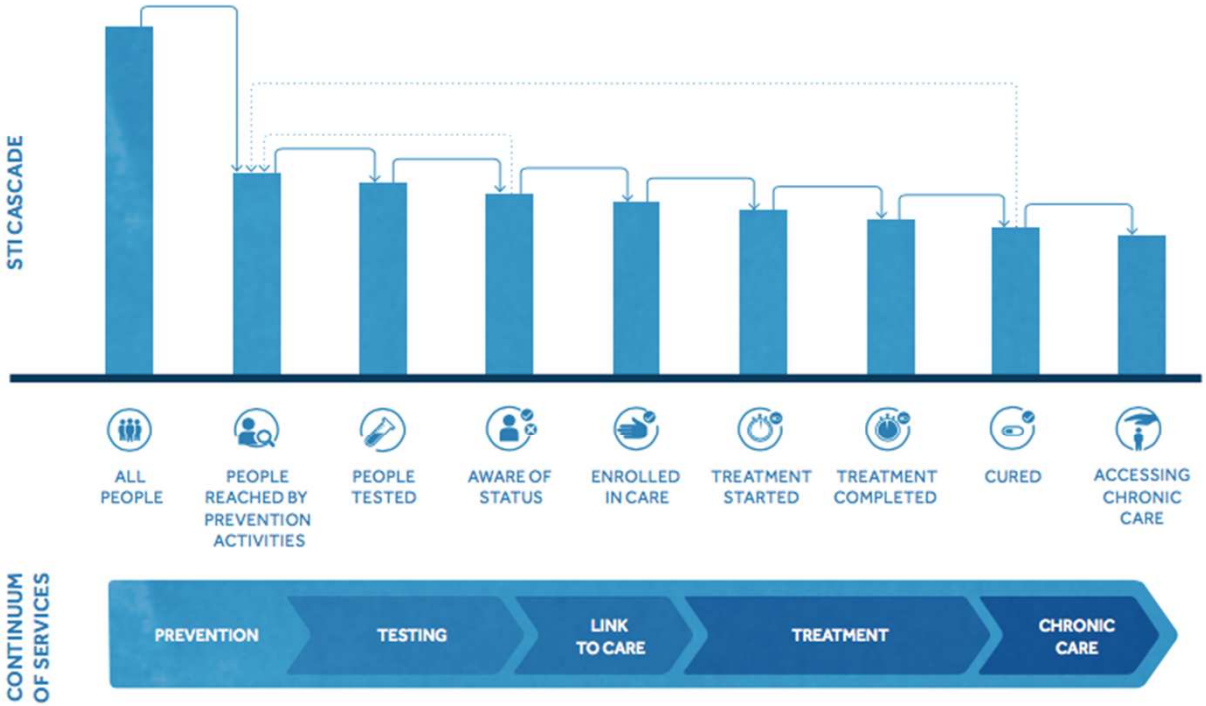


Figure 5. The continuum of sexually transmitted infection services and the cascade



Thank you