

# HIV PREVENTION STRATEGIES



Prof. Margalit Lorber  
Director, HIV Center  
Hillel Yaffe Medical Center  
The Rappaport Faculty of Medicine - Technion

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AIDS IS STILL A LETHAL DISEASE IN CERTAIN COUNTRIES

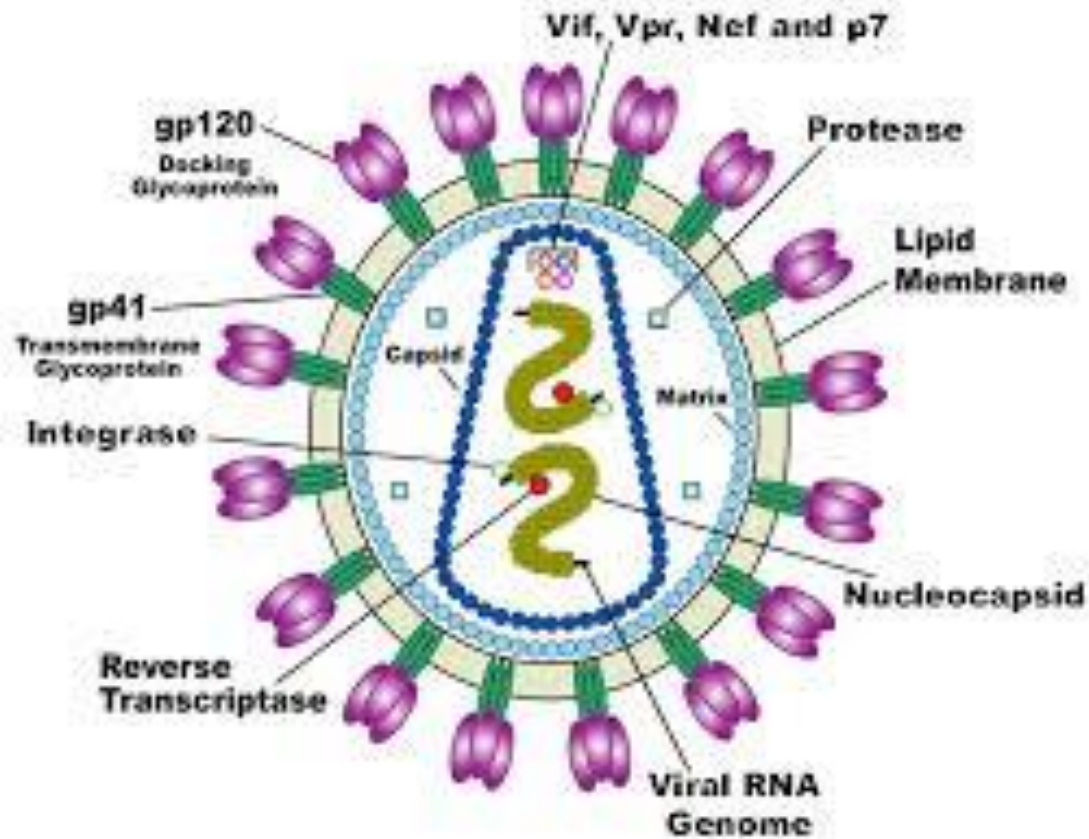




# HIV INFECTION

IS NOW A CHRONIC MANAGABLE DISEASE

# HIV – RETROVIRUS, ssRNA-RT virus

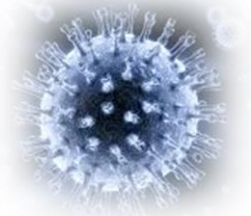


# ENDING THE URBAN AIDS EPIDEMIC

## RARE CANCER SEEN IN 41 HOMOSEXUALS

Outbreak Occurs Among Men in New York and California — 8 Died Inside 2 Years

By LAWRENCE K. ALTMAN  
Doctors in New York and California have diagnosed among homosexual men 41 cases of a rare and often rapidly fatal



+ & + / - & -



2003



2008

2005

2012

2015

1996

1993

1987

1983-4

1981

2030

Pre-exposition prophylaxis



“Test and Treat, Treatment As Prevention”

Swiss Statement

# Biomedical prevention

“What do we have in the bag?”

- Condoms
- Adaptive Behaviors
- Treatment as prevention
- Post Exposure Prophylaxis (PEP)
- Pre-exposure prophylaxis (PrEP)
- Male circumcision
- Needle exchange
- (New microbicides)
- (Vaccines)
- Cure



# HIV prevention

## Not ARV-based

- ❑ Male & female condoms
- ❑ Circumcision
- ❑ Clean injecting equipment
- ❑ Vaccines
- ❑ Voluntary counselling and testing
- ❑ Behaviour change

## ARV-based

- ❑ Vaginal and rectal microbicides
- ❑ Preventing vertical transmission
- ❑ PEP
- ❑ PrEP
- ❑ Treatment-as-prevention

# The most effective HIV prevention tool



# Circumcision reduces new infections by 60% in males



**CUT** the risk of **HIV** by **60%**

"Is a medical male circumcision painful?"  
**YOUR QUESTIONS ANSWERED**

**CHOOSE A QUICK, SAFE MEDICAL MALE CIRCUMCISION**

# ARV – The drugs which changed the disease from Fatal to Chronic

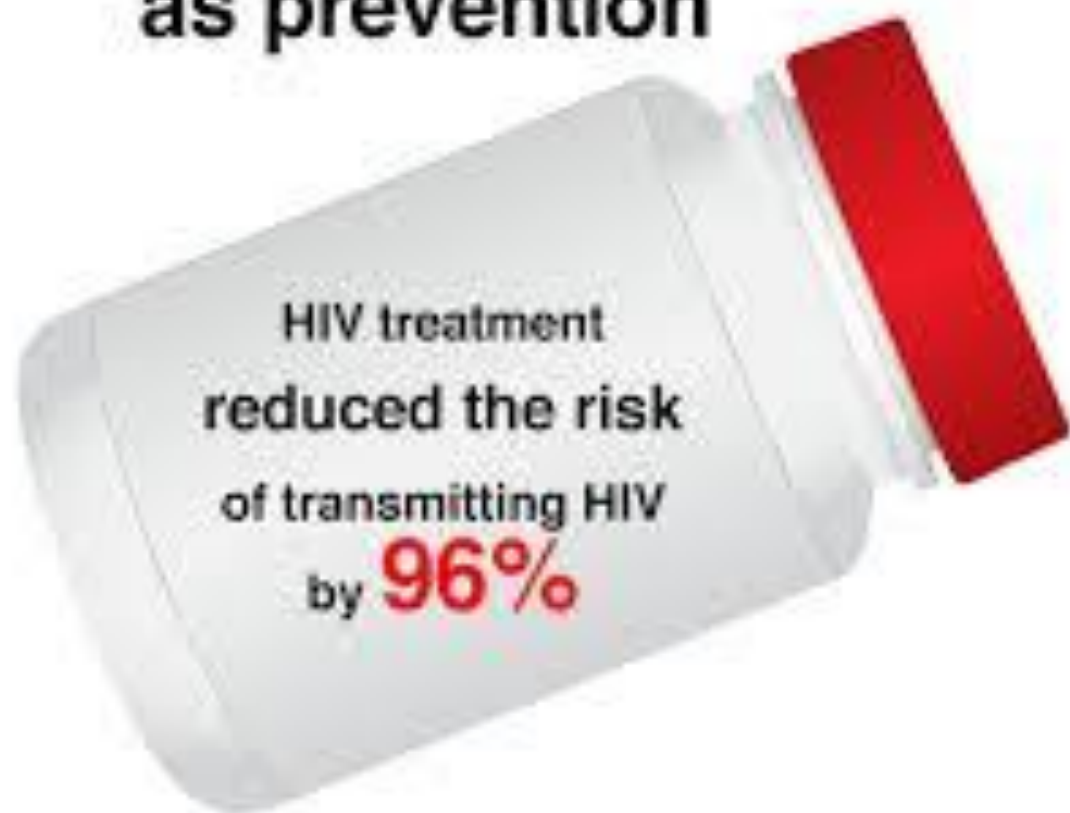
**1996**



**Since 2015**



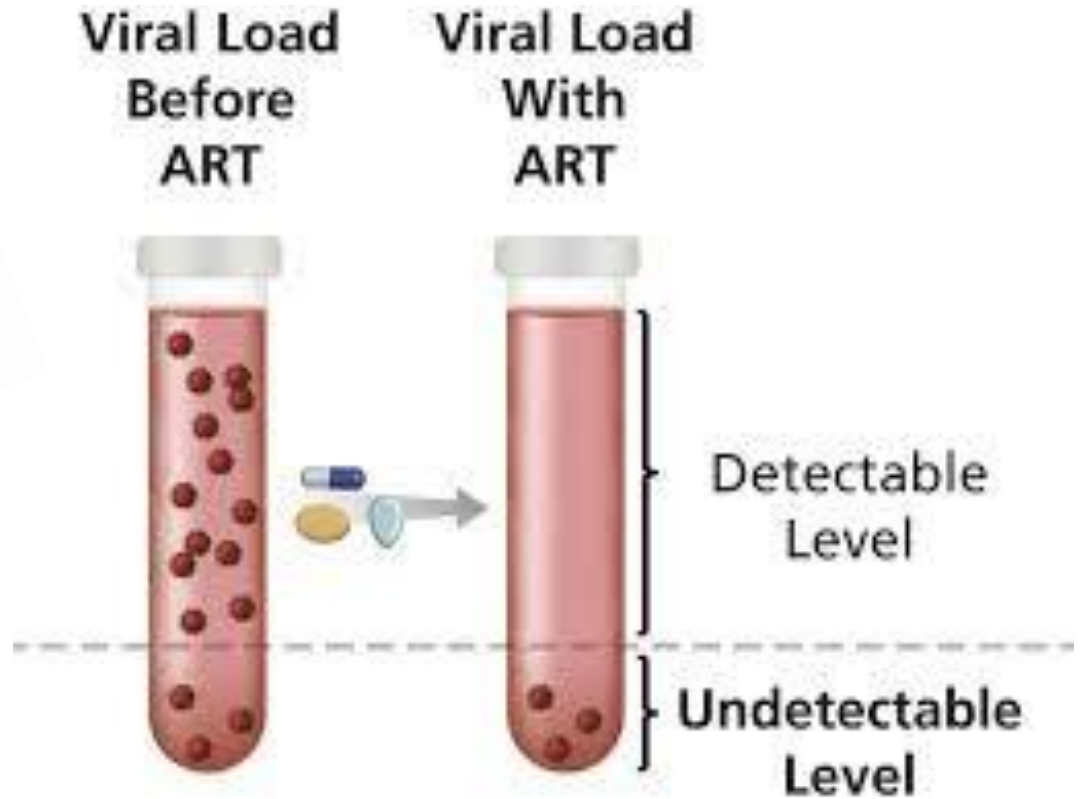
## Treatment as prevention



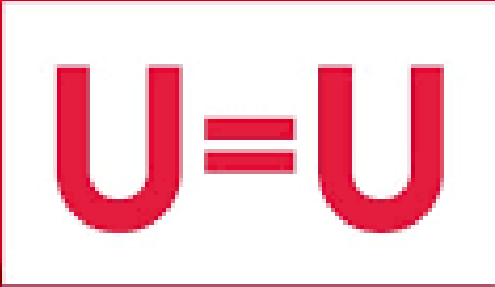
HIV treatment  
reduced the risk  
of transmitting HIV  
by **96%**

# The aim of ARV - UNDETECTED

**HIV STATUS?**  
**UNDETECTABLE**



UNDETECTABLE=UNTRANSMITTABLE



U=U

UNDETECTABLE = UNTRANSMITTABLE

# Rectal Microbicides



## Rectal microbicides

- Anal sex is a risk factor for HIV infection in both men and women
- Rectal mucosa different from the vagina and more vulnerable to HIV
  - single cell layer thick; contains many more CD4 receptors; more alkaline pH which is less protective than the acidic vaginal pH
- Rectal tract has greater surface area



# Vaginal Microbicides



# Elimination of Pediatric HIV

**HIV test in every pregnancy in every woman**

UNDETECTABLE



No Transmission



# Post Exposure Prophylaxis

**Post**

= after

**Exposure**

= a situation where HIV has a chance to get into someone's bloodstream

**Prophylaxis**

= a treatment to stop an infection happening

So...

**PEP**

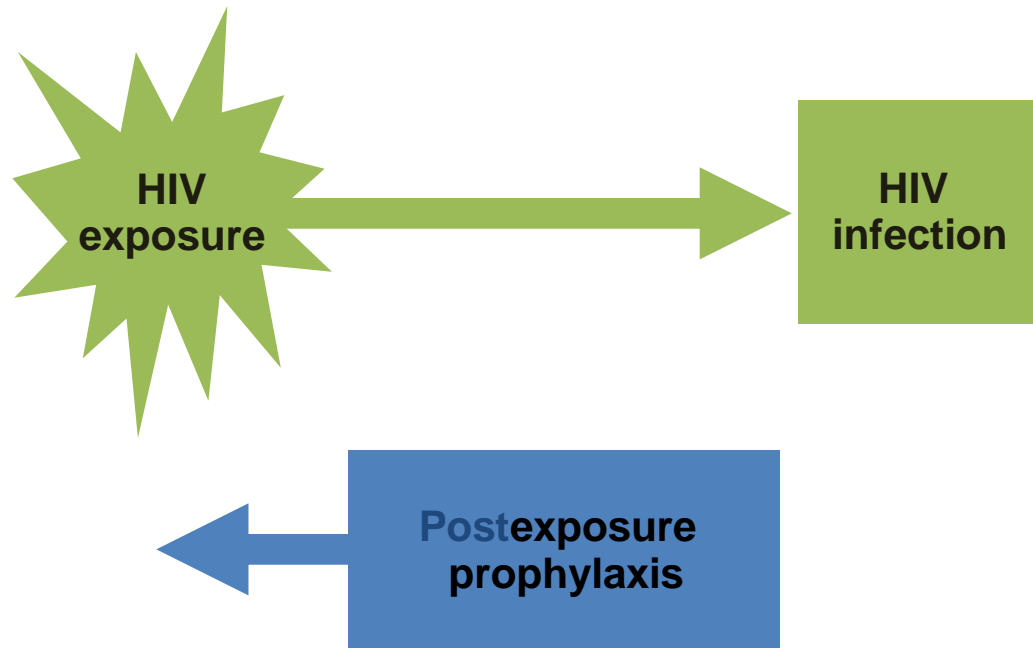
= a treatment to stop a person becoming infected with HIV after it's got into their body

# Pre- vs Postexposure Prophylaxis

- After exposure to HIV, infection may become established

- Postexposure prophylaxis (initiated soon after exposure) reduces the chance of infection

- Pre-exposure prophylaxis begins treatment earlier (before exposure)



0 hr 36 hrs 72 hrs // 1 mos 3 mos 5 mos

PrEP

PrEP



In 2015 PrEP was approved in the US as a prevention tool for HIV infection

I will review the most important studies in :

MSM

Heterosexual population

IVDU

# WHO, CDC, BHIVA, EACS guidelines 2015

## Recommendation

NEW

Oral PrEP containing TDF should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches (*strong recommendation, high-quality evidence*).

## Recommendation

NEW

- ART should be initiated among all adults with HIV regardless of WHO clinical stage and at any CD4 cell count (*strong recommendation, moderate-quality evidence*).
  - As a priority, ART should be initiated among all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with CD4 count  $\leq 350$  cells/mm<sup>3</sup> (*strong recommendation, moderate-quality evidence*).

GUIDELINES

**GUIDELINE ON WHEN  
TO START ANTIRETROVIRAL  
THERAPY AND  
ON PRE-EXPOSURE  
PROPHYLAXIS FOR HIV**

SEPTEMBER 2015

# Proud and Ipergay – 86% effectiveness

PrEP studies offered 86% protection




Public Health England MRC Clinical Trials Unit

## PRE-EXPOSURE PROPHYLAXIS (PrEP)

HIV prevention among gay men, other men who have sex with men and trans-women in the UK

Data published from the PROUD study shows that the anti-retroviral drug Truvada (containing emtricitabine and tenofovir disoproxil fumarate), used as PrEP reduces the risk of acquiring HIV

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 **1 in 17** MSM aged 15 - 59 in the UK living with HIV

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**2800** MSM in UK newly infected with HIV in 2013

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Protection offered against HIV by PrEP **86%**

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**No significant difference** in STIs among MSM on PrEP and those not

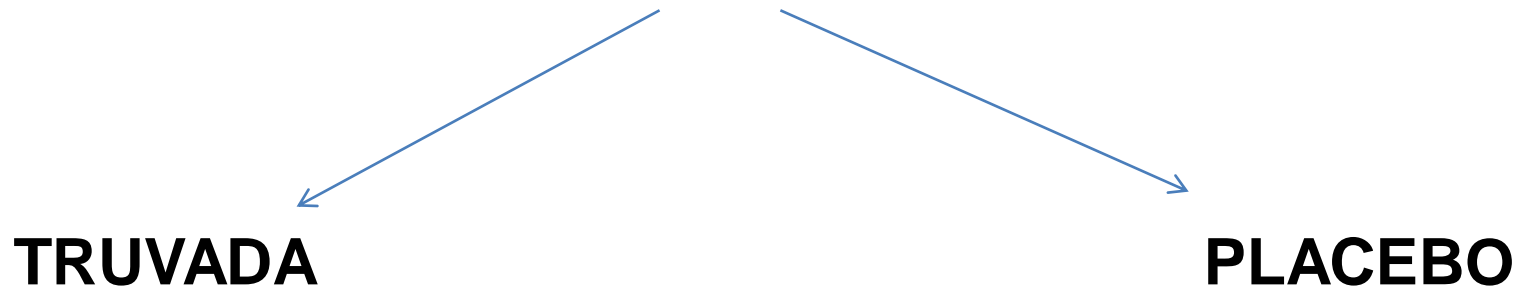
The PROUD study recruited 545 HIV negative gay men, other MSM and trans-women at 13 sexual health clinics in England between November 2012 and April 2014 ([www.proud.mrc.ac.uk/](http://www.proud.mrc.ac.uk/)). Volunteers were randomised to receive PrEP either immediately or after 12 months of follow-up. By October 2014, there had been a total of 22 HIV infections, 3 in the group randomised to PrEP and 19 in the group randomised to wait for a year. This equates to 1.3 infections per 100 people followed up for a year in the group given PrEP, and 6.9 infections per 100 people followed up for a year in the group who did not receive PrEP.

For the UK HIV situation see 'HIV in the United Kingdom: 2014 Report' available at: [www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/401662/2014\\_PHE\\_HIV\\_annual\\_report\\_draft\\_Final\\_07-01-2015.pdf](http://www.gov.uk/government/uploads/system/uploads/attachment_data/file/401662/2014_PHE_HIV_annual_report_draft_Final_07-01-2015.pdf)



# iPrex PrEP study in MSM in the UK

2499 MSM were recruited to a 2-arm study in the UK

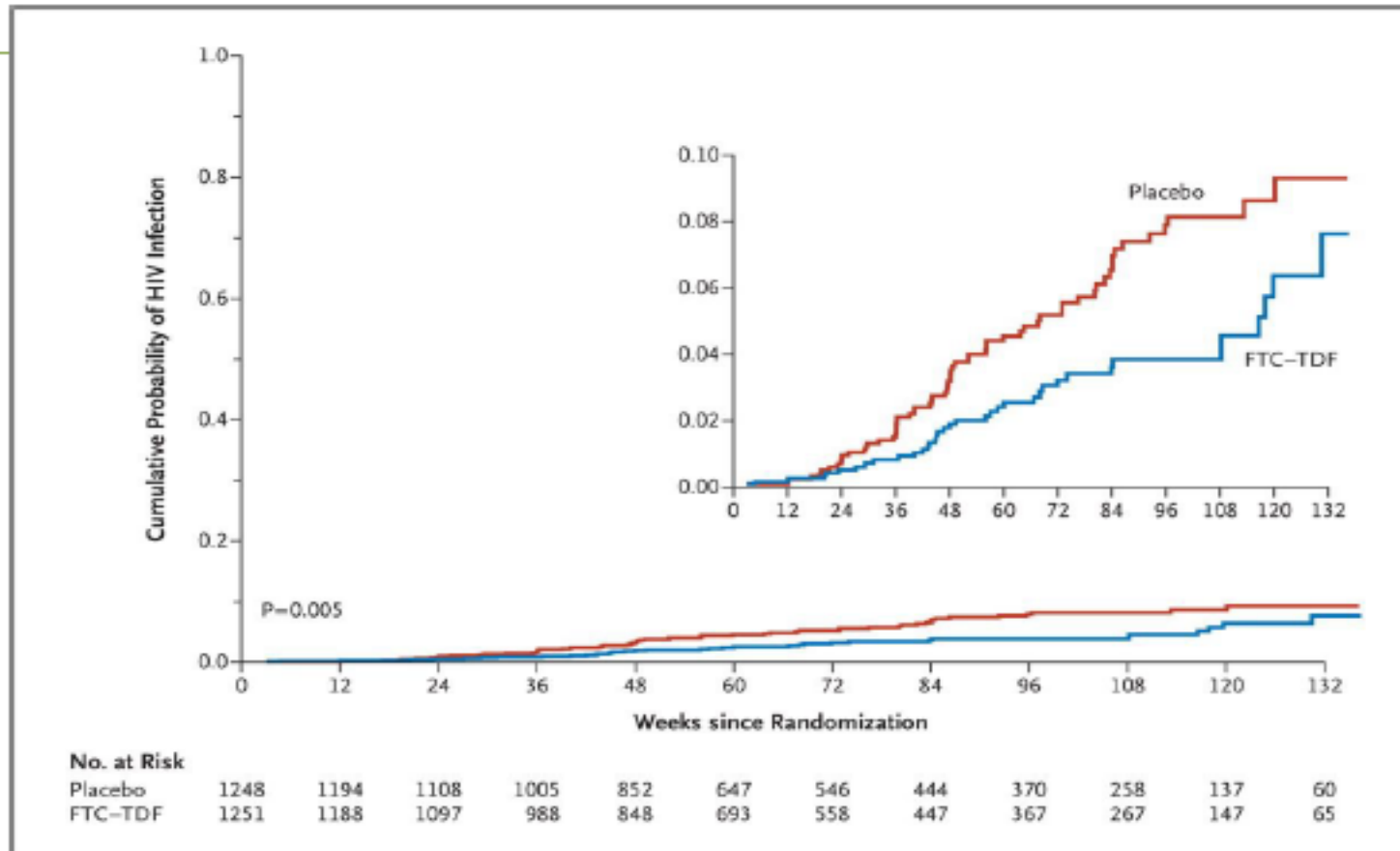


All participants were tested for HIV, STD'd, had consultations and received condoms

Median follow up time 1.2 years

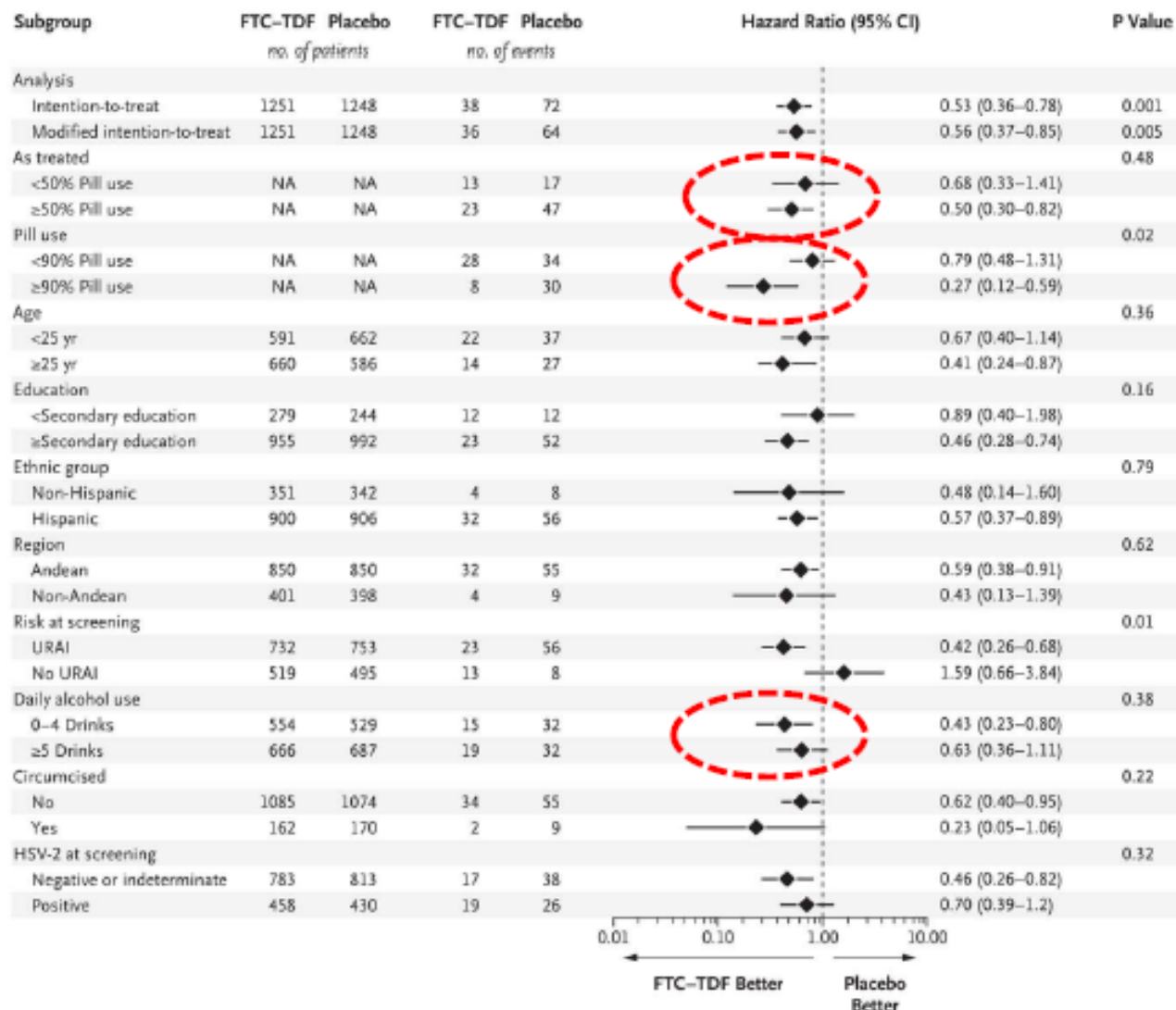
# iPrex PrEP study in MSM in the UK

## Kaplan-Meier Estimates of Time to HIV Infection (Modified Intention-to-Treat Population).



Grant RM et al. *N Engl J Med* 2010;363:2587-2599.





# iPrex Conclusions

- TRUVADA reduced HIV infection by 44% in the treatment group compared to Placebo
- In the TRUVADA group, **effective drug blood level gave 92% protection**
- Drug resistance:
  - 10 were found positive at base-line
  - 3 mutations to FTC
  - 36 New HIV infections during the study w/o mutations

# Iprex Open Label Extension (OLE)

72 Weeks follow up with 1603 HIV negative MSM

Recruited from PrEP studies

Open label

TRUVADA was offered to all participants

72% embarked on treatment immediately

6% later

Higher rates of Unprotected Receptive Anal Intercourse were reported among those who chose to start immediately

# Iprex Open Label Extension (OLE)

Incidence of HIV infection was lower among TRUVADA takers  
(1.8 vs. 2.6 per 100 py)

HR 0.51

No full adherence was required

Treatment with Less than 4 Tabs a week was less effective than  
7 and less than 2 a week was significantly less effective

New HIV Infections occurred due to non-adherence

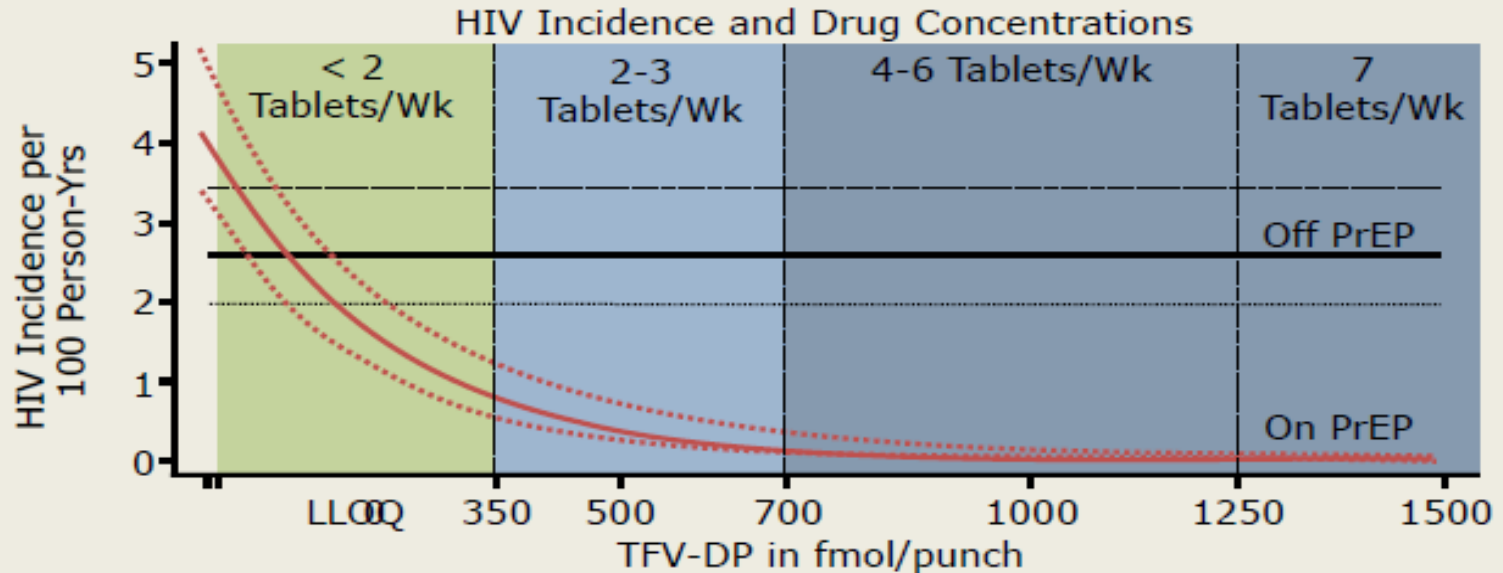
Better adherence : age >30

Unprotected Sex

Many partners

# Treatment with 4 tablets/week is effective

iPrEX OLE: 100% Adherence With Daily PrEP Not Required to Attain Full Benefit



	< 2 Tablets/Wk	2-3 Tablets/Wk	4-6 Tablets/Wk	7 Tablets/Wk
Follow-up, %	26	12	21	12
Risk Reduction, %	44	84	100	100
95% CI, %	-31 to 77	21 to 99	86 to 100 (combined)	

Grant R, et al. AIDS 2014. Abstract TUAC0105LB. Graphic used with permission.

# IPEGAY Background

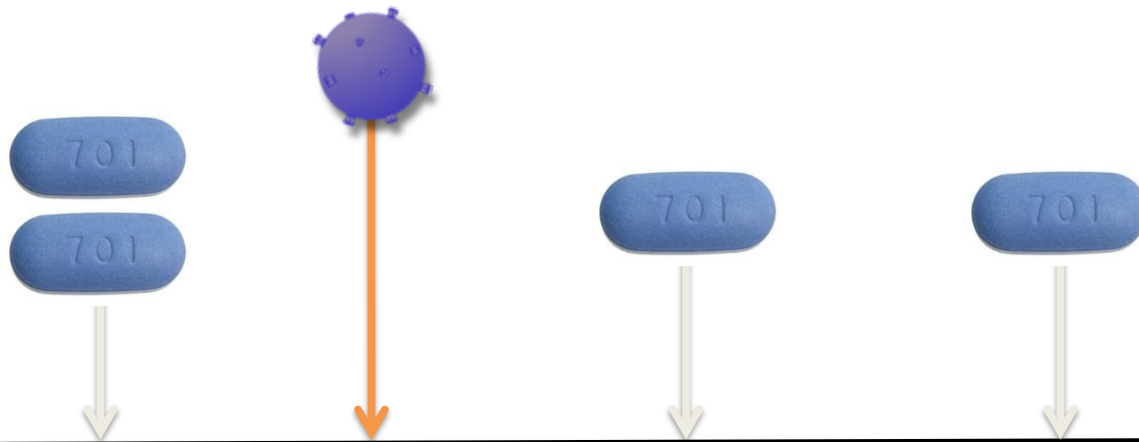
- PrEP trials in Europe and Canada have shown a high incidence of HIV-infection (up to 9%) in high risk MSM
- PROUD and IPEGAY have demonstrated similar high effectiveness of PrEP with oral TDF/FTC **(86%)**
- IPEGAY is assessing coitally-dependent PrEP (2 pills before and 2 pills after sex)
- Participants in IPEGAY have frequent sex and used on average 4 pills/week (15 pills/month)

Off label in Israel



# Intermittent or “On-Demand” Preexposure Prophylaxis Event-Driven Strategy

## HIV Exposure Event



Time

2 tabs 2-24 hours before sex (or 1 pill if most recent dose taken between 1-6 days prior)

1 tab 24 and 48 hours after the last pre-sex dose

# Ipergay: On demand oral PrEP in High Risk MSM

- It is well known that lower compliance will lead to lower efficacy
- The rationale behind the design of the research that ON-demand PrEP and not on a daily basis will increase compliance
- Animal experiments proved efficacy by 2 hours pill pre-event plus 24 hours post exposure pill

# Intermittent or “On-Demand” PrEP for High-Risk MSM

## IPEGAY: Background

### Study Features

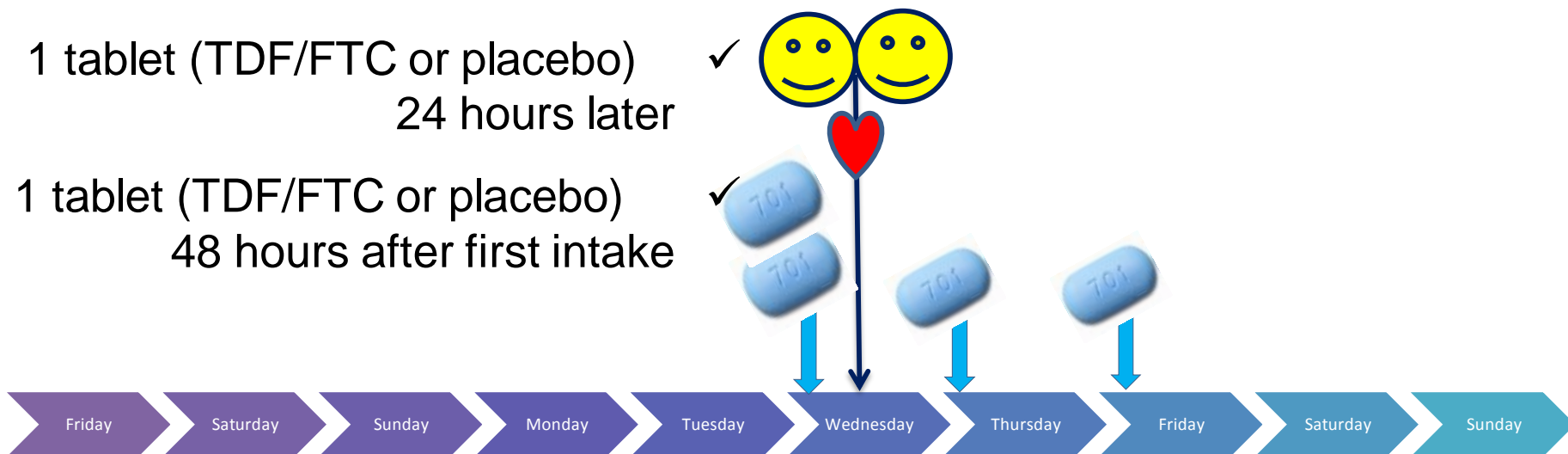
- N = 400 high-risk men-who-have-sex-with-men (MSM)
- Setting: France and Canada
- Condomless anal sex with  $\geq 2$  partners in prior 6 months
- eGFR  $>60$  mL/min
- All received risk-reduction counseling, condoms, and HAV and HBV vaccines if needed, as well as information about PEP
- Randomized to one of two arms

# IPIERGAY : Sex-Driven iPrEP

2 tablets (TDF/FTC or placebo) ✓  
2-24 hours before sex

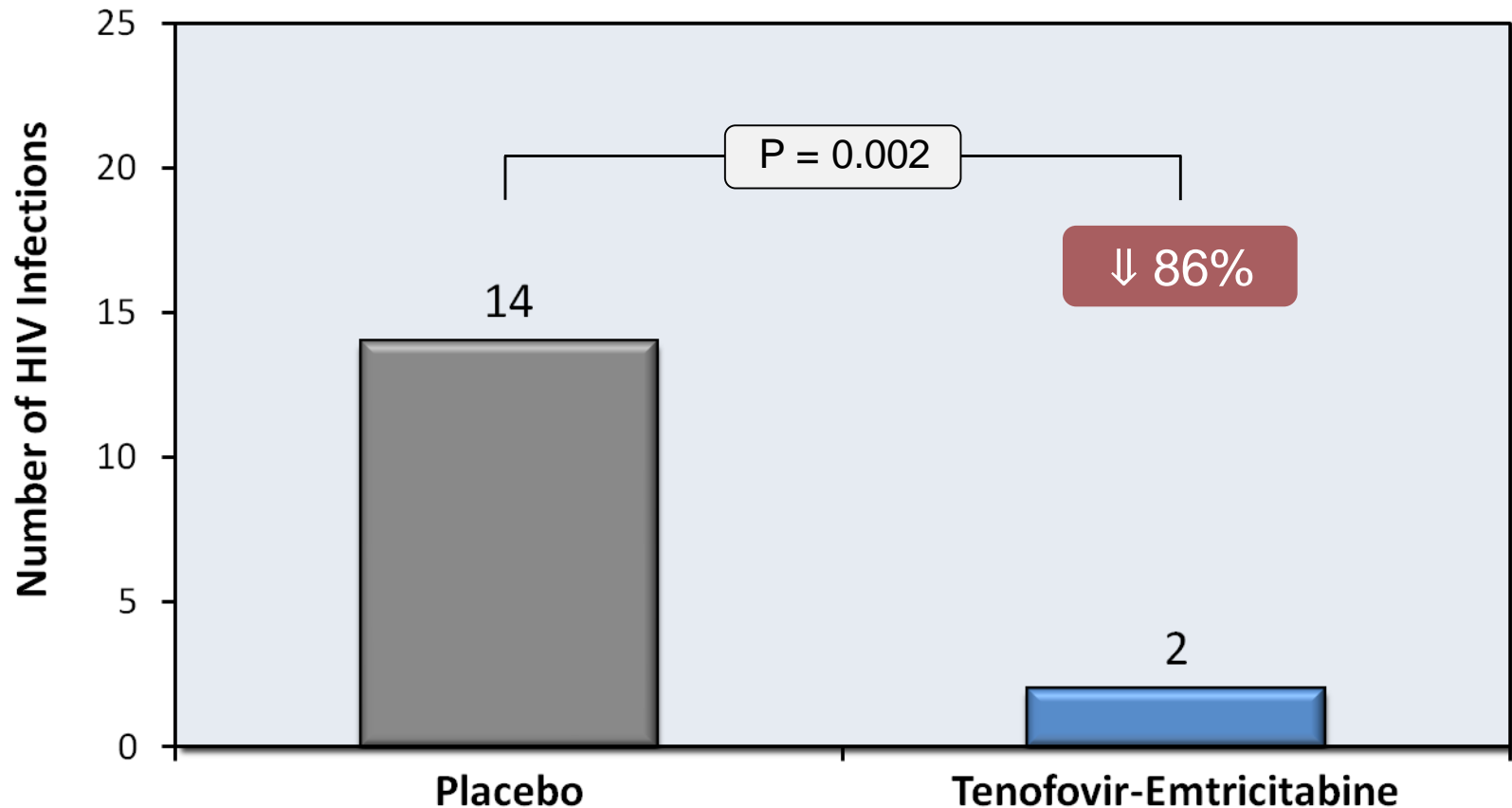
1 tablet (TDF/FTC or placebo) ✓  
24 hours later

1 tablet (TDF/FTC or placebo) ✓  
48 hours after first intake



4 pills of TDF/FTC taken over 3 days to cover one sexual intercourse

# Intermittent or “On-Demand” PrEP for High-Risk MSM IPERGAY: Results



Due to high effectiveness of PrEP, participants unrandomized and all offered PrEP

Source: Molina JM, et al. CROI. 2015; Abstract 23LB.

# Ipergay results

- Truvada ON DEMAND was very effective in HIV prevention in high risk MSM
- 14 New HIV infections in the placebo arm (6.6/100py)
- 2 new HIV infections in the treatment arm – both stopped Truvada prior to infection – **blood drug level was zero (0.9/100py)**
- **Toatal reduction in HIV prevention 86%**
- NNT 18 (Number of individuals neede treatment to prevent 1 infection)
- Participants took mean of 15 tablets/ month

# Intermittent PrEP

*“Yes, a little bit stupid. For me sex is something spontaneous and not something you plan, okay I’m having sex in three days and I’ll start taking PrEP. No, I think that is nonsense.” MSM 9*

## Motives for preferring intermittent PrEP over daily PrEP

The decision to start is easier

Reduction in side-effects

Reduced financial costs

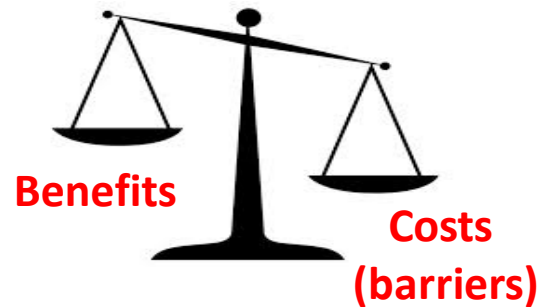
## Motives for preferring daily PrEP over intermittent PrEP

Requires unwanted planning of sex life

Makes adherence to other HIV prevention strategies more difficult

# Benefits vs. Barriers

Future PrEP use depends on personal evaluation of benefits and costs



Intermittent PrEP:

Lower initiation threshold - can reduce economic costs and side-effects  
Rather for men who want/are able to plan their sex life or risk episodes



# **Proud: Immediate vs deferred PrEP in High Risk MSM in “real world”**

- Open label study with daily Truvada  
Was conducted in 13 STD clinics in UK
- Target population – MSM who practiced condomless UAS during the last 90 days
- 275 – Immediate treatment arm
- 269 – deferred arm to 12 months later

**The research was terminated earlier due to significant differences between the 2 arms**

# **Proud: Immediate vs deferred PrEP in High Risk MSM in “real world”**

- 20 individuals contracted HIV in the deferred arm in spite of 174 PEP courses (9/100 py)
- 3 individuals contracted HIV in the treatment arm – all 3 did not take treatment during infection (1.2/100 py)
- **86% reduction in HIV infections**
- NNT - 13 (number persons needed to treat to prevent 1 infection)

# PreP in Heterosexual Partners

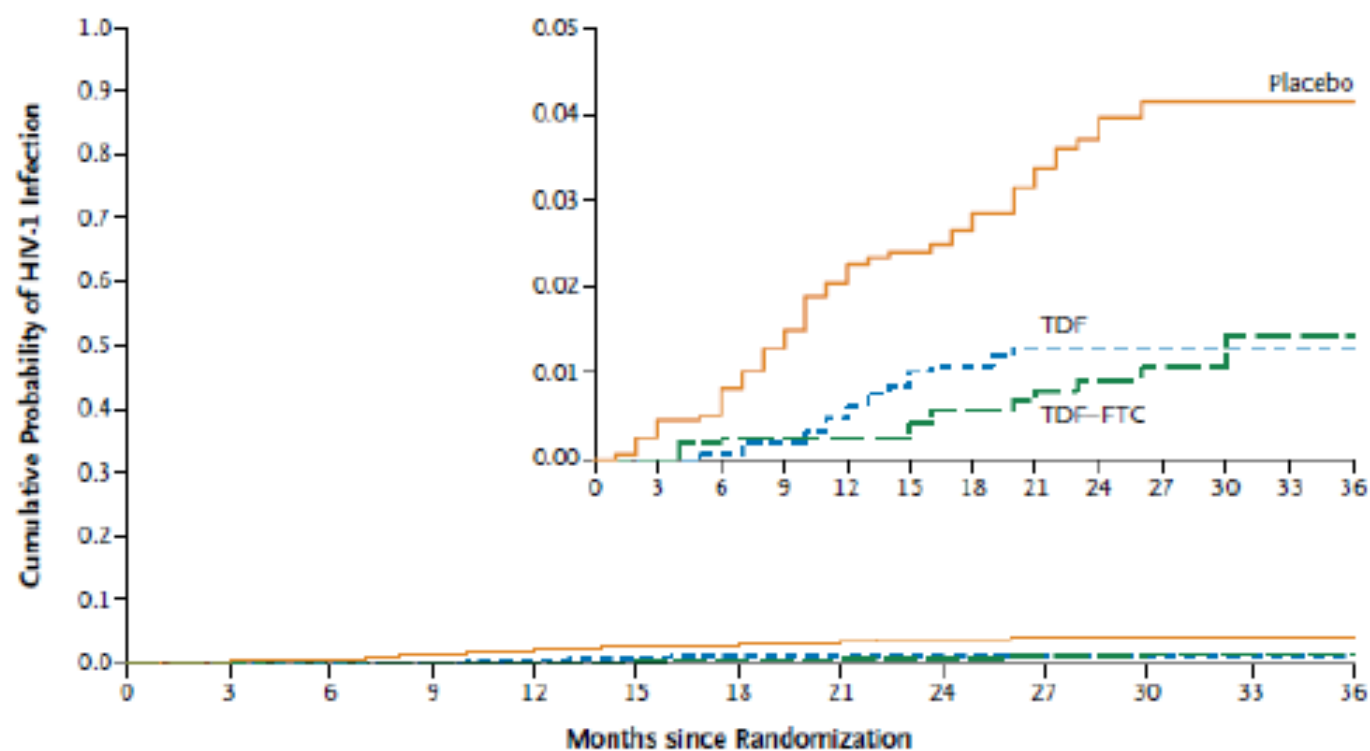
- **Partners PrEP** <sup>(1)</sup>

- 4758 Hetero-discordant couples
- HIV-positive carriers did not receive ARV due to high CD4 levels
- 1584 – TDF
- 1579 – TRUVADA
- 1584 – PLACEBO

**Reduction in HIV acquisition:**

- 67% in TDF
- **75% in TRUVADA**
- **In those with effective blood drug levels – 90%**  
(2)
- Drug resistance: 3/8 on base line (acute infection)
- No Drug Resistance among 23 new infections during the study

# Partners PrEP



## No. at Risk

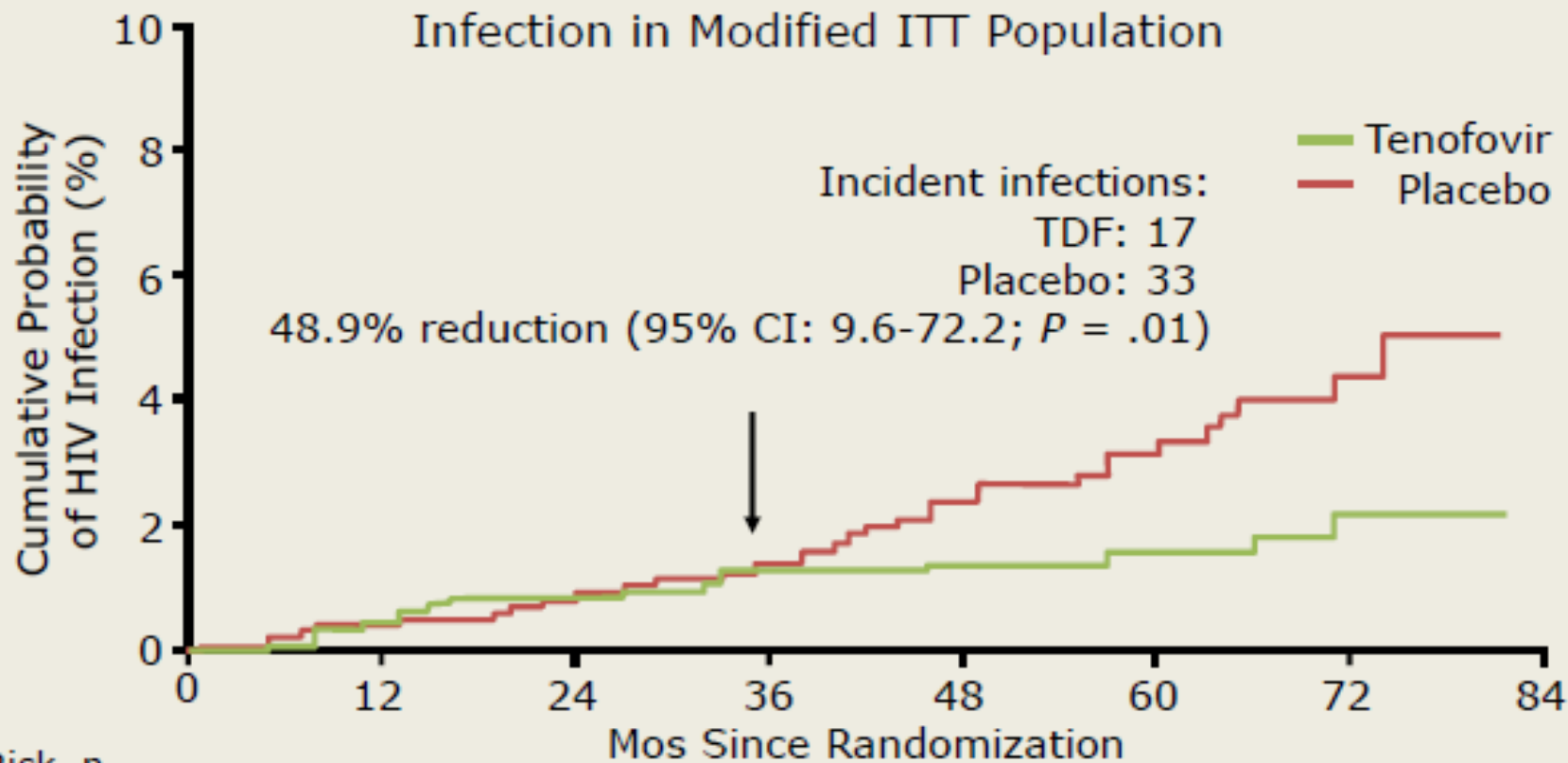
TDF	1572	1559	1547	1498	1350	1223	1062	902	735	510	287	108	15
TDF-FTC	1568	1557	1546	1493	1371	1248	1059	901	743	525	291	114	16
Placebo	1568	1557	1544	1487	1347	1224	1061	902	744	523	295	120	18

**Figure 2.** Kaplan-Meier Estimates of the Primary End Point in the Modified Intention-to-Treat Analysis, According to Study Treatment.

# PrEP for IDUs: Results



Kaplan-Meier Estimates of Time to HIV Infection in Modified ITT Population



Pts at Risk, n

Tenofovir	1204	1007	933	857	736	521	241
Placebo	1207	1029	948	844	722	500	234

# PrEP for IDU results

Efficacy was 40-60% and 74% in those with good blood drug level

Risk behavior decreased over time

No drug resistance during the study

# PrEP in Israel

- PrEP was approved in Israel in September 2017
- The program is in collaboration between the Israeli HIV Association, The patients' NGO, HMO's, TEVA – the Israeli generic drug company
- There is a patients' co-payment (10% of the cost)
- The rest is payed by the medical insurance companies
- Physicians must go through educational program to be eligible to prescribe PrEP



הוועד למלחמה באידס  
ISRAEL AIDS TASK FORCE



Generic EMTRIVIR



Emciticabine/Tenofovir disoproxil  
Fumarate

- Protocol PrEP for Family Physicians with an educational program, include evidence based data about the efficacy of PrEP
- Sexually Transmitted Diseases and treatment
- How to talk about sex with MSM
- The Israeli Program, protocol and follow up





## Criteria for eligible patients on PrEP

- Male or female partner of an HIV + patient which do not take ARV or with poor compliance
- Men who practice unprotected sex with men
- Sexually Transmitted Disease in the last six months
- Commercial sex workers (females and males)

# HIV testing protocol

- Before starting PrEP the patient must have a recent HIV negative test (Combo)
- In a case of symptoms of acute HIV infection and a case of exposure in the last month, PrEP should be delayed in one month till a new negative HIV result is achieved



**Diagnosis - COMBO (Ag+Ab) for HIV**

# Routine follow up during PrEP treatment



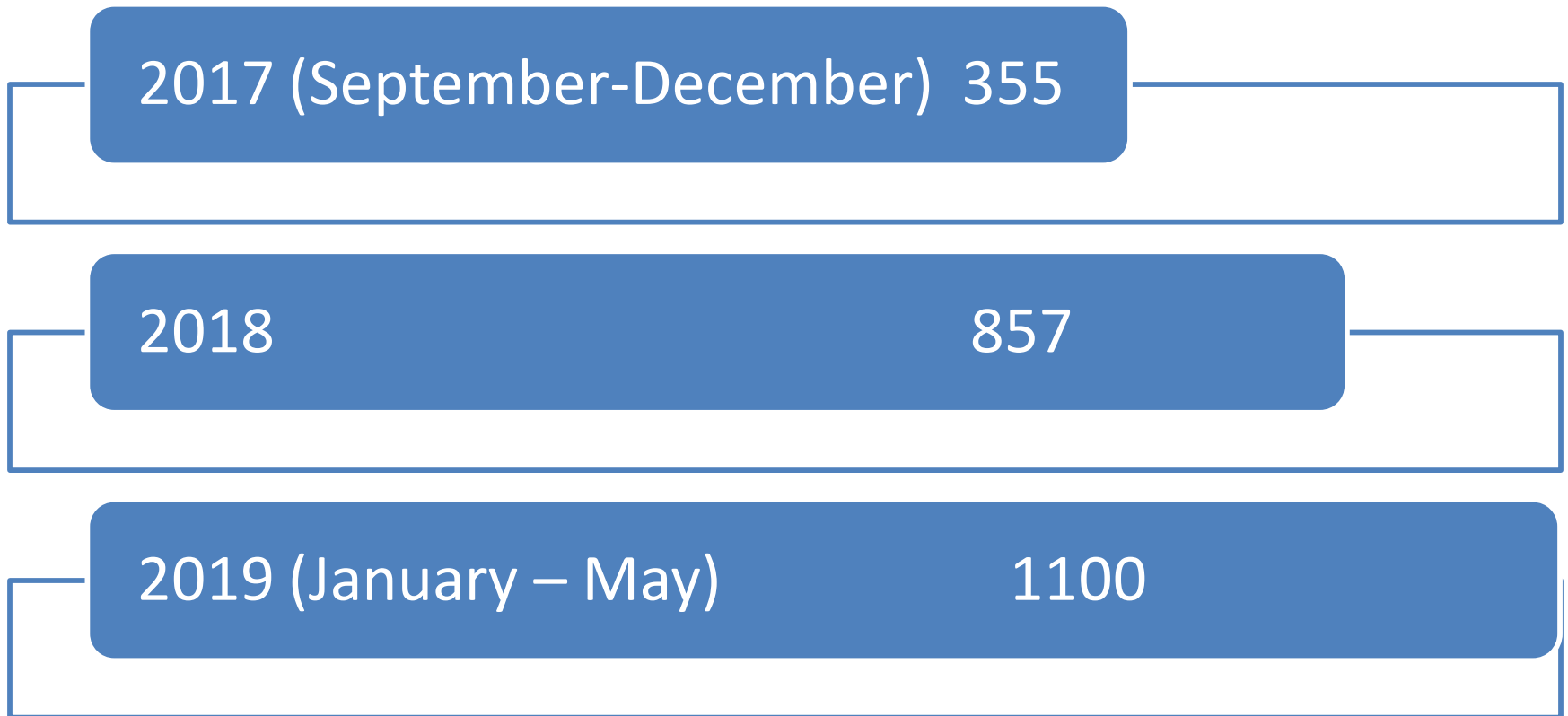
- **HIV test every 3 months**
- **HBV, HCV, Kidney function test, STD'S , urine protein every 3 months**

The logo consists of the text "PrEP" in white, bold, sans-serif font, centered within a light blue rounded rectangle. This rectangle is set against a larger, light beige rounded rectangle background.

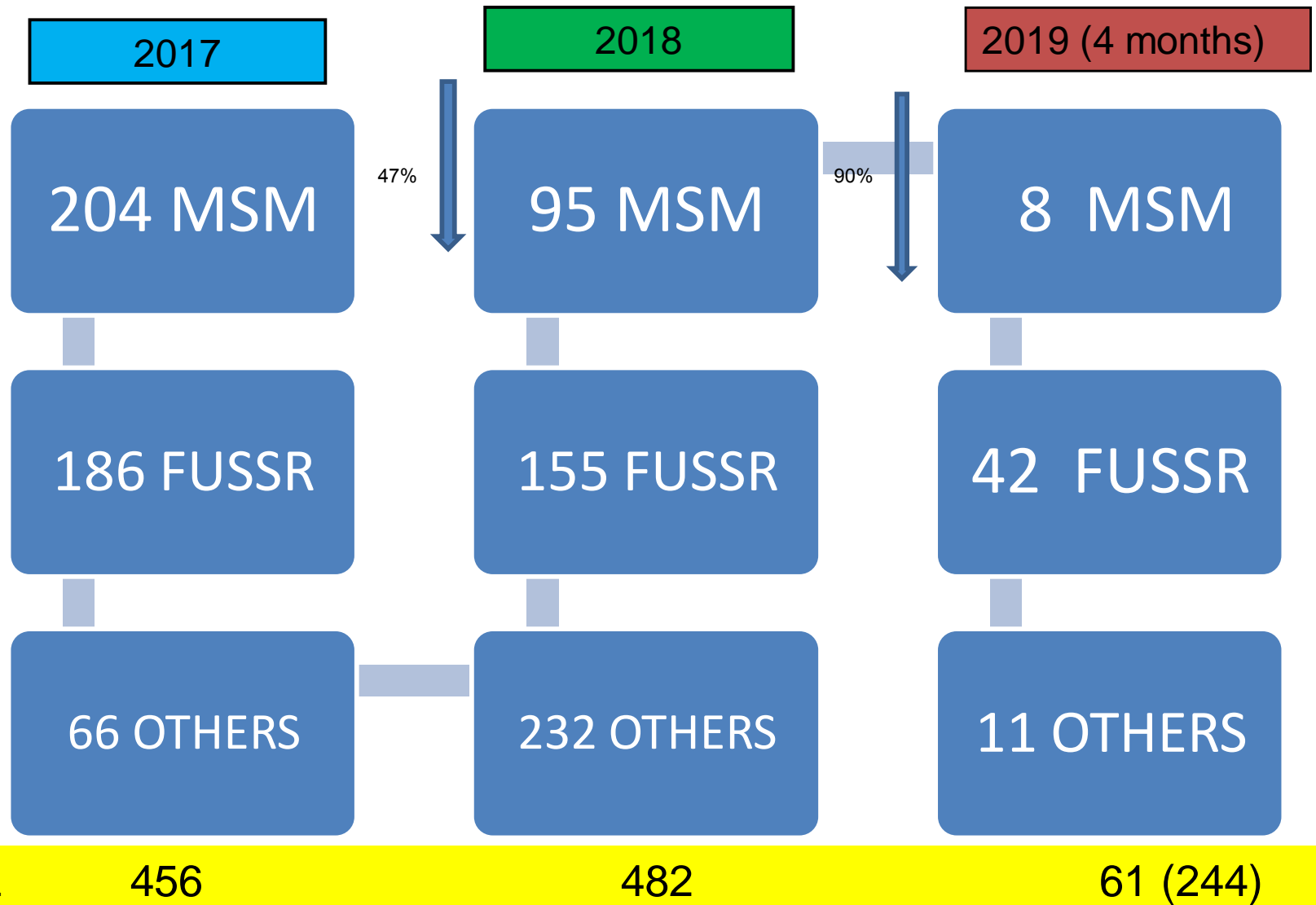
## Time Table for visits and testing

Frequency	Medical Service
Before PrEP and every 3 months	Medical doctor evaluation
Before PrEP and every 3 months Make sure EGFR is > 60	Kidney function evaluation
Before PrEP and every 3 months	HIV Combo test
Before PrEP and every 3 months	Syphilis, gonorrhea, chlamydia test
Before PrEP – if negative - Vaccinate	HBV serology
Before PrEP and every 3 months	HCV serology
Every 3 months	Prescription to PrEP

# PrEP uptake in Israel (numbers of takers)



# New HIV infections in Israel

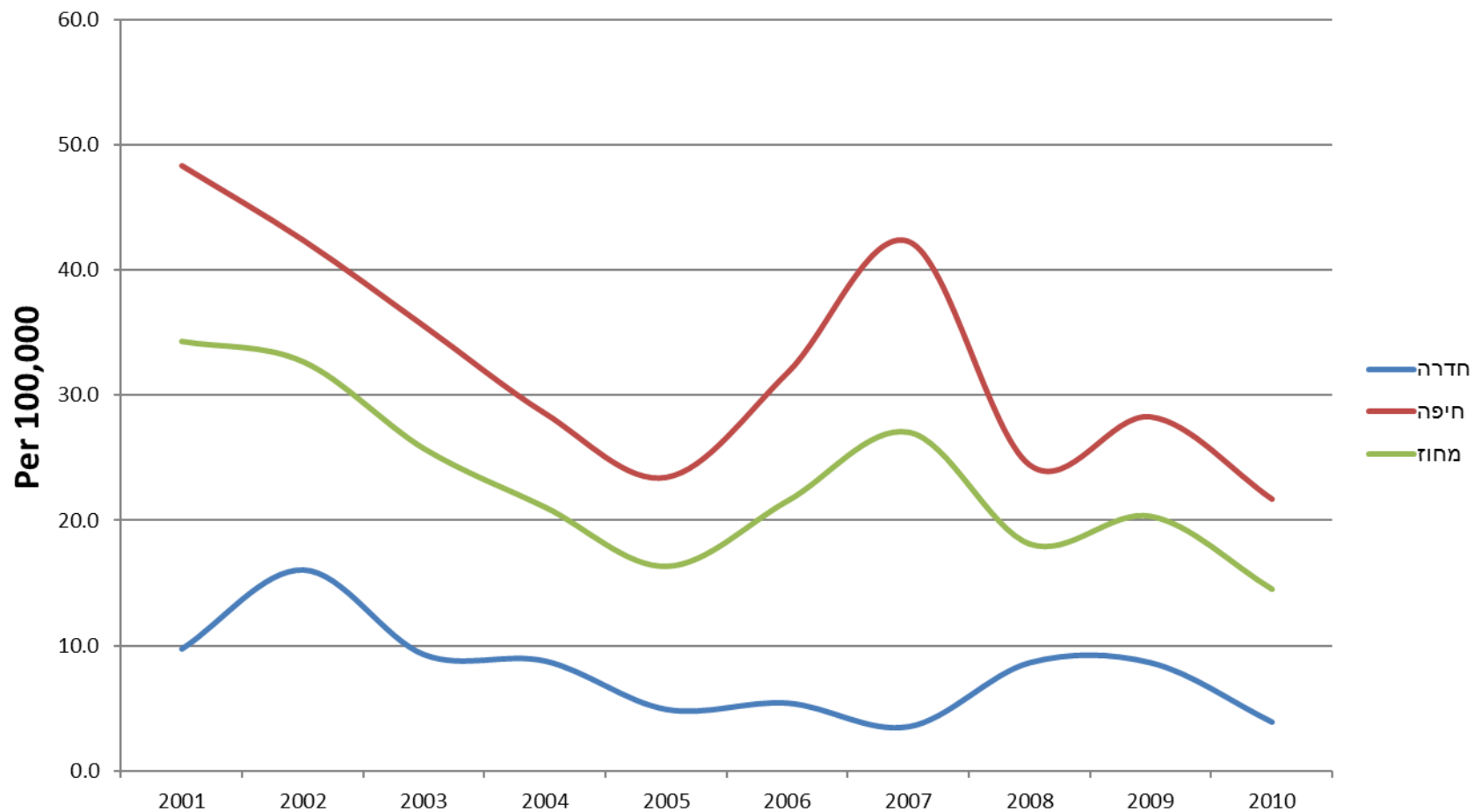


Others: immigrants from Ethiopia, hetero, women

# Sexually Transmitted Diseases in North Israel

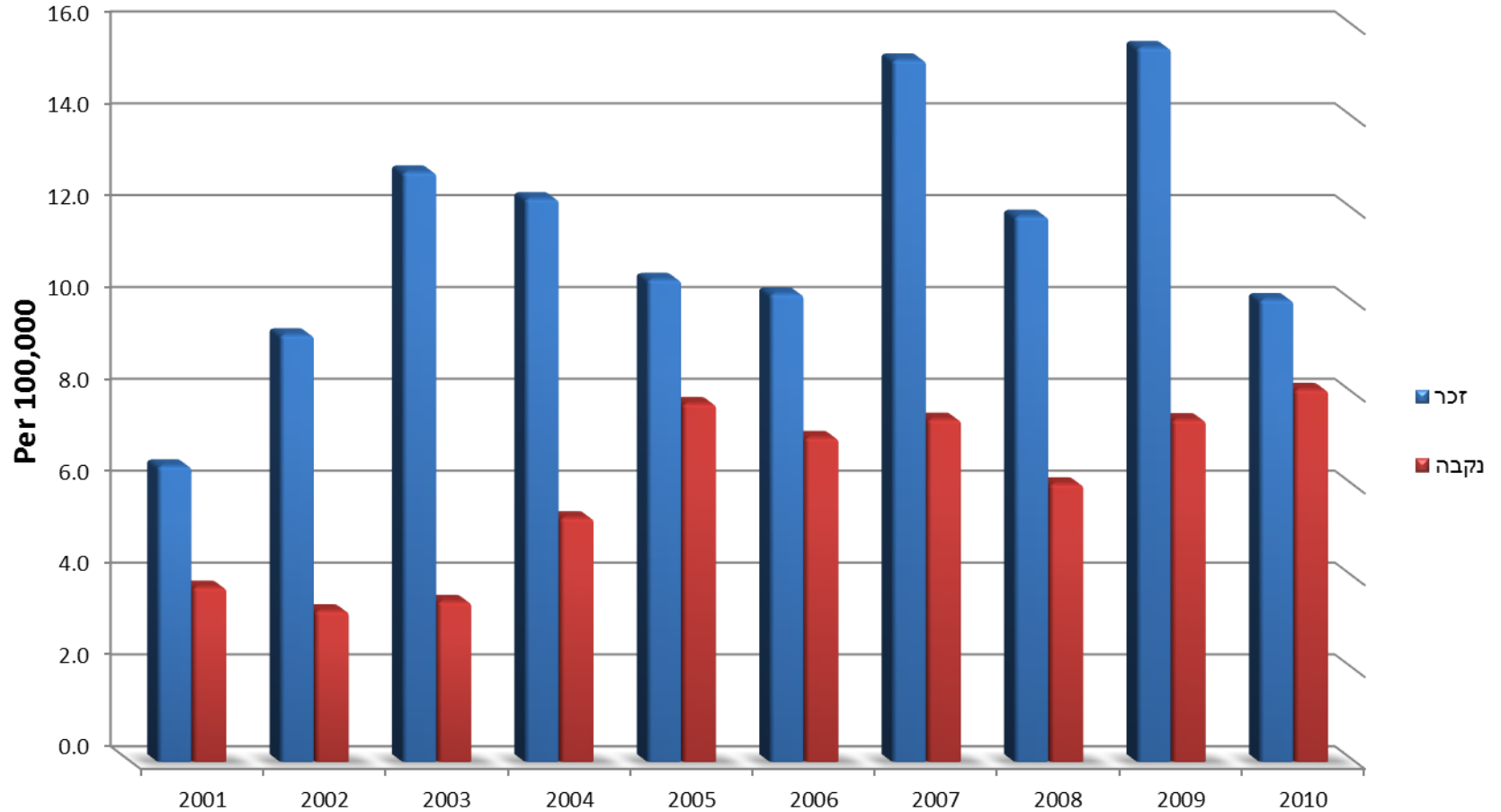
	Years										
Total	2010	2009	2008	2007	2006	2005	2004	2003	2002	2001	
681	21	38	30	53	26	19	57	108	160	169	Gonorrhea
748	81	102	78	99	74	78	74	68	52	42	Chlamydia Trachomatis
86	11	16	16	25	9	8	0	1	0	0	Other STD's
129	2	5	1	1	3	3	6	10	34	64	Syphilis – primary & secondary
340	15	21	34	57	74	32	42	30	27	8	Syphilis - late
1984	130	182	159	235	186	140	179	217	273	83	Total

# Prevalence of STD's in north Israel

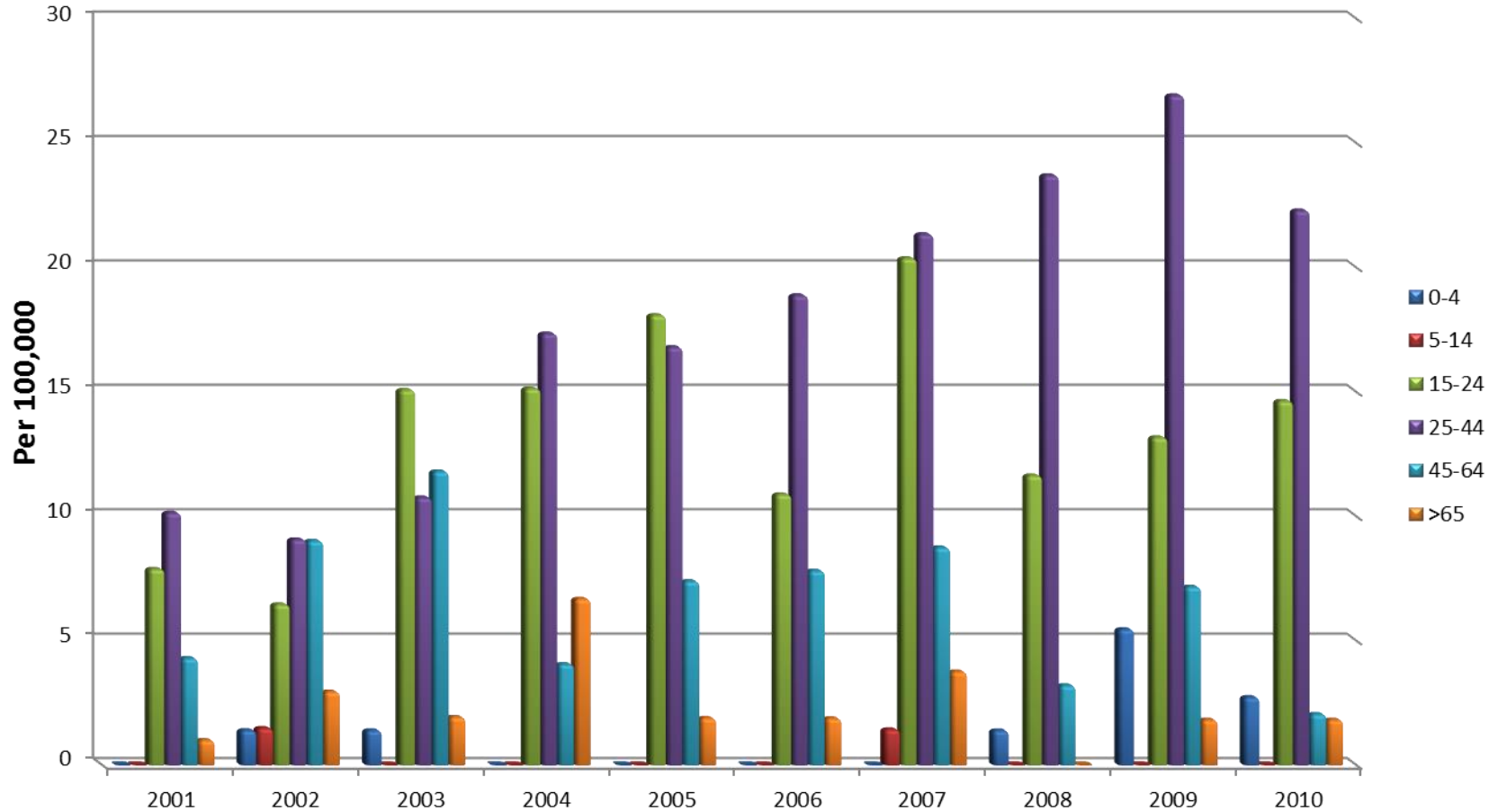




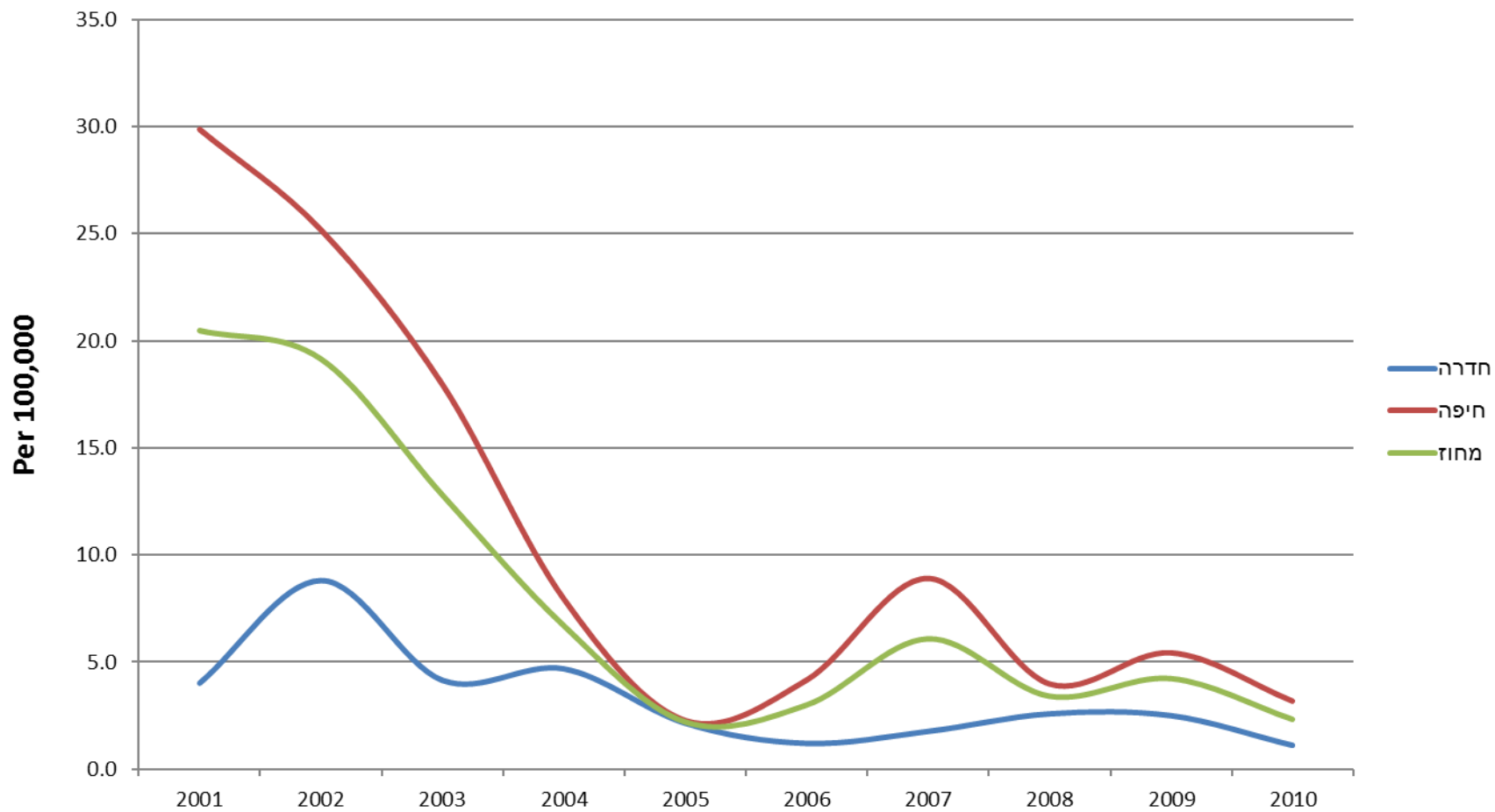
# Prevalence of Chlamydia



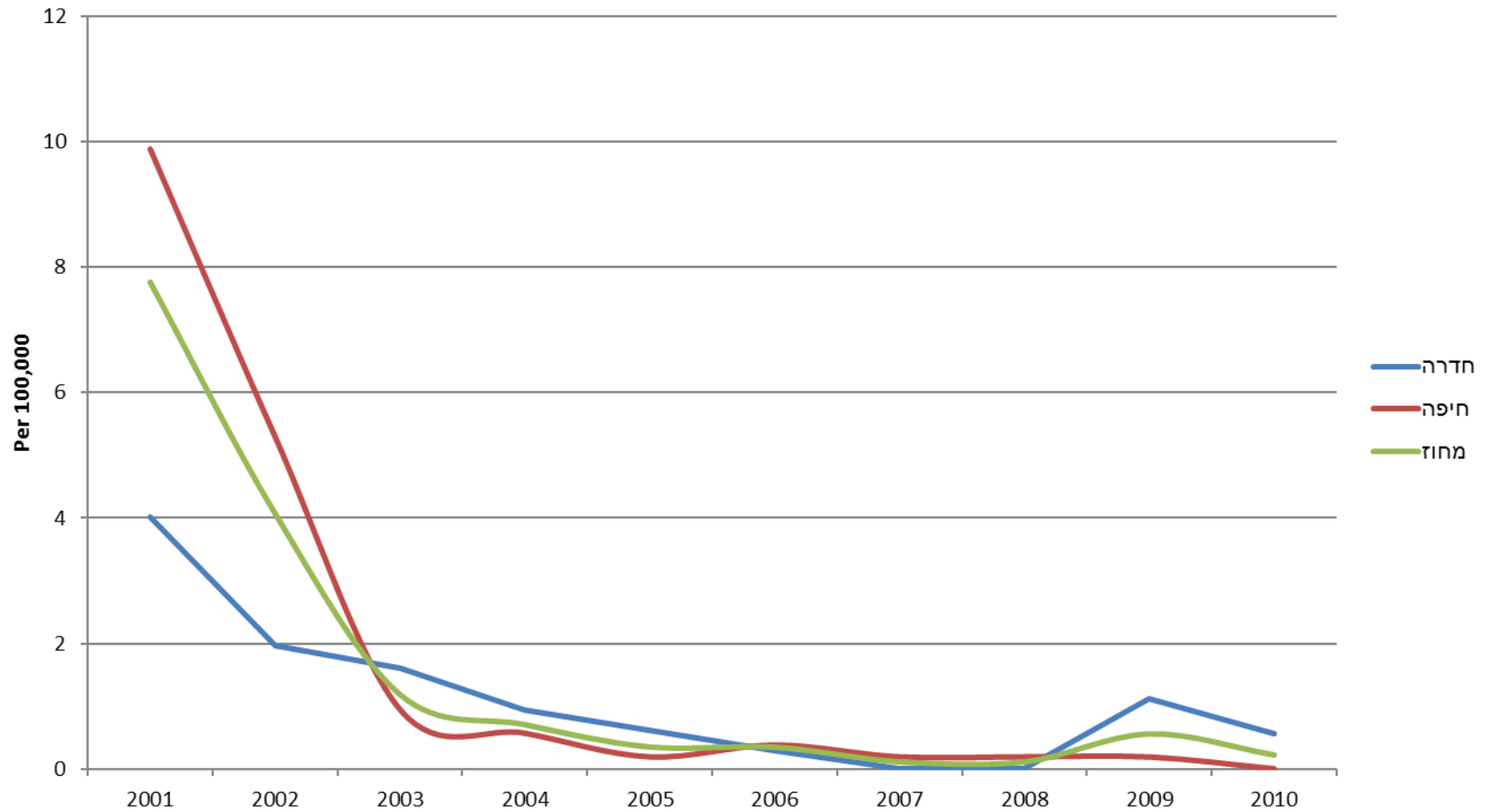
# Prevalence of chlamydia by age



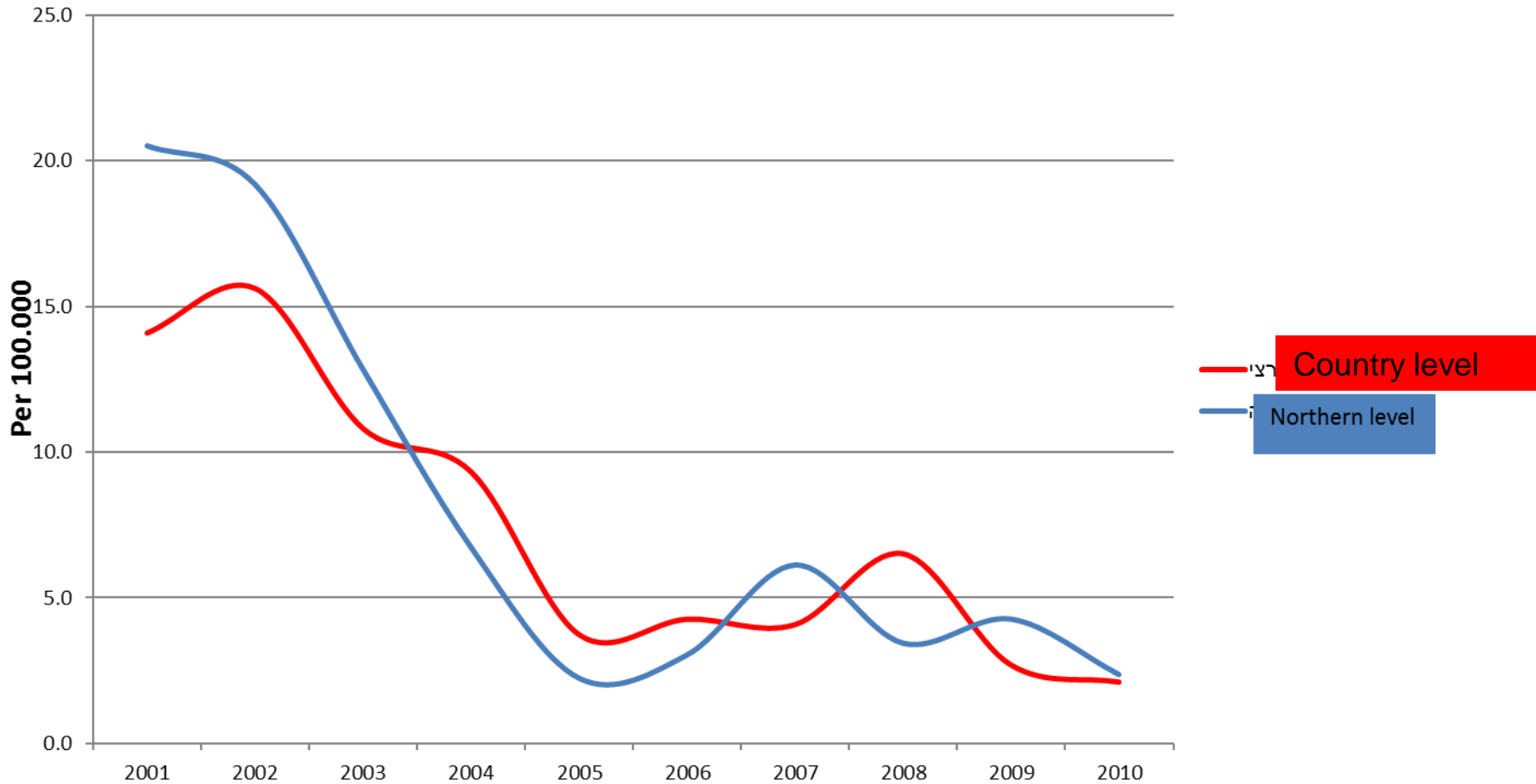
# Prevalence of Gonorrhea



# Prevalence of Syphilis – primary & secondary

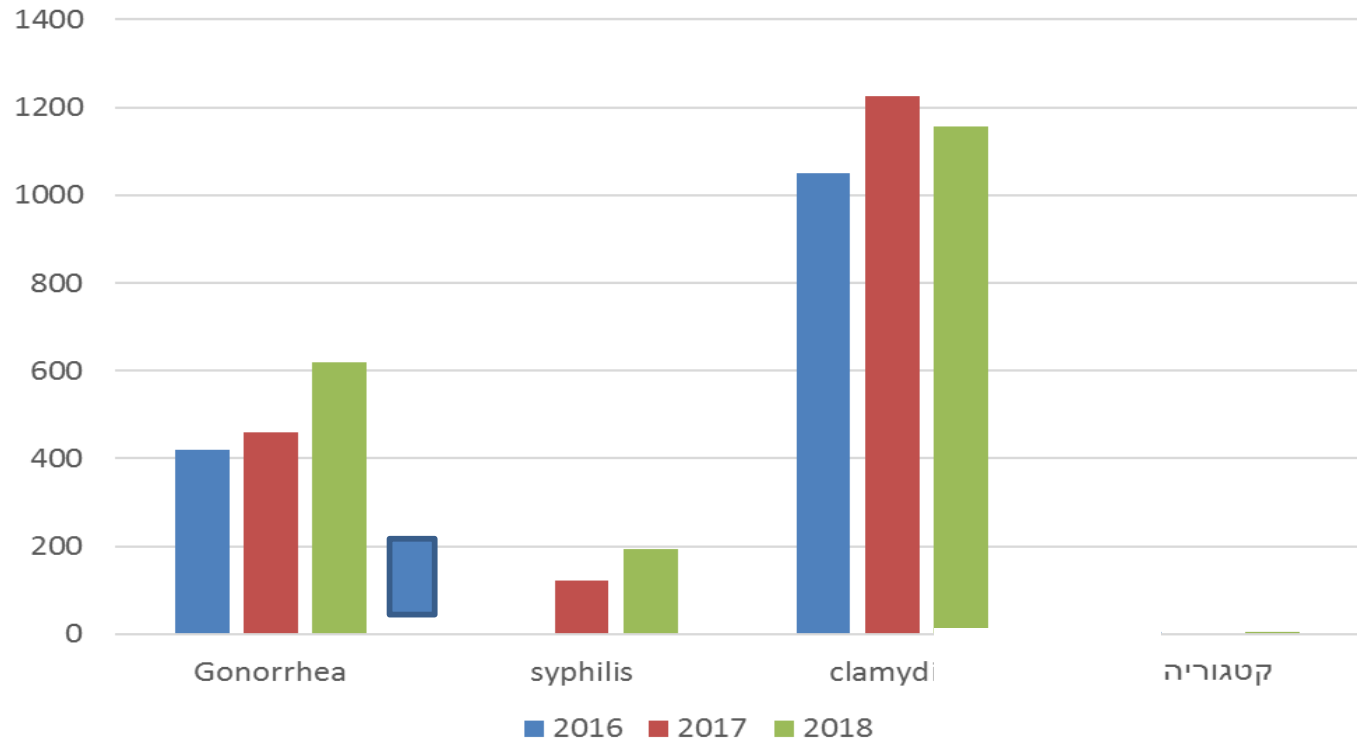


# Prevalence of Gonorrhoea in Northern Israel as compared to Country level



# No evidence of a rise in STD's since PrEP program in Israel

## Gonorrhea cases in Israel 2016-2018

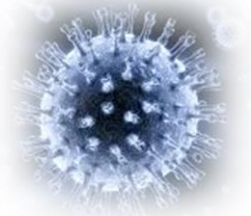


# ENDING THE URBAN AIDS EPIDEMIC

## RARE CANCER SEEN IN 41 HOMOSEXUALS

Outbreak Occurs Among Men in New York and California — 8 Died Inside 2 Years

By LAWRENCE K. ALTMAN  
Doctors in New York and California have diagnosed among homosexual men 41 cases of a rare and often rapidly fatal



+ & + / - & -



2003



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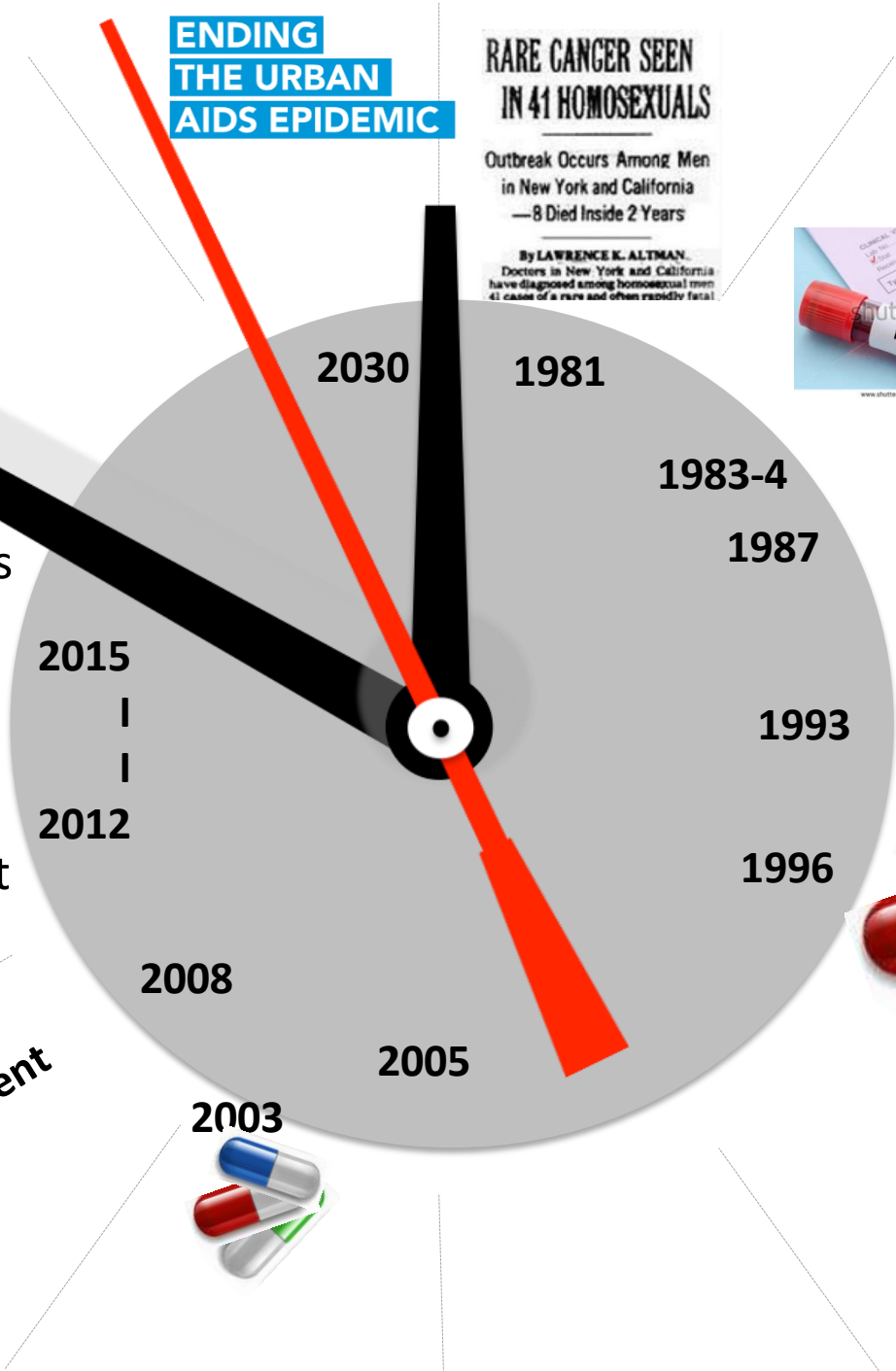
2030

Pre-exposition prophylaxis

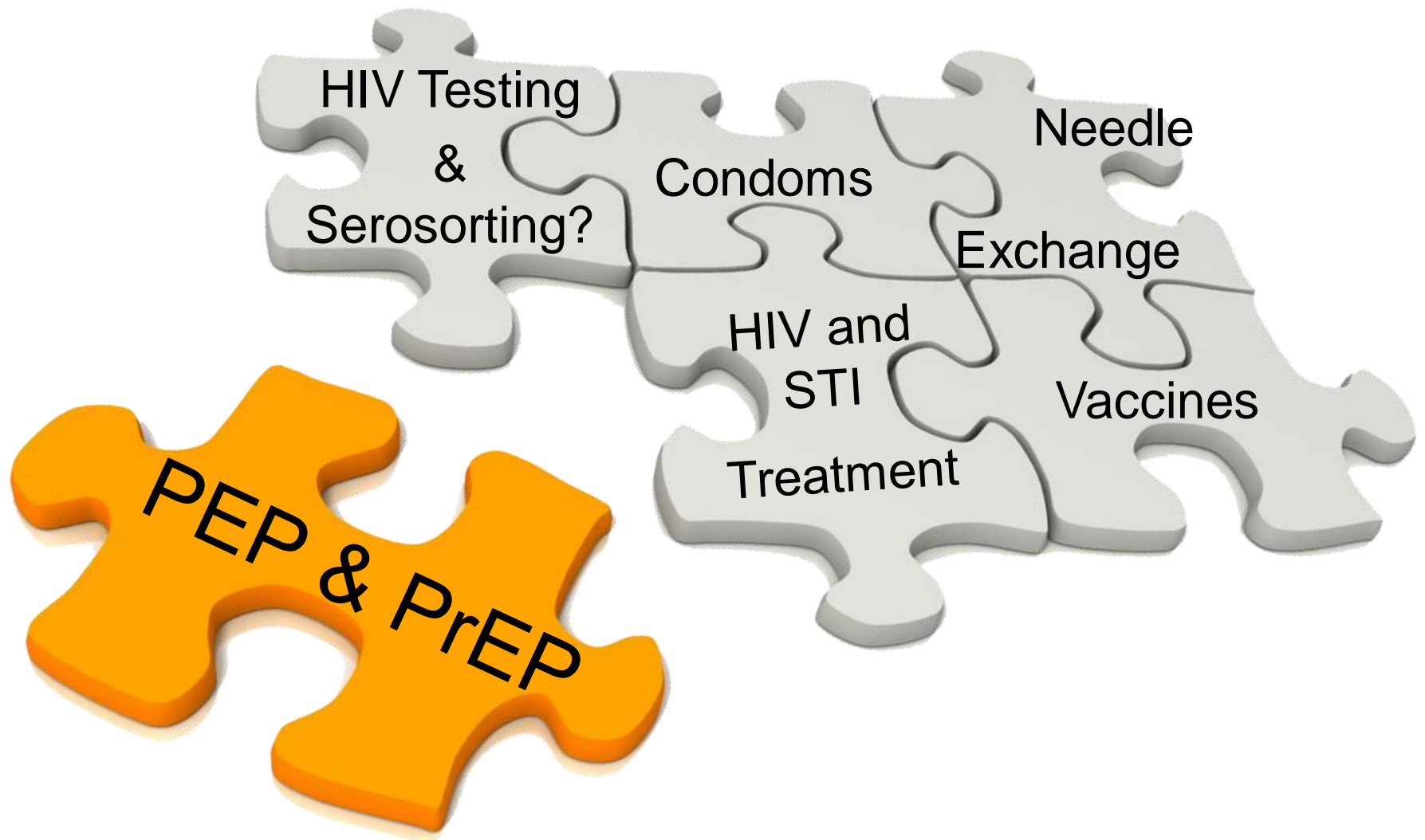


“Test and Treat, Treatment As Prevention”

Swiss Statement



# Conclusion: “Highly active HIV prevention”





GETTING  
TO ZERO

ZERO  
NEW  
INFECTIONS

ZERO  
DISCRIMINATION

ZERO  
AIDS RELATED  
DEATHS

It does not care  
**“Getting to Zero”**  
about color, race  
religion or culture.

LET'S

END IT

