

Ending HIV: the treatment revolution and the cure

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The Treatment Revolution

Which side of the barricade?



UN Political Declaration on HIV/AIDS – Australia a signatory (June 2011)

- **reducing transmission of HIV by 50 per cent by 2015;**
- **elimination of mother-to-child transmission of HIV and substantially reducing AIDS-related maternal deaths by 2015,**

NSW goal and targets.

- Vision: To achieve the virtual elimination of HIV transmission by 2018.
- Targets. By 2015,
 - To sustain the virtual elimination of HIV transmission:
 - from mother to child
 - among people who inject drugs
 - among sex workers
 - To reduce the sexual transmission of HIV by 50%
 - among Aboriginal people – 50%
 - among Gay and homosexually active men – 50-80%

Do not ask “how's the revolution going” to:

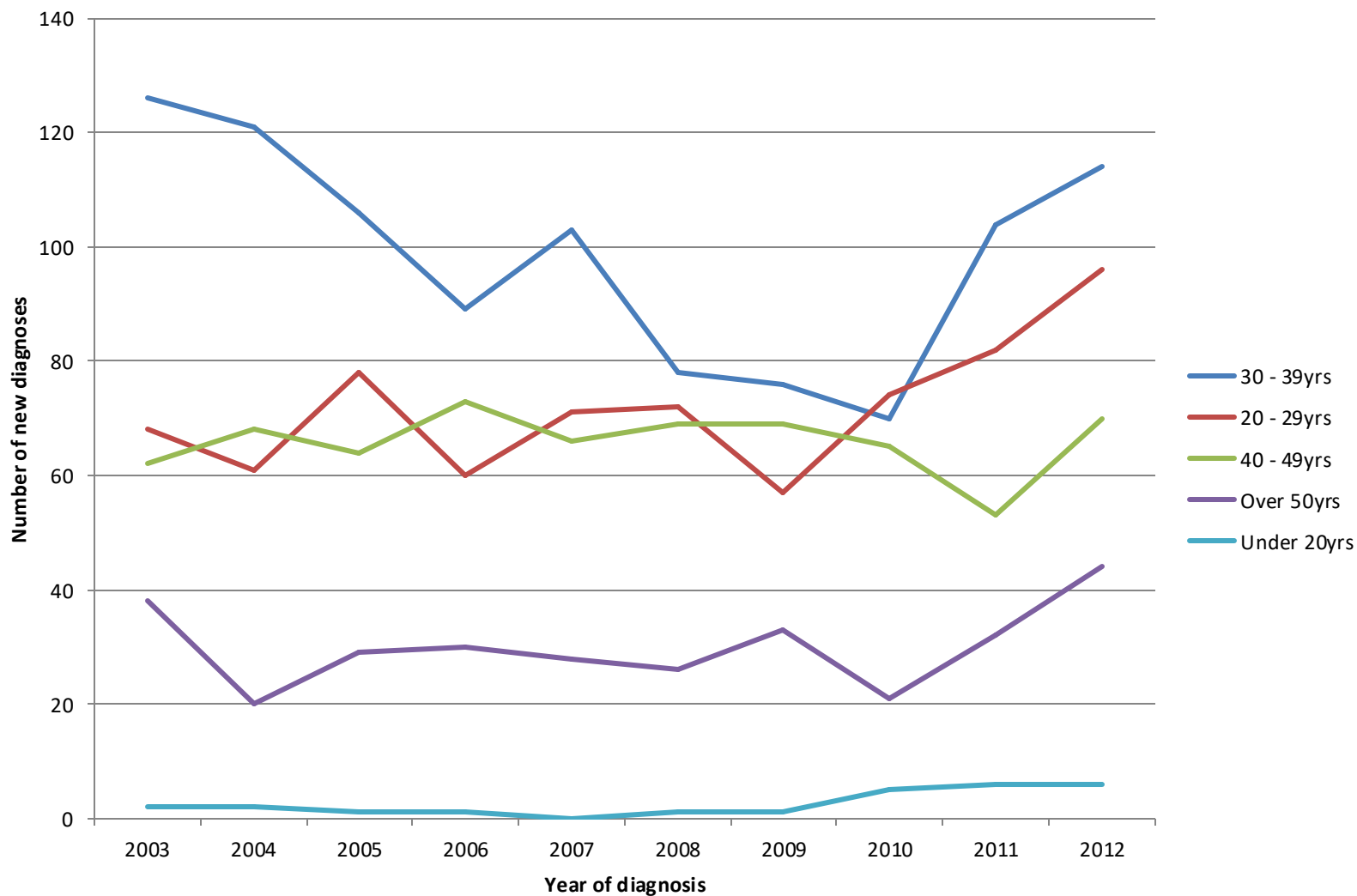
- **Syrian,**
- **Egyptian,**
- **Libyan,**
- **North Korean,**
- **Sydney HIV clinician**

HIV infections (NSW) by exposure category, 2012

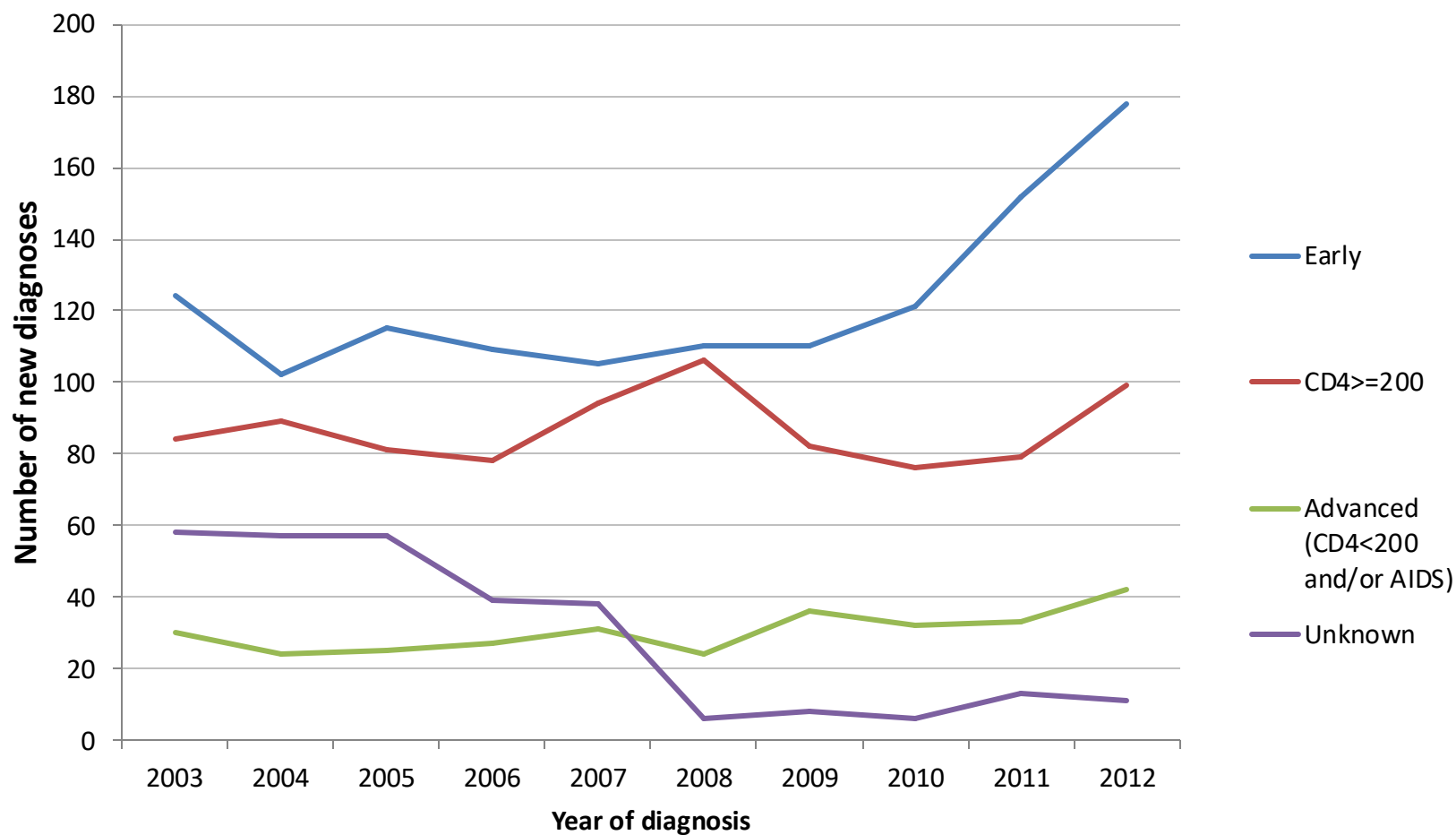
Risk exposure	Previous 4 yr average (2008-11)	2012 n (%)	Proportional change in counts
Homosexually acquired (excl MSM IDU)	237 (74%)	318 (78%)	+ 34%
Homosexually acquired – IDU	11 (3.5%)	12 (2.9%)	+ 9%
Heterosexually acq'd – high prev	16 (4.8%)	10 (2.4%)	- 38 %
Heterosexually acq'd – other	43 (13%)	46 (11%)	+ 7 %
IDU	10 (3.1%)	10 (2.4%)	-
All others	2 (0.6%)	2 (0.5%)	-
Unknown	4 (1.3%)	12 (2.9%)	
Total	323	410	+ 27 %

NB: No mother-to-child transmission notified in 2012

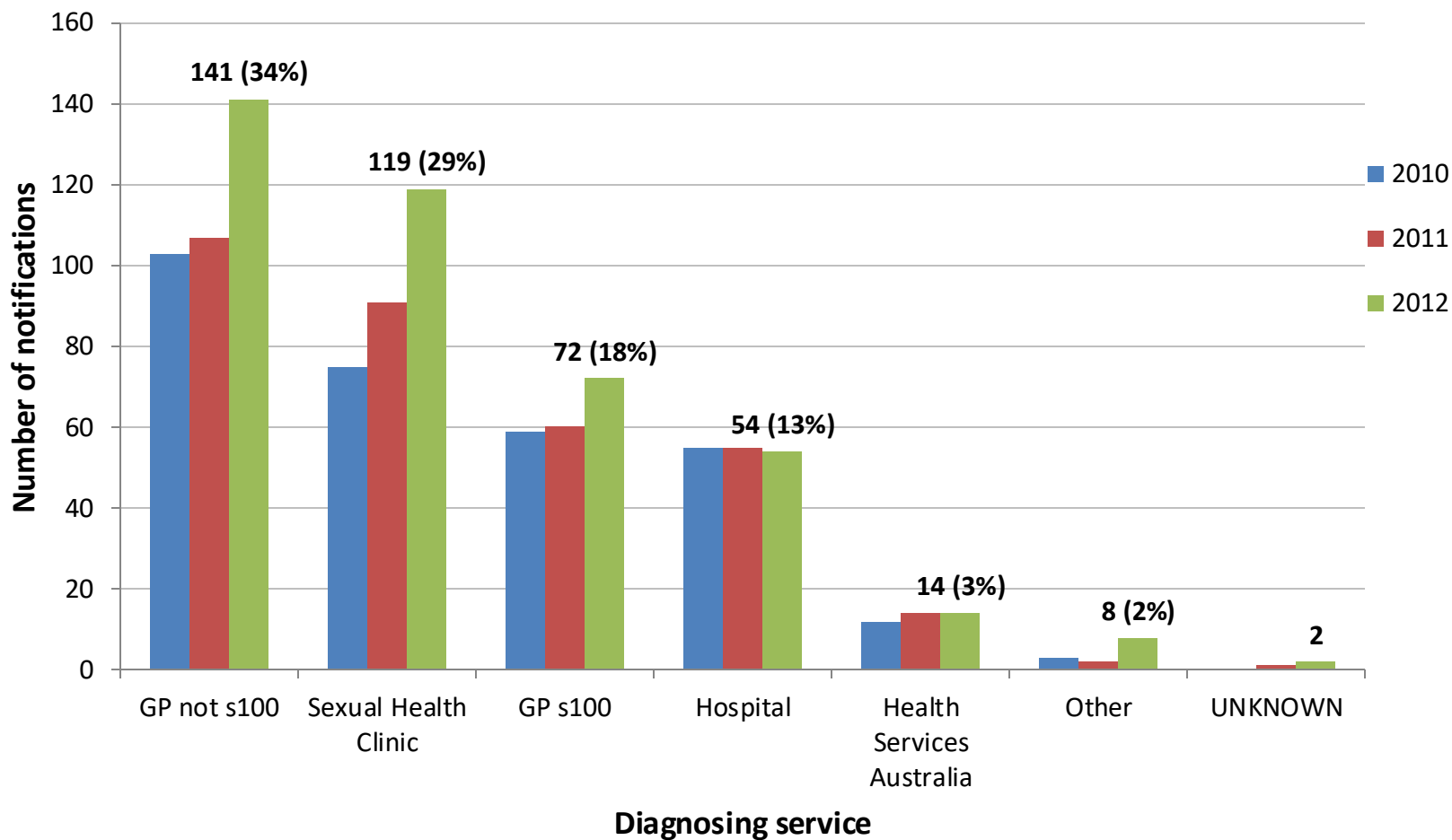
Homosexually acquired HIV by age group, NSW 2003 - 2012



Homosexually acquired HIV by stage of disease at diagnosis, NSW, 2003 - 2012



New diagnoses of HIV infection by diagnosing service, NSW, 2010-2012



DHHS Guidelines, 2012:

When to Start

- **ART recommended for all HIV-infected patients; *strength* of recommendation varies**

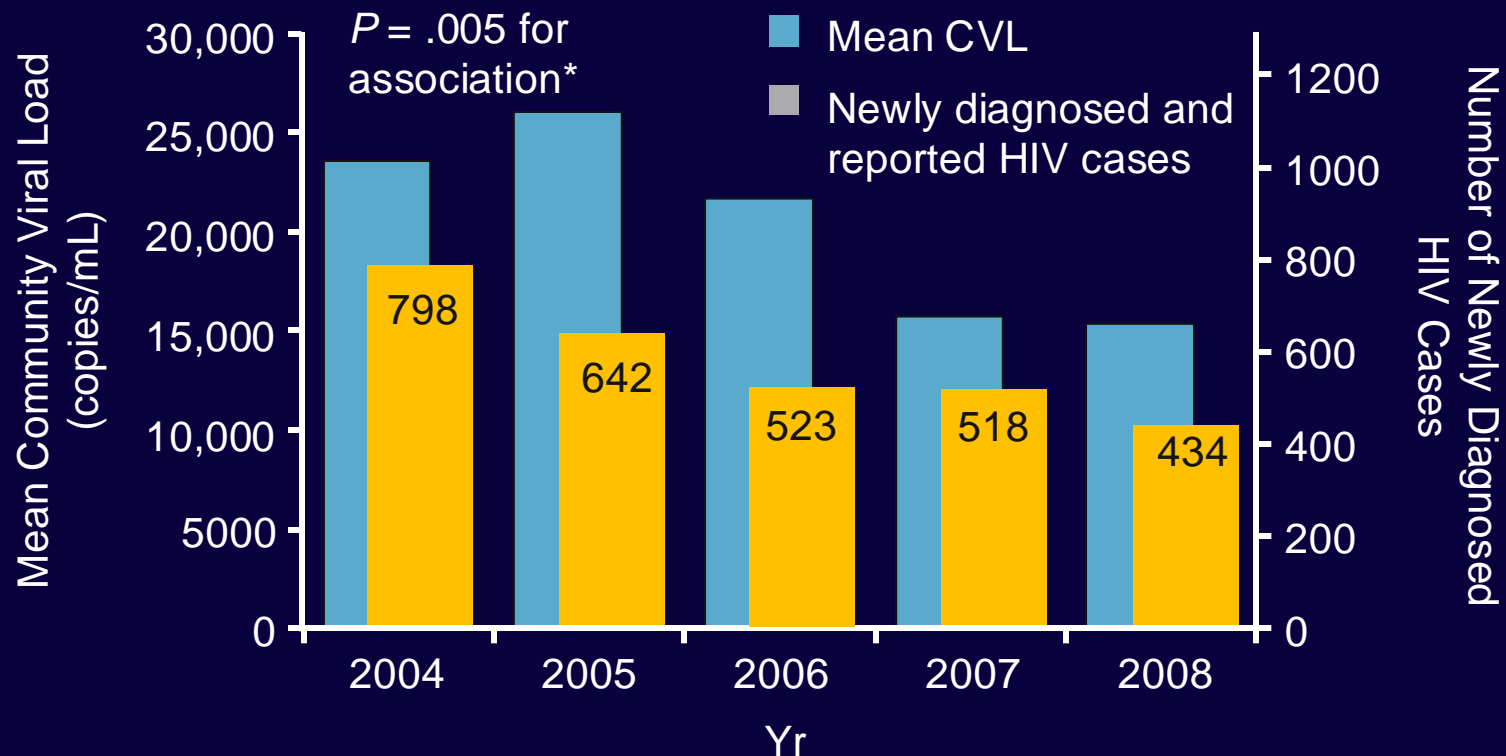
CD4+ Cell Count	Recommendation
▪ < 350 cells/mm ³	▪ Start ART (AI)
▪ 350-500 cells/mm ³	▪ Start ART (AII)
▪ > 500 cells/mm ³	▪ Start ART (BIII)
Clinical Conditions Favoring Initiation of Therapy Regardless of CD4+ Cell Count	
<ul style="list-style-type: none"> ▪ History of AIDS-defining illness (AI) ▪ Pregnancy (AI) ▪ HIV-associated nephropathy (AII) ▪ HBV coinfection (AII) ▪ Patients at risk of transmitting HIV to sexual partners (AI, heterosexuals; AIII, others) ▪ HCV coinfection* (BII) ▪ Patients > 50 years of age (BIII) 	

*Including those with high CD4+ cell count and/or with cirrhosis. Some pts with CD4+ counts > 500 cells/mm³ may elect to defer ART until after HCV therapy is completed.

DHHS Guidelines for Antiretroviral Therapy in Adults and Adolescents. **March 27, 2012.**

Community Viral Load Mirrors Reduced Rate of New HIV Cases in San Francisco

- Retrospective analysis of relationship between community viral load (CVL; mean of summed individual HIV-1 RNA results per yr) and new HIV diagnoses



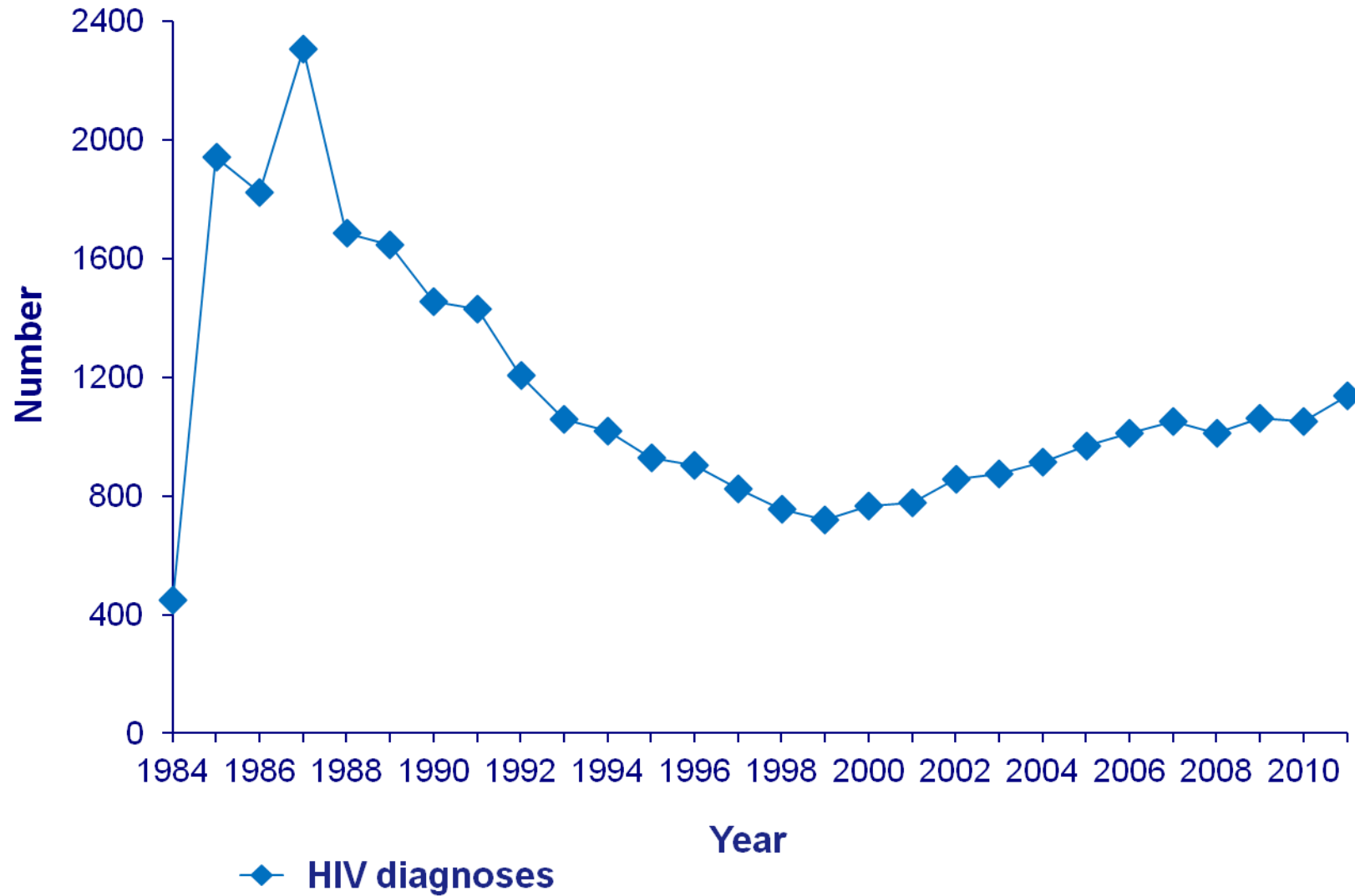
*Data insufficient to prove significant association with reduced HIV incidence.

Das-Douglas M, et al. CROI 2010. Abstract 33. Reproduced with permission.

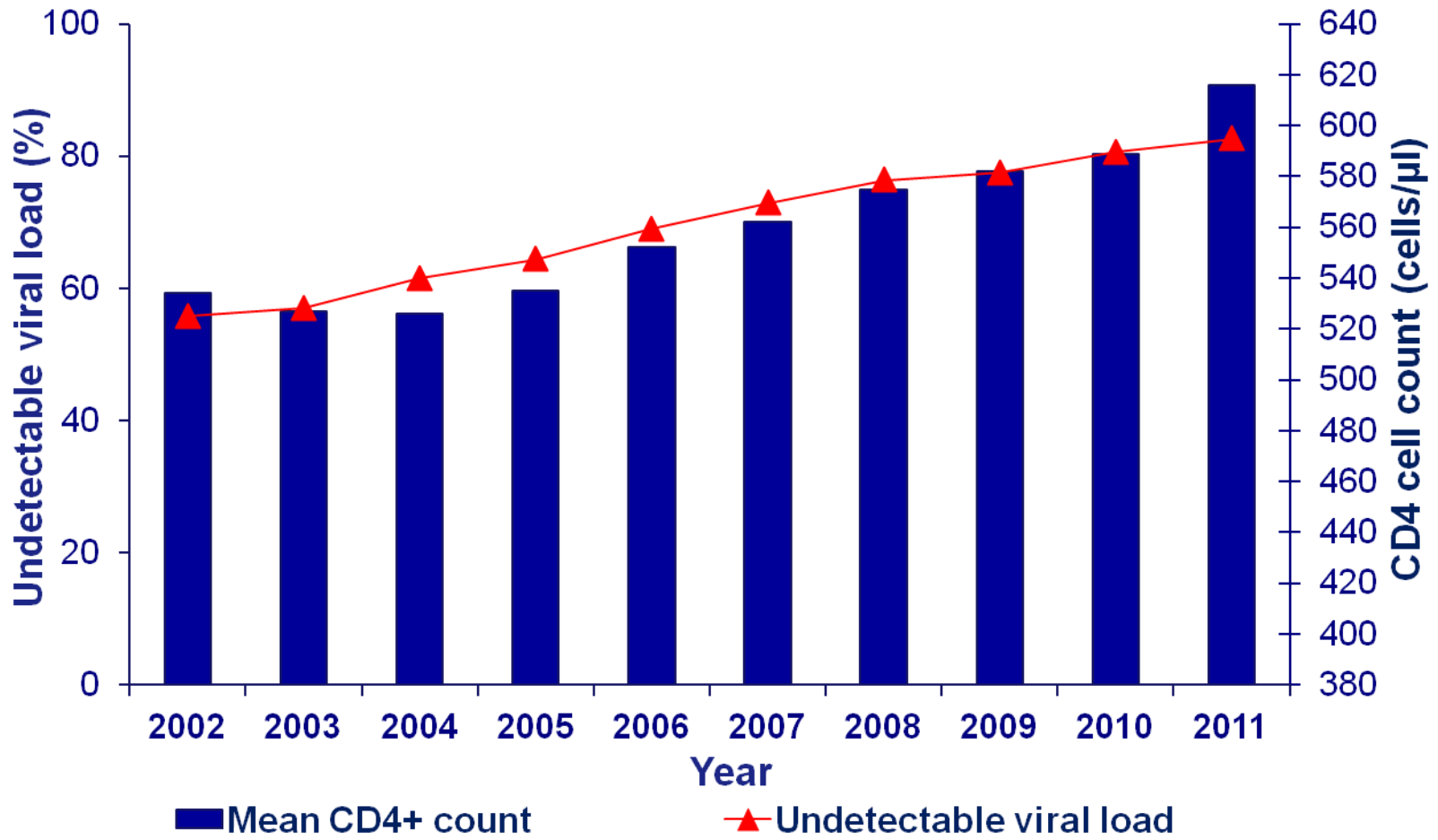
clinicaloptions.com/hiv

But...

Newly diagnosed HIV infection in Australia



HIV viral load and CD4+cell count among people enrolled on the Australian HIV Observational Database, 2002 – 2011, by year



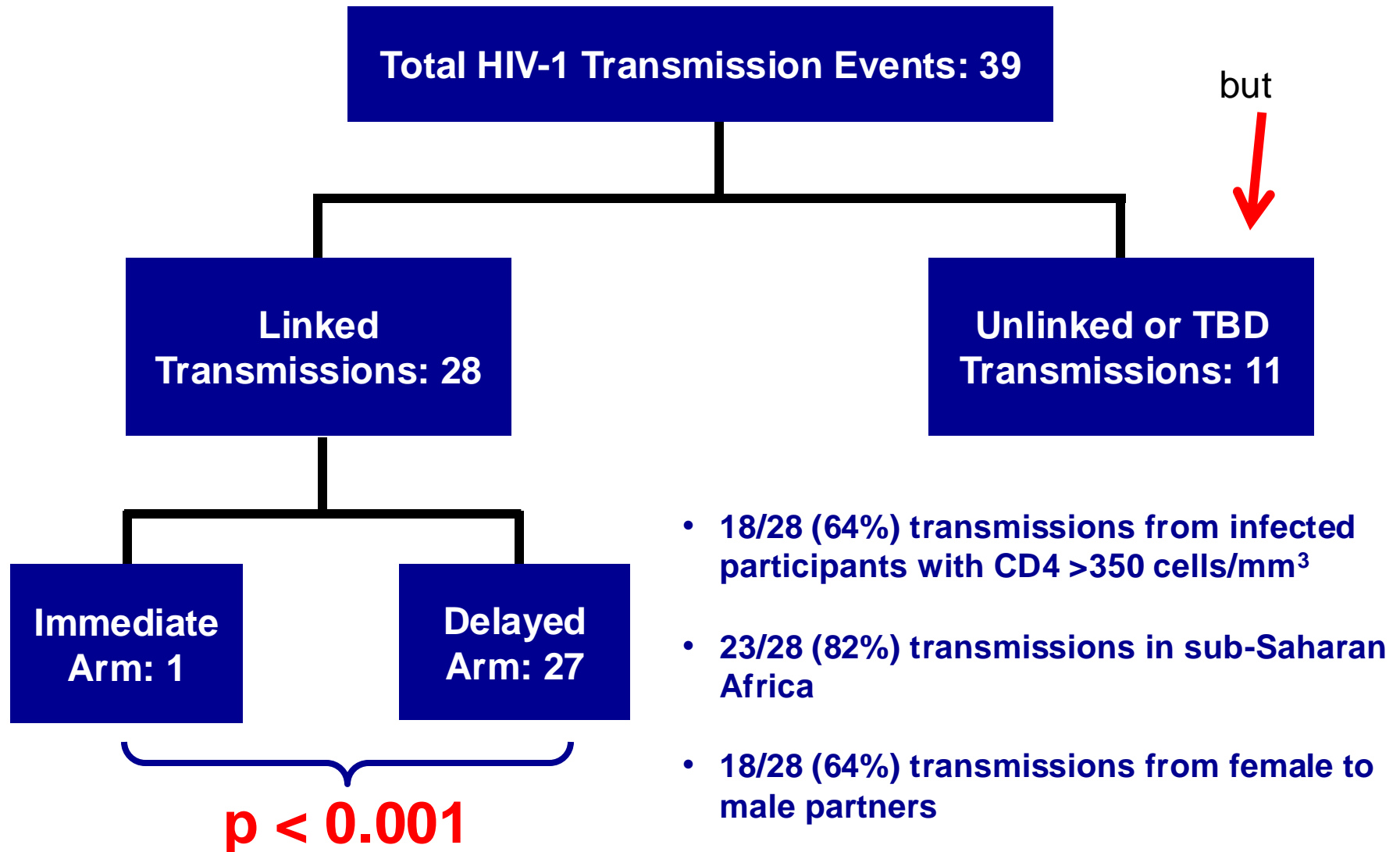
1. Undetectable viral load equals 50 copies/ml or less

Reduced infectivity - patients in care;

Last 1,000 patients seen at Albion Centre

Viral load	<20	<=400	<=1000	
% of patients	74.8	88.9	90.3	

HPTN 052: HIV-1 Transmission



HIV vaccines

200 phase I trials started since 1987, only 4 vaccine regimens have been valuated in phase III efficacy studies

- STEP (adeno virus-vector) vaccine; increased risk of HIV acquisition.
- RV144 (Prime –Boost)study; 33% protective effect in 1 statistical analysis

“Monkey vaccine key to HIV cure” *The Australian* 13Sept 2013

- new SIV vaccine – a modified version or “vector” of a common herpes virus, known as cytomegalovirus or CMV – was able to “functionally cure” the monkeys without completely removing the infection.

Monkeys lie !



Hansen et al. Nature(2013)
doi:10.1038/nature12519

HIV vaccine development; a bit of Star Trek mentality

HIV multiples in activated CD4 cells

- Vaccination stimulates rapid release of activated CD4 cells once encountering real infection

- Why would it make any sense to bring HIV and CD4 cells together more effectively?



Pre-exposure prophylaxis (PrEP)

FDA Panel Clears Way For HIV Prevention Pill

Observers say federal approval could be a watershed moment in the fight against AIDS.

By Rachael Levy and Ankita Rao | Posted Friday, May 11, 2012, at 10:26 AM ET

43



Like

118



Tweet

10



Some researchers hope that daily doses of Truvada could help prevent healthy people from contracting HIV.
Photo illustration by Justin Sullivan/Getty Images.

UPDATE: The FDA's advisory panel on Thursday signed off on using a popular HIV-fighting pill as a preemptive measure to prevent healthy people from contracting the virus in the first place, a landmark decision that could play a major role in the worldwide fight against AIDS.

The move was the latest in a series that most likely puts Gilead Science's Truvada on track for final federal approval next month. While the FDA isn't bound to follow the independent panel's advice, it traditionally does, and federal drug regulators have already affirmed existing research showing the pill is effective at preemptive protection.

While there was overwhelming support for approving the medication for the highest-risk group (men who have sex with me), there was more substantial dissent among the panel when it came to approving Truvada for use in the wider population, [Reuters](#) reports. The

PrEP Trials to Date

Trial	Population/Setting	Intervention	Reduction in HIV Infection Rate, %
CAPRISA ^[1] (N = 899)	High-risk women in South Africa	▪ Coitally applied vaginal TFV gel	39
iPrEX ^[2] (N = 2499)	MSM, transgender women, 11 sites in US, South America, Africa, Thailand	▪ Daily oral TDF/FTC	44
Partners PrEP ^[3] (N = 4747)	Serodiscordant couples in Africa	▪ Daily oral TDF ▪ Daily oral TDF/FTC	▪ Women: 71; men: 63 ▪ Women: 66; men: 84
TDF2 ^[4] (N = 1219)	Heterosexual males and females in Botswana	▪ Daily oral TDF/FTC	62*
FEM-PrEP ^[5] (N = 2120)	High-risk women in Africa	▪ Daily oral TDF/FTC	▪ Equal numbers of infections in active and control arms ▪ Study stopped for lack of efficacy
BKK-PrEP (N = 2413)	IVDU in Bangkok	▪ Daily oral TDF DOTs	49

1. Abdool Karim Q, et al. Science. 2010;329:1168-1174. 2. Grant RM, et al. N Engl J Med. 2010;363:2587-2599. 3. Baeten JM, et al. N Engl J Med. 2012;367:399-410. 4. Thigpen MC, et al. N Engl J Med. 2012;367:423-434. 5. Van Damme L, et al. N Engl J Med. 2012;367:411-422. clinicaloptions.com/hiv

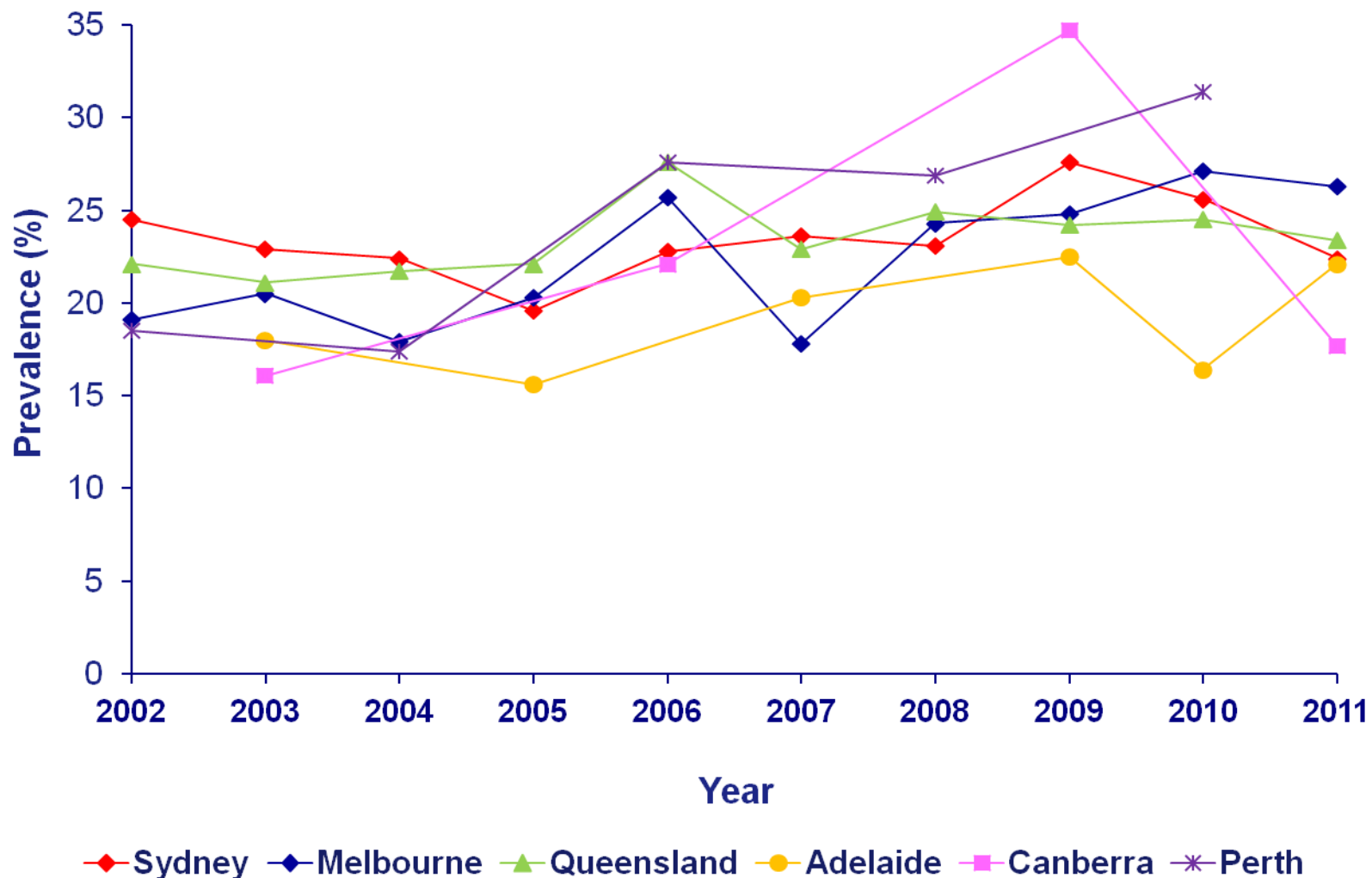
Additional Data on PrEP

- GSK1265744, dolutegravir analogue packaged in **nanoparticles** (GSK744LAP), permitting monthly or quarterly dosing in humans by IM injection
 - 8/8 macaques injected with GSK744LAP and rectally challenged with SHIV protected from infection; 8/8 controls became infected ($P < .0001$)^[1]
- Intravaginal rings containing TDF protected against SHIV infection in 6/6 macaques; 11/12 controls became infected ($P < .0004$)^[2]

1. Andrews C, et al. CROI 2013. Abstract 24LB. 2. Smith J, et al. CROI 2013. Abstract 25LB.

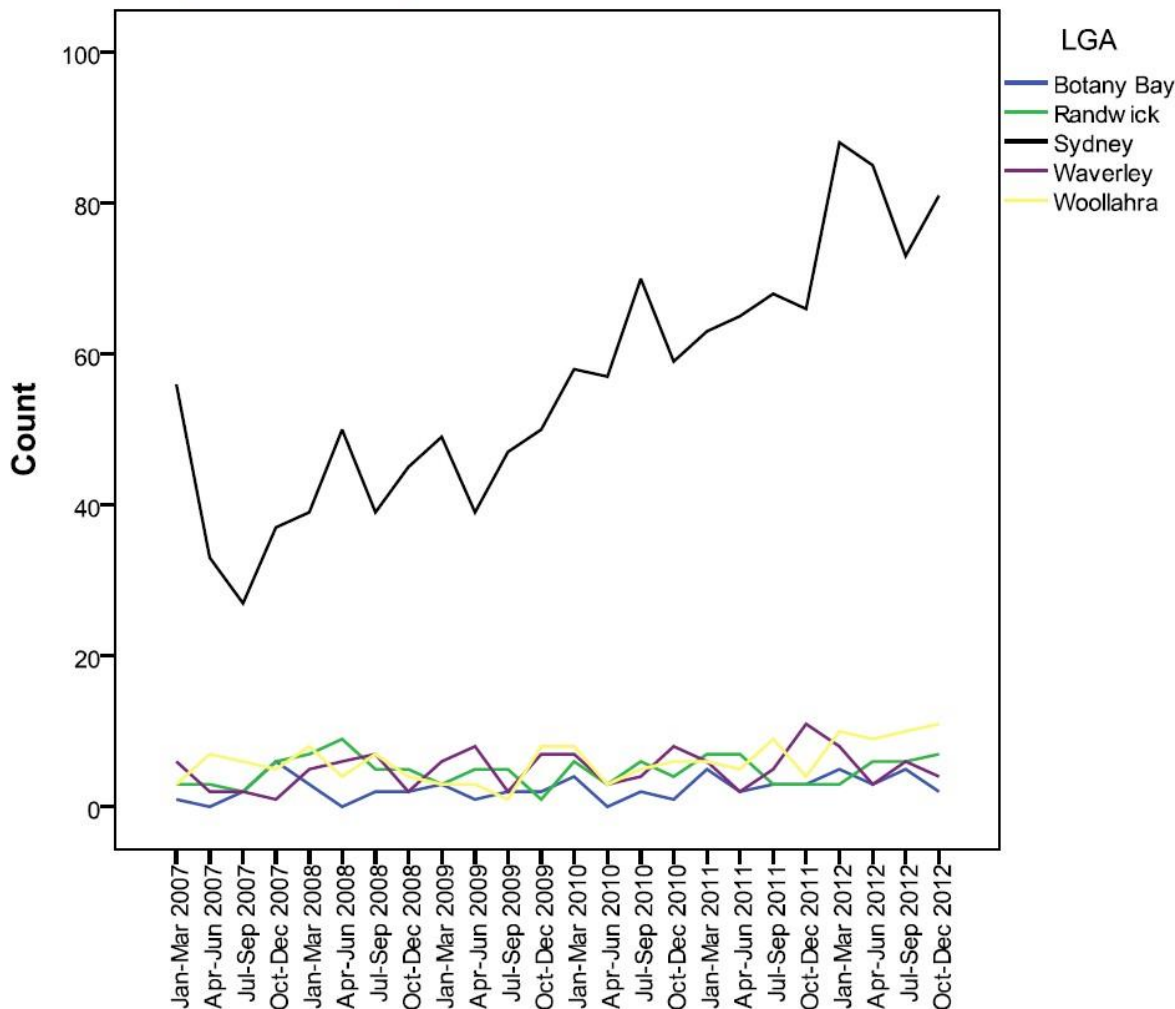
3. Grant R, et al. CROI 2013. Abstract 27.

Prevalence of unprotected anal intercourse with casual partners, 2002 – 2011, reported by men in Gay Community Periodic Surveys



Increasing STIs will affect HIV transmission risks

Figure 8: Quarterly rectal chlamydia notification in males in the Northern network 2008 - 2012



“I want the cure!”

- Berlin patient
- 2 Boston patients
- 1 Mississippi baby
- Quite a few monkeys

Very Early Triple-Drug ART Elicits “Functional Cure” in HIV-Infected Child

- Infant born to untreated HIV-infected mother at 35 wks’ gestation via spontaneous vaginal delivery^[1]
 - Maternal HIV infection identified during labor via ELISA and Western blot
 - Infant HIV infection confirmed via HIV-1 DNA PCR, HIV-1 RNA analysis of 2 separate samples at 30 and 31 hrs of age^[2]
 - ZDV/3TC + NVP (at therapeutic dose) initiated at 31 hrs of age, continued for 7 days
 - ZDV/3TC + LPV/RTV continued from 7 days to 18 mos of age
 - HIV-1 RNA undetectable by Day 30
 - Mother removed patient from care at 18 mos of age

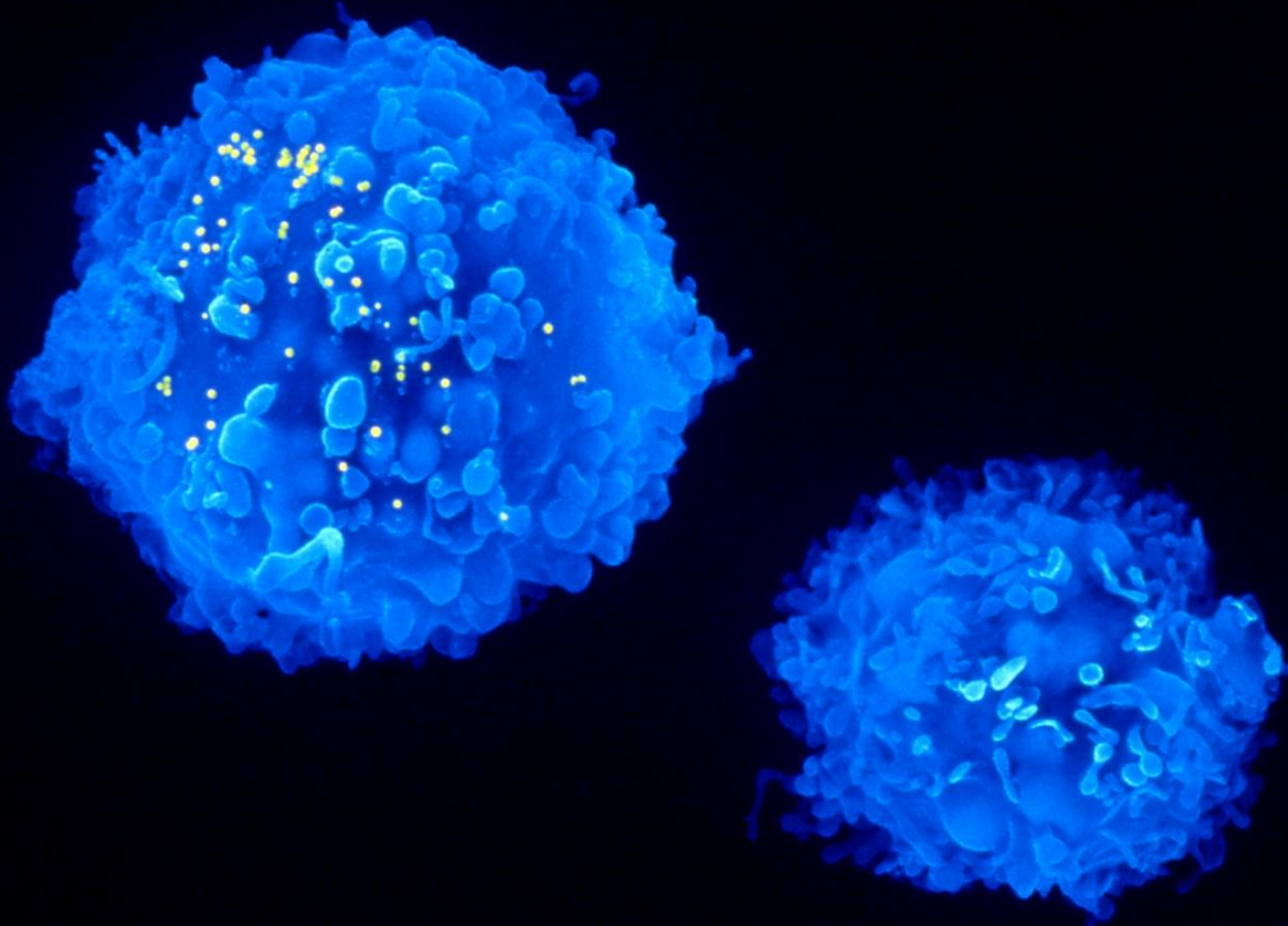
“Functional Cure” Child: Standard HIV-1 Assays Undetectable to Age 26 Mos

- ART regimens: ZDV/3TC + NVP (31 hours – 7 days)
- ZDV/3TC + LPV/RTV (7 days – 18 months)
- Plasma VL 19,812 c/mL
 - VL undetectable by < 30d of age
 - VL remained undetectable though > 80d of age
- Assessments at Mos 24 and 26
 - Western blot negative
 - Standard HIV-1 RNA and HIV-1 DNA undetectable
 - By ultrasensitive assays
 - **Mo 24:** HIV-1 RNA 1 c/mL; HIV-1 DNA < 2.7 c/million PBMCs
 - **Mo 26:** HIV-1 DNA 4 c/million PBMCs
- Clinical trials of exposed infants treated with ART recommended

Vorinostat Activates HIV Transcription in Latently Infected CD4+ T Cells

- Vorinostat investigated as possible strategy to eliminate latent HIV infection in pts on stable ART
 - Histone deacetylase inhibitor approved for cutaneous T-cell lymphoma
 - Single dose increases HIV-1 RNA expression in resting memory CD4+ cells of HIV-infected patients
 - Activation may result in elimination of latently infected T cells
- Current study is a single-arm trial of vorinostat 400 mg QD for 14 days (N = 20) in pts on stable ART, CD4+ count > 500 cells/mm³
- 18/20 pts had significant increase in cell-associated unspliced HIV-1 RNA on ≥ 2 occasions while on drug
 - Mean 2.65-fold increase
- All AEs mild (grade 1/2)
 - Most common: diarrhea, lethargy, thrombocytopenia, dysgeusia
- No significant changes in HIV-1 DNA in PBMCs or rectal tissue
 - Suggests vorinostat alone not likely to eliminate latent infected cells

activated and latently infected CD4 lymphocytes



“I still want the cure!”



Berlin patient;

high dose chemotherapy for leukaemia (twice),
rescued with bone marrow transplants (twice).
Stopped ARV and undetectable for 4 years
(although HIV found on “deep sequencing”)

Boston patients:

2 men given bone marrow transplants after
chemotherapy. Stopped ARV and undetectable at
5 and 8 weeks.

“You cant handle the cure!”



- 20% of patients die following bone marrow transplants

“I still want the cure!”



- Sydney patient:
 - treated with ARVs in 1998. CD4 690, VL 10,000. Very compliant. Switched therapy for lipodystrophy after 2 years.
 - Wanted to have a treatment break
 - Off ARVs for 7 years with no detectable virus
- Dutch cohort study: 1 patient in every 100 can maintain a normal CD4 count, of these 1:100 has VL <50 copies without therapy i.e.. 1 in 10,000

Failed cure attempts



- Whole body microwave therapy
- Ozone rectal insufflations
- Rattlesnake venom
- Crystal therapy
- Echinacea
- Having sex with a virgin
- prayer
- Hit hard hit early

Ending HIV: still a way to go

