BHIVA 'Best of CROI' Feedback Meetings

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BHIVA 'BEST OF CROI' FEEDBACK MEETINGS

2010

British HIV Association

BHIVA

Simon Collins

HIV i-Base & UK-CAB

Perspectives from the community

- Safety issues in previous presentations
- ARVs, new drugs, D:A:D (smoking/TG)
- Key theme: treatment as prevention
  - individual level
  - population level
  ** important for all settings
- PrEP, PEP and microbicides
- Intensification studies
- Other studies

Treatment as prevention

Treatment as prevention

- Association between viral load and all individual transmission risks: sexual, IDU, needlestick, MTCT (at delivery and breastfeeding).
- Population level supported by modeling studies – 'test and treat', 'seek and treat'
- Theory to 'reduce new transmissions'
- Case studies document infection still possible
- Major theme at IAS and now CROI and will continue
- Important for treatment access in all settings

ART and transmission modelling

Symposium webcast Tues 2.30: Brian Williams

- Test and treat + PrEP in high-risk groups – reduce RR of transmission on ART by 96% to ~4%.
  - Eliminate transmission in 5-10 years
  - Eliminate HIV in 40 years
  - Cost neutral

Abs 996 – Charlesbois et al.

- 4 models "Test and Treat" in MSM in San Francisco

Compared to status quo:

Treat all if CD4 <500	49% reduction
Treat all	71% reduction
Treat all and test annually	91% reduction

Impact of ART on transmission [1]

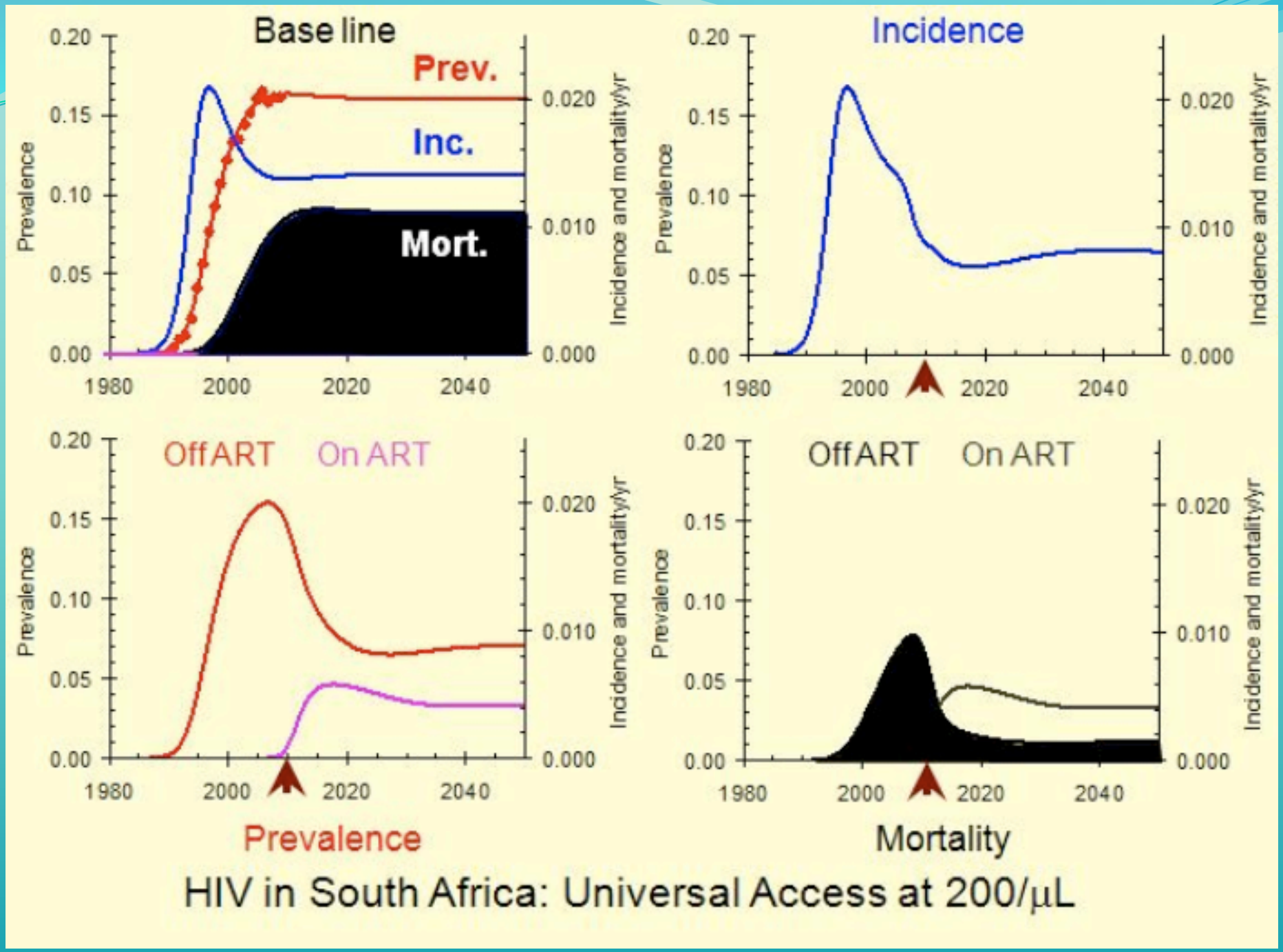
1. Infectivity is low: ~ 0.001 per heterosexual encounter [2]
2. Infectivity is highly variable: ~ 10-fold [2]
3. Infectivity is slow: doubling time ~ 1 to 3 years [3]
4. Disease duration is long: 5 to 15 years depending on age [4]
5. R0 ~ 7 (ie no more transmissions if reduced by 7-fold [5]

Impact of ART on transmission

- ART reduces viral loads (V) by ~ 10,000 times [1]
- Infectivity ~ $V^{0.35}$ [2]
- Relative risk of transmission on ART reduced to ~4%
- R 0~7 [5]

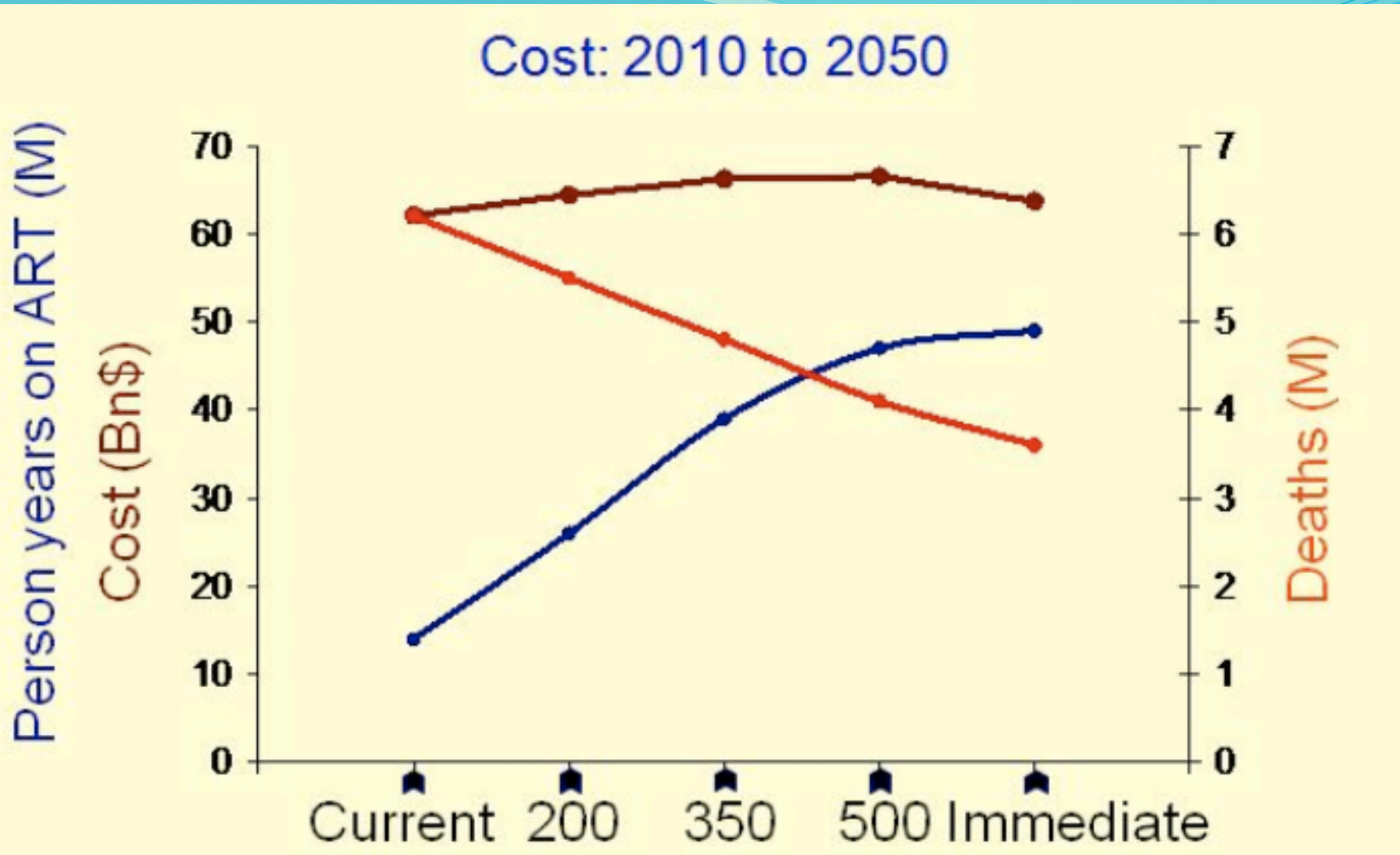
Refs: all before 1990.

Symposium webcast: Brian Williams, CROI 2010



HIV in South Africa: Universal Access at 200/μL

Symposium webcast: Brian Williams, CROI 2010



Economics of ART up to 2050 in South Africa
Current policy v. Universal Access at different CD4 counts

Abs 965 Granich *In prep.* 2010; CROI Poster Wednesday 14:00-16:00

Partners in prevention HSV/HIV transmission study

- Abs 136. Donnell et al. Webcast Friday 9.30.
- 3381 HIV-1 serodifferent HS couples, none on ARVs, followed 12-24m, quarterly visits: to see impact of acyclovir on HIV transmission.
- Intensive couples prevention counselling, free condoms
- 349 initiated ART in study (~200 CD4)
  - ART therapy by self report every 3m
  - ART initiation at median 13m
  - Most frequent regimen d4T/3TC/NVP

Donnell et al. Abs 136

Partners in prevention HSV/HIV transmission study

- 151 transmissions
- 108 linked HIV-1 transmissions
- 5 excluded: 103 included

	Unlinked HIV transmission	Person years	Rate	95% CI
No ART initiation	102	4558	2,24	(1.84-2.72)
After ART initiation	1	273	0.37	(0.09-2.04)
Adjusted RR	0.08	CI 0.002-0.57		P=0.004

Donnell et al. Abs 136

Partners in prevention HSV/HIV transmission study

- Risk of HIV-1 transmission substantially lower after initiation (risk reduction 92%)
- For people with CD4 counts <200, HIV transmissions rates are high (8.9%/y)
- Transmissions significant at all CD4 counts (2%/y)
- No increase in sexual risk after ART initiation

Donnell et al. Abs 136

Community viral load

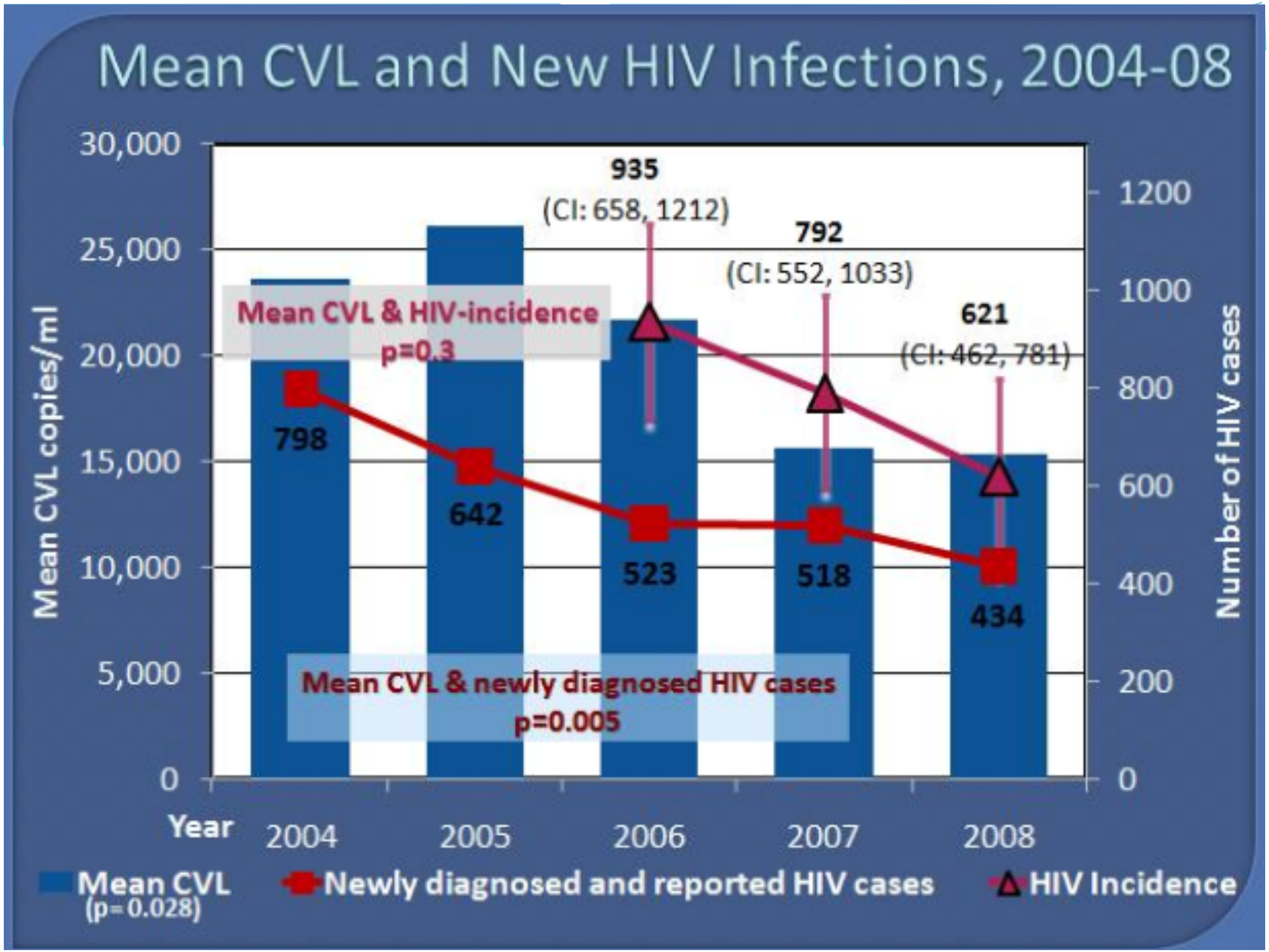
- Abs 33. Webcast: Wed 9.30 oral. Das-Douglas et al.
- San Francisco public health programme 2004-8:

  Increased testing/patients in-care/ART coverage/ VL suppression/HIV testing in MSM/

  Decreased unaware of status:
- Modelled total estimated viral load in a population
- Compared new infections in reference to expected incidence
- Supported by other analysis (ie STI rate/serosorting)

Community programme: San Francisco

Test and treat parameters	2004 (%)	2008 (%)
MSM testing in last 12 mo.	65	72
MSM testing in last 6 mo.	41	53
HIV-positive aware of status	24	14,5
Engaged in care	71	78
ART coverage	74 (2005)	90
Virologic suppression	52 (2005)	72


Mean CVL and New HIV Infections, 2004-08
30,000
25,000
20,000
15,000
10,000
5,000
0
Mean CVL copies/ml
1200
1000
800
600
400
200
0
Number of HIV cases
935
(CI: 658, 1212)
792
(CI: 552, 1033)
621
(CI: 462, 781)
Mean CVL & HIV-incidence
p=0.3
798
642
523
518
434
Mean CVL & newly diagnosed HIV cases
p=0.005
Year
2004
2005
2006
2007
2008
Mean CVL
(p= 0.028)
Newly diagnosed and reported HIV cases
HIV Incidence

Community viral load summary

- Increased testing and ART reduced community VL is associated with reduction in newly diagnoses
- Abs 34 – Washington DC incr. testing, higher BL CD4, reduced late diagnoses
- Abs 997 – IDU – seek and treat – Vancouver BC.
- Abs 525 – CASCADE - 50% start Tx +1, 4, 8 yrs after infection. If treatment started at CD4=500, 350, 200 ~ 50/30/10% within 1 year).

Although limitations, further support for early testing and treatment

However 'TREATMENT ALWAYS NEEDS TO BE BASED ON INDIVIDUAL RISK/BENEFIT and CHOICE'.

PrEP, iPrEP and PEP

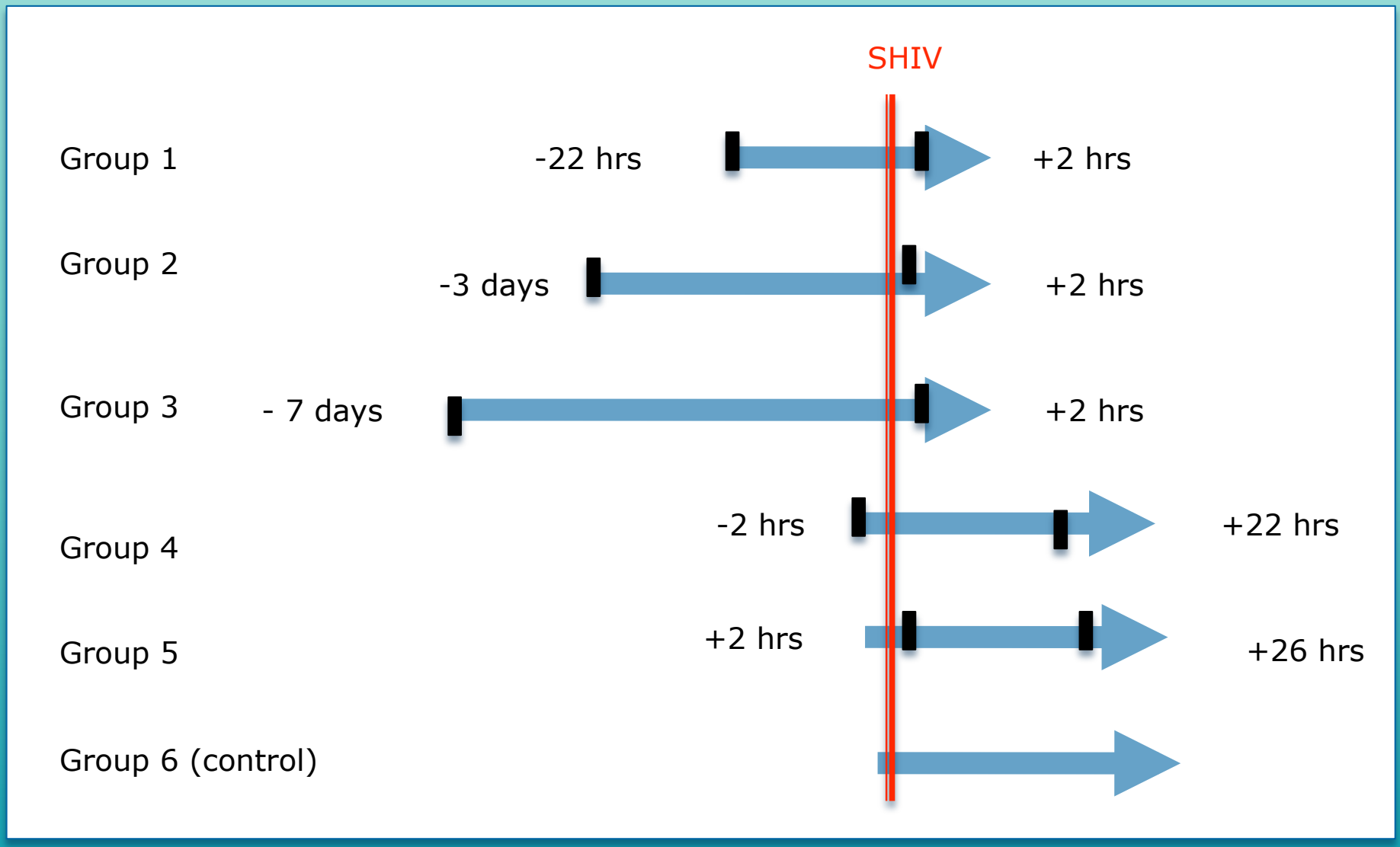
PrEP, iPrEP and PEP

- Macaque data from 2000 for TDF.
- First PrEP/PEP studies designed using daily dosing.

Abs 83 Garcia-Lerma et al. Webcast Thurs 9.30.

- Intermittant PrEP (iPrEP) +/- PEP with oral TVD in macaque study (n=6, 7 groups) – more applicable to real life need.
- weekly rectal exposure up to 14wks
- – 16-fold reduction with 24-72hr before *and* 2hr after.
- Supported by separate PK properties of TDF and FTC
- Suggested the need for TDF + FTC together.
- No effect with GS7340 PrEP.

Efficacy of intermittent PrEP with Truvada in the repeat low-dose macaque model: design



Conclusions

- Combined with single dose PEP, iPrEP with TDF/FTC was highly protective
- A single -3d pre-exposure dose with TDF/FTC or long-acting GS7340 was not sufficient despite long intracellular drug half-lives
- Rapid FTC penetration in tissues suggests that FTC plays an important role in the protection contributed by the PEP dose with TDF/FTC

Gerardo Garcia-Lerma*1 CROI 2010 Abs 83

Microbicides

- Abs 949 Dobard et al.

  Once-weekly gel, exposure at 30m and 3 days

  1% TDF gel protected 4/6 macaques after up to 20 exposures following vaginal application - vs 9/10 placebo gel after median 4 challenges (2-11).
- Abs 84LB Moore et al.

  Maraviroc gel protected macaques from vaginal challenge. Protection time-limited to PK (50% at 4 hrs)

  Cost: single $15 tablet to protect 25 times.
- Abs 87LB Chisembele et al. PRO 2000 failed in Phase 3.

  Neither dose or sub analysis showed protection.

Intensification

Intensification

Background

- No impact after 4 weeks adding EFV or LPV/r [1]
  ~80% of pts stable <50 c/mL are >1c/mL
  median plasma VL~ 3 c/mL
- ACTG 5244 intensification with raltegravir [2]
  12-week placebo cross over study in 53 pts
  median plasma VL ~ 1.7 c/mL
- Viral evolution stopped on HAART. [3]
  8/11 children, followed > 5 years.

References
1. Maldarelli F IHDRW 2008, Sitges. Abs 72;
2. Gandhi et al, IAS 2009. Abs WELBB104;
3. Fenkl L J Virology 2005.

Intensification

CROI intensification studies

- Abs 431. No impact of MVC, LPV/r. T-20 as control arm. 5 x LP. Baseline median VL 3.9 c/mL in plasma and <2 c/mL in CSF. No impact.
- Abs 286 – no impact from RAL in CSF in 5 pts
- Abs 280 – n=8 pts, median 4 previous failed Rx
- Abs 283 – 24 wk MVC no impact but tiny study. n=6 early treated pts, low levels in galt unaffected.
- Abs 277 – RAL intensification in 7 pts
  No impact on PBMC or gut, trend in ileum?

See poster discussion: Friday Webcast of 7 studies

Intensification

CROI low viremia studies

- Abs 499 – > 700 treatment experienced pts, cross-sectional study since March 2009
  60% <1 copy/mL – interesting to see reproduced
- Abs 504 - blip/rebounding study
  Transient blips (<50 c/mL >75% time, never >1000 c/mL) had similar risk to full suppression.
  Higher frequency blips and higher rebound levels associated with mortality
- Abs 505 Geretti et al. RFH study. VL 40-50 vs <40 was predictive of future rebound.
  Non-randomised limits interpretation of EFV vs LPV/r effects

Intensification: blips/rebound

Med VL f/u median 36 (IQR 25 to 53) months for classification
Group 1(fully suppressed) VL<50 c/mL throughout
Group 2 (transient VL) <50 c/mL for ≥75% of f/u, always <1000 copies/mL.
Group 3 (short-term VL) <50 c/mL for 25% to 75% of f/u,
[3a <200 c/mL, 3b any level]
Group 4 (long-term) VL<50 c/mL for ≤25% remainder >1000 c/mL.

Mortality median 51 (IQR 35 to 70) months for mortality:

Hazard ratios (95% CI) compared to Group 1:

Group 2	1.12;	(0.62 to 2.01) – NS
Group 3a	4.95;	(2.29 to 10.69)
Group 3b	6.05;	(4.06 to 9.02)
Group 4	20.46;	(11.40 to 36.74)

Abs 504, Hull et al.

Intensification summary

- Current treatments are maximally suppressive in plasma, and likely many other compartments (CSF) for most pts <50 c/mL.
- At <5 c/mL there is no ongoing residual replication – matches baseline, even after many years. Virus is from latent cells.
- Unclear whether <5-<50 has clinical significance in the long-term. Currently <50 seems sufficient not to develop resistance?
- Repeating blips >50 may warranr closer management to reach suppression

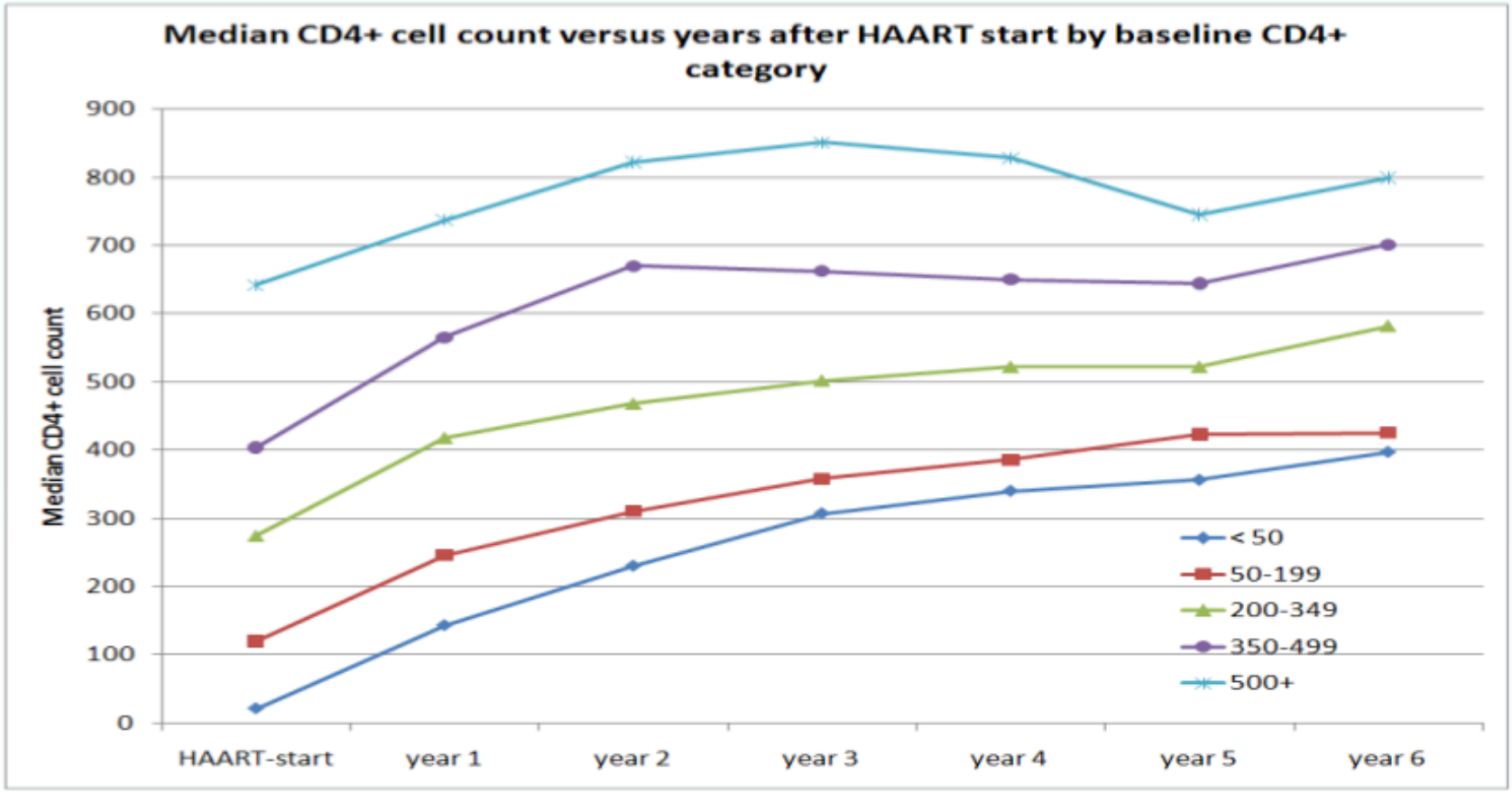
Other studies

Other studies

Webcasts and online access

- Few RCT, new drugs, comparison studies
- Abs 688 – faster transplant referral for HIV-positive people with haemophilia
- Abs 642 –increased liver stiffness on Fibroscan during acute HCV
- Abs 660 – SMART biomarkers IL-6/d-dimer in HCV/HIV
- Abs 983 – HOPS – CD_4 response by BL CD_4 – supports START trial (about to enroll)
- Abs 526 – life expectancy 25 yo add +50/55yrs

Figure 3: Median CD4+ cell count versus years after HAART-start by baseline CD4+ cell range



N	HAART-start	year 1	year 2	year 3	year 4	year 5	year 6
< 50	278	250	222	189	153	137	109
50-199	323	292	249	205	173	146	123
200-349	361	323	266	204	174	132	101
350-499	198	180	158	141	112	89	73
500+	218	198	177	149	135	112	104

Abs 983, Palella et al.

Life expectancy

Fast track to community review?

- Modelling studies predict narrowing of gap between life expectancy of HIV-positive and HIV-negative
- Abs 526: van Sighem et al. Athena.

Modeling based on >4,00 pts and 15,000 PYFU
Median addition yrs from diagnosis at age 25:
Men: +52.4 yrs (IQR 43.5 to 59.2) vs 53.1 gen pop
Women: +57.4 yrs (48.5 to 63.5) vs 58.1

- Model included different ages but, on personal level, how can I set my clock back to 25?

Thank you

www.i-Base.info

www.ukcab.net