Feedback from 4th IAS Conference
22-25 July 2007

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HIV i-Base

Feedback from 4th IAS Conference

1. New ARVs: maraviroc

2. Approved drug trials: TITAN

3. Stragegy: SMART and START

4. Other: CHER, circumcision (MSM), washing, PrEP for pregnancy, nuke sparing

Feedback from 4th IAS Conference

1. New ARVs:

- maraviroc;
- raltegravir;
- etravirine (TMC-125);
- rilpivirine (TMC-278)
- early compounds: apricitabine, UK-453,061 (NNRTI); INCB00947 (CCR5); PRO140 (CCR5 antibody)

Maraviroc

MERIT study, CCR5 inhibitor: naïve vs EFV

- 'non-inferior' at 48wk by <400 but NOT <50 (69 vs 65%)
- fewer pts <50 with baseline VL >100,000 copies/mL (67 vs 60%)
- CD4 count +170 vs +144 - favoured maraviroc
- Similar side effects - more malignancies with EFV, lipids ok
- driven by Northern vs Southern differences
- FDA approved (6 August 2007)
- Tropism questions - 50% experienced pts fail screening; test only sensitive when >5-10% dual/mixed X4/R5; change between screening & BL
- **How and when is best use for this drug?**

Saag M, et al. Abstract WESS104.

Raltegravir

Protocol 004 study, integrase inhibitor: naïve vs EFV

- 24 week responses continue to week 48
- similar efficacy (viral load) to EFV at 48wks (all doses) - approx 88% <50 copies/mL
- similar CD4 increases
- similar tolerability (less CNS; 0 nightmares)
- rapid early viral load drop (clinical significance?)
- similar resistance (3%; 5 vs 1; still very low numbers but XRx)
- better lipids (TC, LDL, TG, but similar reductions in TC:HDL ratio)
- **continued strong results: important to use with other active drugs**

Markowitz M, et al. Abs TUAB104.

Etravirine (ETV, TMC-125, NNRTI)

DUET study: 3-class experienced

- All received darunavir/r + OBR +/- ETV/placebo
- ETV produced increased viral load decrease (20-30% more)
- ≥ 3 mutations from 13 (DUET) = decreased response

[V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V, G190A/S]

- K103N not associated with ETV resistance
- Single/dual mutations present in ~20% NNRTI-experienced pts (n=1700) but ≥ in <2% (ANRS Cotte et al)
- **confirms activity in people with NNRTI resistance: caution that needs supported regimen (active PI and/or nukes)**

Katlama C, et al. Abs WESS204.2. Mills A, et al. Abs WESS204

rilpivirine (TMC-278, NNRTI)

48 wk dose finding study: treatment naïve vs EFV

- All received TDF/FTC or AZT/3TC
  + TMC (3 doses) or EFV
- ~ 90 pts each group
- Similar viral load decrease (~80% <50 c/mL wk48)
- Similar change in CD4 (~ +125 c/mm3)
- Similar lipids
- **Potential alternative to efavirenz?**

Pozniak A, et al. Abstract WEPEA105

Ruxrungtham K, et al. Abstract TUAB105.

.

New drugs

1. Apricitabine: -0.7 log in 3TC Rx (M184V)
2. UK-453,061 (NNRTI): -1.5-2 log at day 10
3. INCB00947 (CCR5): -1.8log at day 14
4. PRO140: single CCR5 antibody IV infusion: -1.7log at highest dose at day 10, only returning to baseline by day 30

1, Cahn P, et al. WESS203.
2. Fätkenheuer G, et al. WESS202.
3. Cohen C, et al. TUAB106.
4. Saag MS, et al. WESS201.

Feedback from 4th IAS Conference

2. Approved drug trials:

- darunavir/r vs Kaletra (TITAN)
- boosted atazanavir vs unboosted (BMS-089 and ATAZIP - LPV/r switch to ATV/r)
- fosamprenavir/r vs atazanavir/r (ALERT)
- saquinavir/r vs Kaletra (GEMINI)
- choice of AZT/3TC

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darunavir/r vs lopinavir/r (TITAN): 48wk experience (LPV/r-naïve) (ITT)

- ~600 pts randomised to OBT+open label PI/r, BID, in 'early' failure, 30% PI naïve, 80% sensitive >3 PIs
- DRV/r more potent: 71% vs 60% at <50 c/mL and 77% vs 67% <400 c/mL
- DRV/r superior statistically
- less virological failure (10% vs 22%)
- similar CD4 increase (+88 vs +81)
- similar tolerability (diarrhoea less - 32% vs 42%; rash higher 16% vs 8%)
- **impact on guidelines and prescribing practice?**

Valdez-Madruga J, et al. Abs TUAB101 and Lancet 7 July 2007

ATZ/r in treatment naive

ATZ vs ATZ/r (BMS-089): 96wk naïve [1]

- ~ 100 each arm; d4T-XR+3TC backbone
- Boosted more effective: 55% vs 65% <50 c/mL (NS)
- 20 vs 5 virological failures, inc. more resistance (184V)
- CD4: +315 vs +276 (NS)
- lipids increased more with RTV (TC+0.18 vs +0.52 mmol/L (p<0.01); LDL by +0.36 vs +0.70 mmol/L (p<0.05); and HDL by +0.59 vs + 0.85 mmol/L (p=NS)

ATZ/r +ABC/3TC (n=111, 50% CD4<200): 87% <50 c/mL wk 48 [2]

- naïve data for atazanavir is limited, RTV-boosted improves this option but LPV/r to ATV/r switch study showed little lipid benefit (chol and TG decrease but no HDL or LDL benefit?) [3]

1. Malan N, et al. Abs WEPEB024; 2. Elion R et al Abs WEPEB033; 3. Mallola et al. Abs WEPEB117LB

Fasting LIPIDS. Median values and Changes From Baseline in Lipid Parameters at month 12

Fasting Lipids	ATV/r			LPV/r			P value
	BL	m12	Change Δ mg/dL	BL	m12	Change Δ mg/dL	
TG, mg/dL	181	145	-51 (-29%)	191	202	-3 (-1%)	<0.0001
Total Chol, mg/dL	202	193	-19 (-9%)	205	207	-4 (-2%)	<0.0001
LDL-c, mg/dL	107	111	-8 (-7%)	111	111	-2 (-3%)	0.163
HDL-c, mg/dL	50	46	-3 (-6%)	49	46	-2 (-3%)	0.375

Mallola et al. Abs WEPEB117LB

LIPIDS: % above NCEP treatment recommendations at baseline and month 12

	ATV/r N=121			LPV/r N=127		
	BL	Mo 12	Change	BL	Mo 12	Change
TG m12 > 500 mg/dL	3%	4%	+1%	10%	17%	+7%
Total Chol > 240 mg/dL	23%	20%	-3%	20%	26%	+6%
LDL > 130 mg/dL	20%	25%	+5%	20%	30%	+10%
HDL < 40 mg/dL	16%	32%	+16%	21%	29%	+8%

No significant changes were obseved in Lipid Lowering Agents (LLA) usage during the follow-up in both arms.

Mallola et al. Abs WEPEB117LB

Lipids - HIV infection untreated

Very complicated!!!

Effect of HIV (vs HIV-) - proatherogenic profile

- **Early HDL drop**
- **then LDL drop**
- **then late TG increase**
- **then VLDL increase**

<u>HDL drop is probably worse than LDL drop is protective</u>

Lipids - response by HAART

Very complicated!!!

Untreated		HAART effect?
• Early HDL drop	>	reverses modestly (NNRTI, ATV more?)
• then LDL drop	>	reverses modestly (no drug effects in HIV-neg - 'return to health' effect)
• late TG increase	>	no decrease, (some drugs increase, RTV, some PI, d4T; high TG makes LDL difficult to measure)

• Smoking, (then exercise and diet) are most important modifyable risk factors for heart disease

Continued use of AZT/3TC

- UK guidelines recommend TDF/FTC or ABC/3TC over AZT/3TC
- AZT/3TC still widely used, and switch is slow
- TDF/FTC benefit out to 3 years in viral suppression (<400, p=0.004; <50 c/mL, p=0.08, NS); lipids (fasting chol, TG) and limb fat.
- Switch to TDF/FTC improves chol + TG (not HDL or LDL)
- B*5701 sensitive for predicting abacavir reaction

TDF/FTC: Arribas JR et al. Abs WEPEB029. Moyle G et al. Abs WEPEB028

B*5701: PREDICT, Mallal S Abs WESS101. Saag M Abs WEAB305; Philips E Abs MOPEB001)

Feedback from 4th IAS Conference

3. Earlier treatment

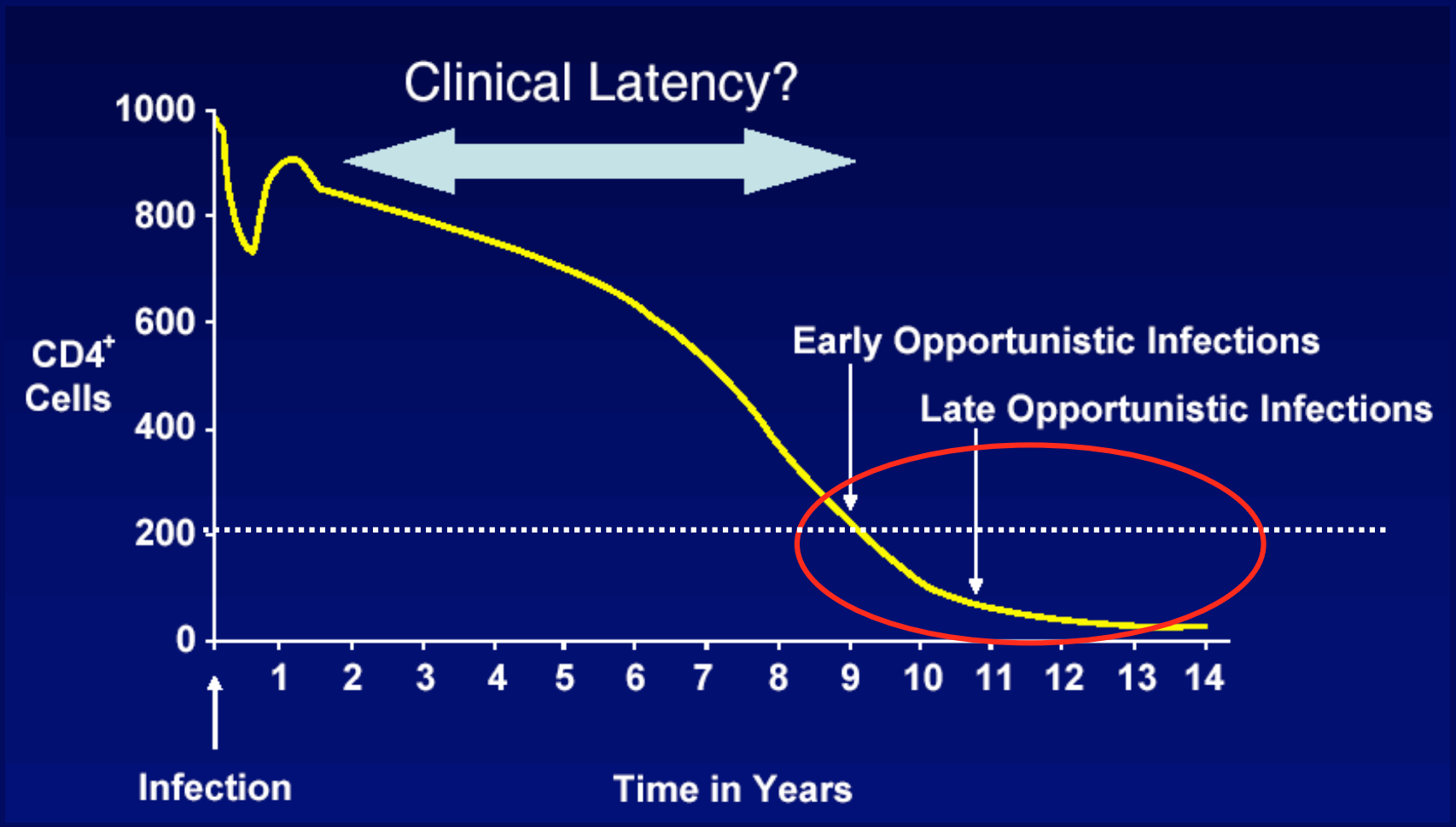
- Symposium on proposed START trial
- Data from SMART - STI study: naïve, D-dimer

Earlier treatment symposium

http://www.ias2007.org/pag/PSession.aspx?s=18

- **No data on using at higher CD4 count (guidelines are not based on randomised trials): scientific question**
- **Any decision to treat is based on risk vs benefit**
- **Will earlier treatment reduce AIDS and non-AIDS events, cancers, heart disease etc? Many studies now show event rate at CD4 >350 vs >600 etc**
- **Are current treatments effective and tolerable enough for 3000 people, using treatment 1-3 years earlier, in a trail, to answer these questions?**

Natural history - without treatment



Changing demands from HAART

- Pre-HAART - first demand from treatment was to reduce high death rate
- Then, to make treatment more effective and tolerable
- 2007 life expectancy = +35 years for a 20 year old diagnosed today with access to treatment
- But why not 55 years - as HIV-negative?
- Now demand is to fine tune treatment strategies to give even longer life expectancy

Risks at higher CD4 (off-treatment)

Many studies show that AIDS and non-AIDS events occur at CD4 counts >350

- SMART - Emery et al WEPE018
- UK-CHIC and CASCADE cohorts - higher rate CD4 350 vs >650 in early vs delayed
- What research would you want to see to persuade you to take treatment earlier?

Continuous use of ART Associated with decreased rate of serious non-AIDS Events in Subset of Patients Naïve or on no ART for > 6 Months at Entry in SMART

	DC Group		VS Group		HR (DC/VS) Deferred vs. Early	
	N	Rate	N	Rate	95% CI	P-value
OD or death	15	4.8	4	1.1	4.4 [1.5, 13.2]	0.009
OD fatal or non-fatal	11	3.5	3	0.8	4.4 [1.2, 15.8]	0.02
Serious non-AIDS	12	3.9	2	0.5	7.1 [1.6, 31.5]	0.01
Composite	21*	7.0	5	1.3	5.1 [1.9, 13.5]	0.001

Emery et al. IAS 2007 WEPEB018

Use of ART Associated with Decrease Risk of AIDS/death at Higher CD4+ Strata

CD4+ count		UKCHIC		CASCADE	
		ART-naïve	Started ART	ART-naïve	Started ART
≥650	Rate (per 100PY)	1.0 (0.7-1.2)	0.9 (0.7-1.1)	0.9 (0.7-1.1)	0.6 (0.4-0.8)
500-649	Rate	1.6 (1.2-1.9)	1.0 (0.8-1.2)	1.1 (0.9-1.3)	0.8(0.6-1.1)
350-499	Rate	2.5 (2.1-2.8)	1.4 (1.2-1.6)	2.1 (1.8-2.4)	1.1 (0.8-1.1)
200-349	Rate	4.9 (4.4-5.5)	2.5 (2.2-2.8)	4.6 (4.0-5.1)	2.1 (1.6-2.6)

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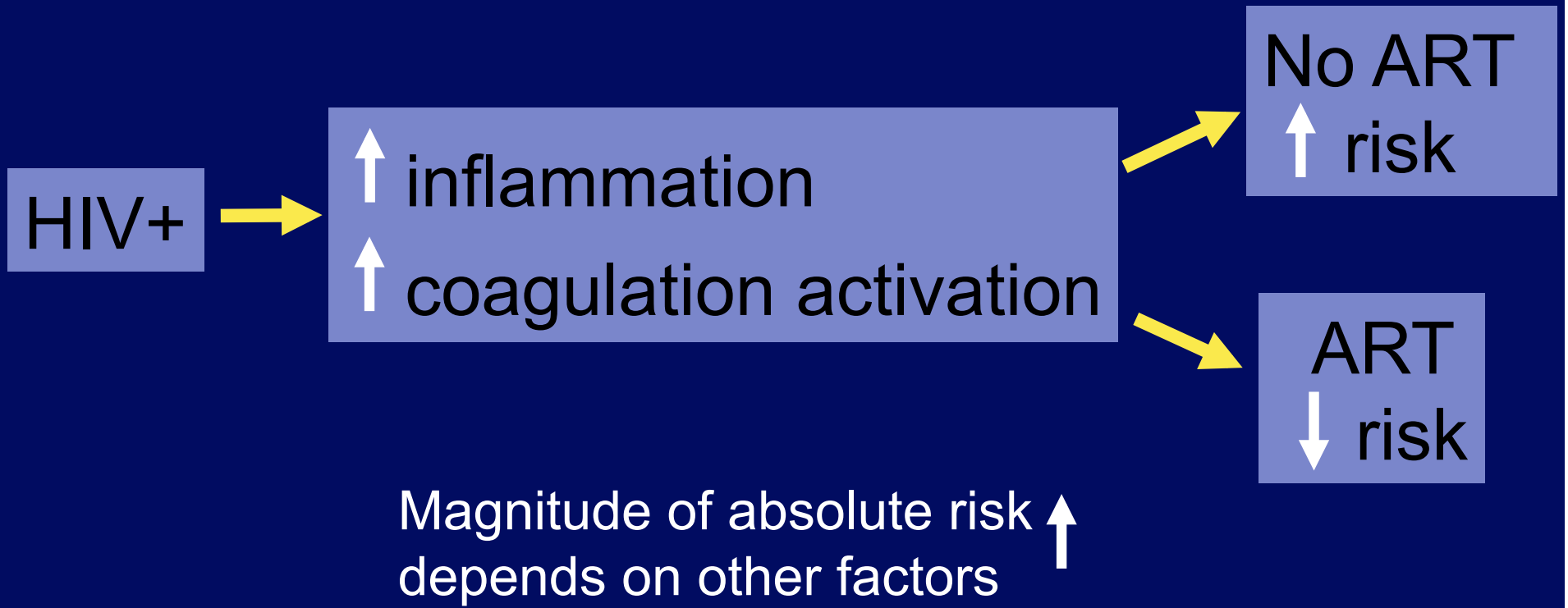
Hypothesis: HIV and Non-AIDS Disease Risk



Magnitude of absolute risk ↑ depends on other factors

Neaton J - Early Treatment symposium.

New data from SMART

- SHOCK (from SMART): serious 'side effects' occurred more often in the treatment interruption arm: ie treatment is PROTECTIVE
- Theory: risk linked to immune activation: large sample bank to analyse
- D-dimer is a marker of risk of heart disease in HIV-negative people (thicker blood). In HIV+ people not on treatment it is higher than HIV-
- In SMART, D-dimer increased off treatment, and reduced when on treatment - related to viral load
- Risk for event related to baseline D-dimer levels

D-Dimer Level (µg/mL) by ART Status at Baseline

Baseline ART	No.	Mean (SD)	
No ART	128	0.69 (0.95)	P=0.02
ART	368	0.48 (0.78)	
Total	496	0.53 (0.83)	

Normal range: 0 – 0.3 or 0.5 (µg/mL); 34% > 0.5

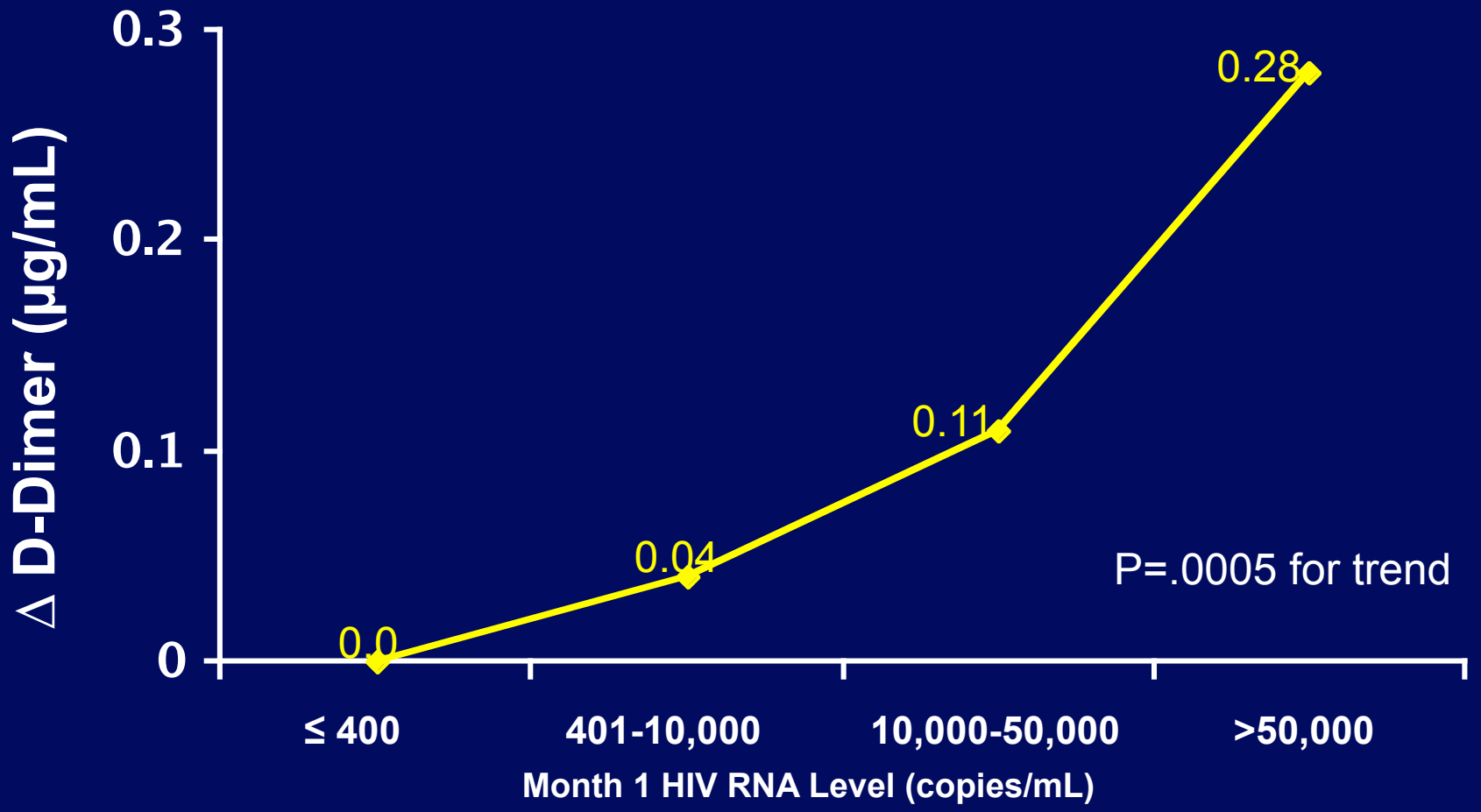
Neaton J - Early Treatment symposium.

Change in D-Dimer (µg/mL) from Baseline to 1 Month by Treatment Group

	DC		VS		Adj.	
	No.	Mean	No.	Mean	Diff.	P-value
No ART	67	0.02	61	-0.22	0.14	0.052
ART	181	0.10	187	-0.03	0.14	<0.001
Total	248	0.08	248	-0.08	0.15	<0.001

Neaton J - Early Treatment symposium.

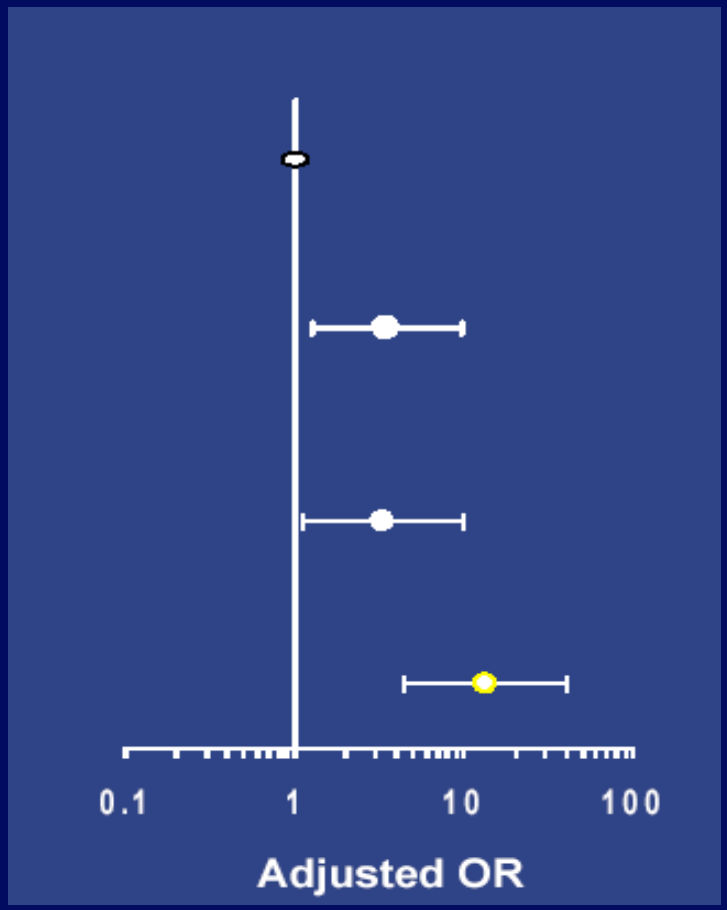
Change in D-Dimer* (µg/mL) from Baseline to 1 Month



Neaton J - Early Treatment symposium.

* DC patients on ART at baseline with HIV RNA ≤ 400 copies/mL

Adj. Odds Ratios for Death by Baseline D-dimer



D-Dimer (quartile)	OR	P-value
<.18	1.00	ref.
.18 - .34	3.46	.02
.34 - .64	3.30	.03
.64 +	13.37	<.0001

P<0.0001 for trend

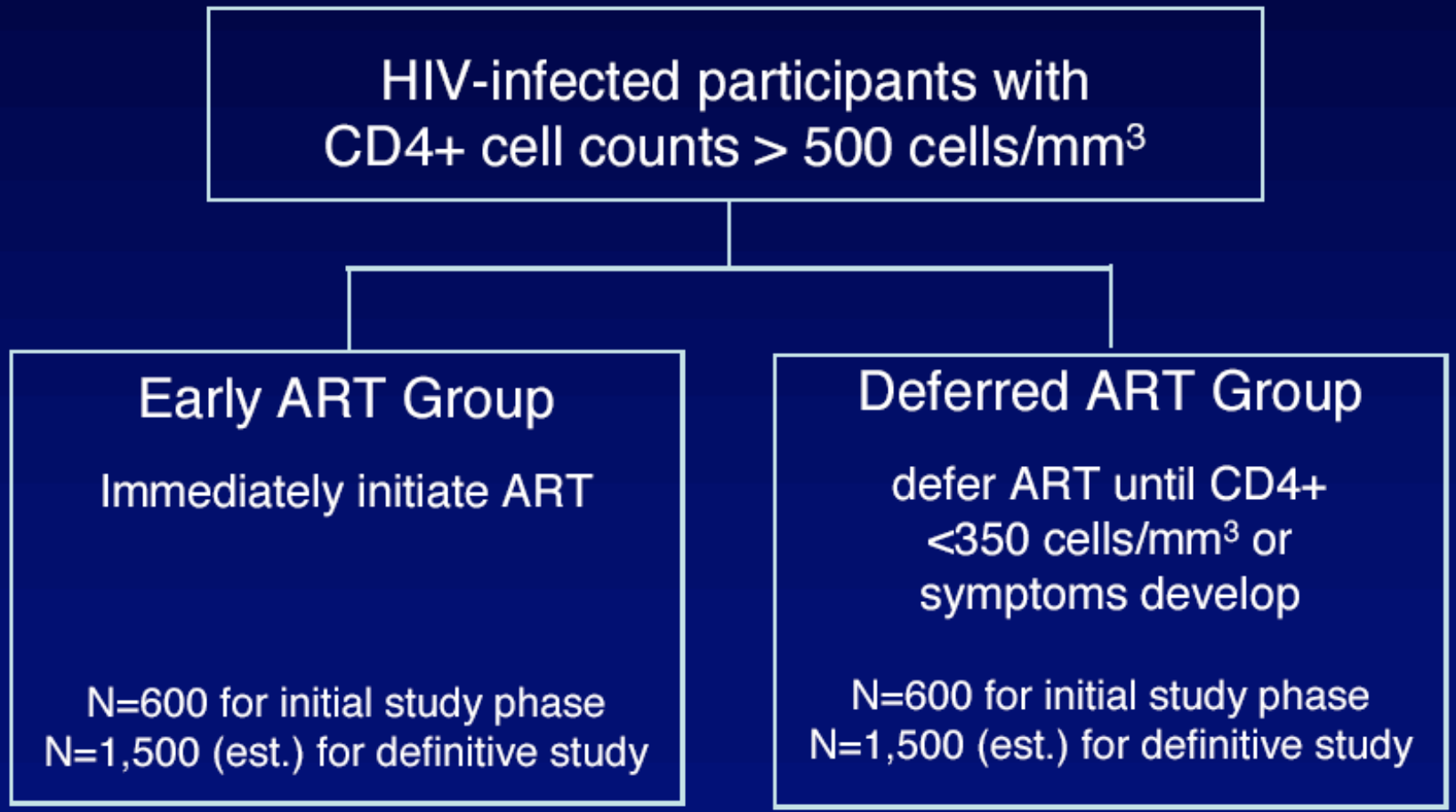
Neaton J - Early Treatment symposium.

Summary

- First data linking ongoing HIV replication (high viral load) to risk of death
- Mechanism for why treatment was protective in SMART study
- May lead to risk assessment for future treatment interruptions ie NOT if D-dimer is high
- Adds to data supporting research in earlier infection?

INSIGHT: the START trial

Strategic Timing of Antiretroviral Treatment

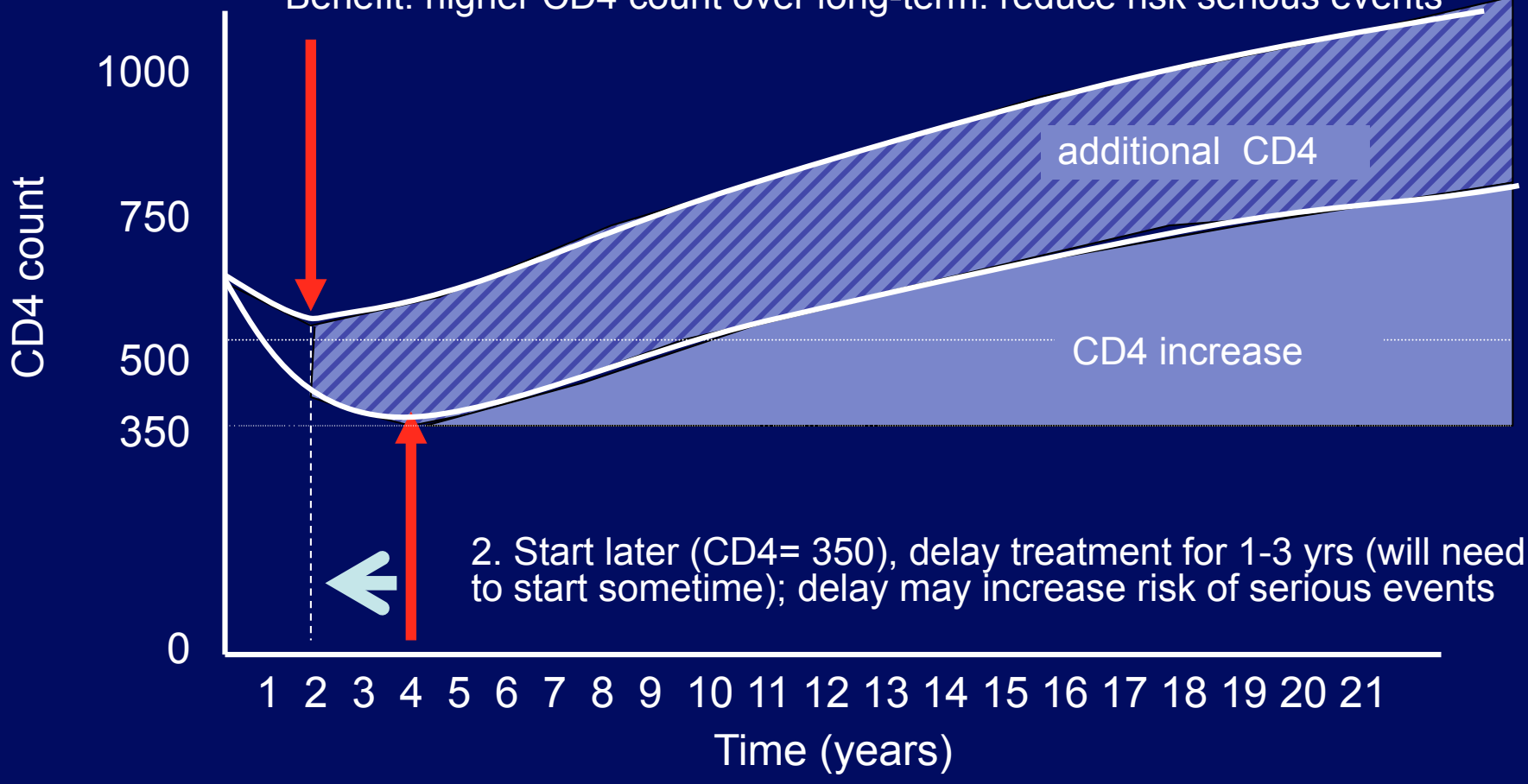


Neaton J - Early Treatment symposium.

Proposed risk:benefit

1. Start early (CD4= 500)

Benefit: higher CD4 count over long-term: reduce risk serious events



2 yrs vs 20 + years of sustained higher CD4 counts

Feedback from 4th IAS Conference

4. Other:

paediatrics; prevention

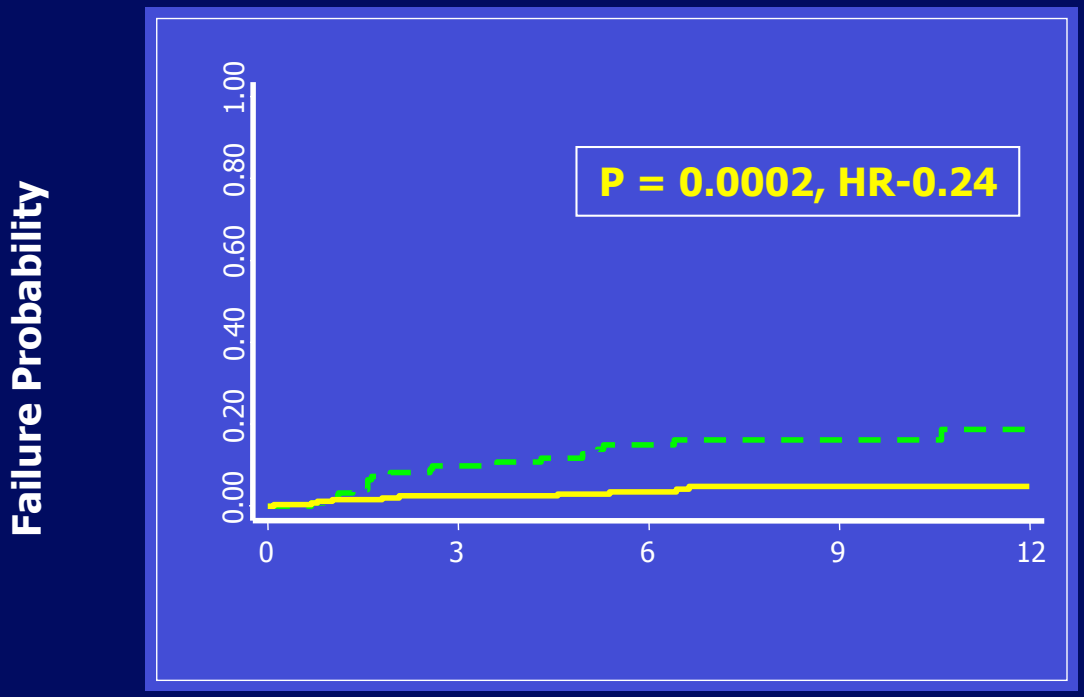
CHER

- 375 babies diagnosed with HIV before 12wks old
- Randomised to deferred treatment or immediate treatment to either 1st or 2nd birthday
- Start or restart when CD4% <25;
- Trial stopped early
- Death rate per 100 person-years (deferred vs immediate)

3 months	41 vs 10
3 to 6 months	23 vs 4
6 to 12 months	9 vs 3

WESS103: Violari et al. CHER STUDY

CHER: Time to Death



4.0% vs 16% of babies died
6.0 vs 25.3 d/ 100 PY

Patients at risk

	Month 0	Month 3	Month 6	Month 9	Month 12
Arm 1	125	104	72	44	22
Arm 2 & Arm 3	252	213	145	99	52

WESS103: Violari et al. CHER STUDY

Prevention

1. **Additional supportive data that circumcision is a protective intervention for sexually active men in high prevalence populations**
2. **Consistent washing was not associated with a reduction HIV-incidence, and early washing with an increased risk**
3. **Circumcision didn't show protection in population studies of gay men and MSM in Australia**
4. **PrEP with TDF used in sero-different couples with treatment and <50 copies VL and urine LH peak**

Oral session on circumcision, available online:

http://www.ias2007.org/pag/PSession.aspx?s=55

Back-up slides

Summary

- Post-coital penile cleansing was common
- Post-coital penile cleansing, as practiced in the rural population of Rakai, did not protect from male HIV acquisition among uncircumcised men
- Washing less than 10 minutes after intercourse may increase HIV risk, relative to delayed cleansing
- Washing with water had higher risk than dry cloth
- Washing-alone is associated with a non-significant increase in HIV-incidence among uncircumcised men

Makumbi FE et al. Abs WEAC1LB

PrEP for serodifferent couples and pregnancy

- 21 HIV-different couples. All male partners 50 copies/mL for at least three months. Semen viral load was undetectable in all men (though only tested at the start of the study).
- Urine LH-peak measurement to determine ovulation and pre-exposure prophylaxis
- tenofovir 36 and 12 hours before intercourse
- > 50% pregnancies achieved after 3 cycles (11/21) and 70% women (15/21) became pregnant after up to 10 attempts. All women tested negative for HIV-antibodies 3 months after the last exposure.
- pregnancy rates of natural conception in this study were substantially higher than by artificial reproduction techniques (40%)

Vernazza P. Abstract MoPDC01.

D-dimer and Mortality in SMART

- D-dimer is a fibrin degradation product that reflects ongoing activation of blood coagulation and fibronolytic systems
- A useful diagnostic tool for venous thromboembolism
- Related to CVD in several cohort studies of non-HIV-infected individuals
- Studied to a more limited extent in HIV:
  - D-dimer was higher in HIV+ patients than HIV- controls and was reduced with ART (41 HIV+ patients in the Swiss Cohort Study and 21 HIV- controls) JID 2002
  - Coagulation markers increased with advancing HIV disease and were greater than HIV- controls in women (144 participants in WIHS) JAIDS 2006

Change in D-Dimer (µg/mL) from Baseline to 1 Month by Treatment Group and Baseline HIV RNA Level*

	DC		VS		Adj.	
	No.	Mean	No.	Mean	Diff.	P-value
HIV RNA ≤400	134	0.13	127	-0.05	0.18	<0.001
HIV RNA >400	47	0.03	60	0.00	0.04	0.54

* Patients taking ART at entry

Results -1

Adjusted IRR of HIV incidence by post-coital cleansing

	Follow-up intervals	Incident cases/py	Incidence per 100py	Adjusted* IRR (95%CI)
Post coital washing with partners				
Overall	4,378	42/2629.3	1.60	
Never washed with any partner	567	4/326.7	1.22	1.0
Washed with some partners	178	1/111.5	0.90	0.47 (0.05 4.67)
Washed with all partners	3,633	37/2191.1	1.69	1.20 (0.42 3.38)

**** Adjusted for Condom use, marital status, age, non-marital partnerships, alcohol use with sex, perceived partners' HIV status, sex freq, number of sexual partners***

Consistent washing was not associated with a reduction HIV-incidence

Makumbi FE et al. Abs WEAC1LB

Results -2

Adjusted IRR of HIV incidence by duration from sex to penile washing among men who reported washing with all partners

	Follow-up intervals	Incident cases/py	Incidence per 100py	Adjusted IRR* (95%CI)
Duration from sex to penile washing (in minutes)				
Overall	3,632	37/2190.6	1.69	
0-3	1,787	25/1078.6	2.32	1.0
>3-10	984	10/596.0	1.68	0.62 (0.29 1.31)
>10	861	2/515.9	0.39	***0.13 (0.03 0.54)***

Chi-sq for trend=7.14, p=0.0076

HIV-incidence was significantly lower if washing was delayed > 10 minutes after sexual intercourse

Makumbi FE et al. Abs WEAC1LB

Results -3

Adjusted IRR of HIV incidence by post-coital penile cleansing methods

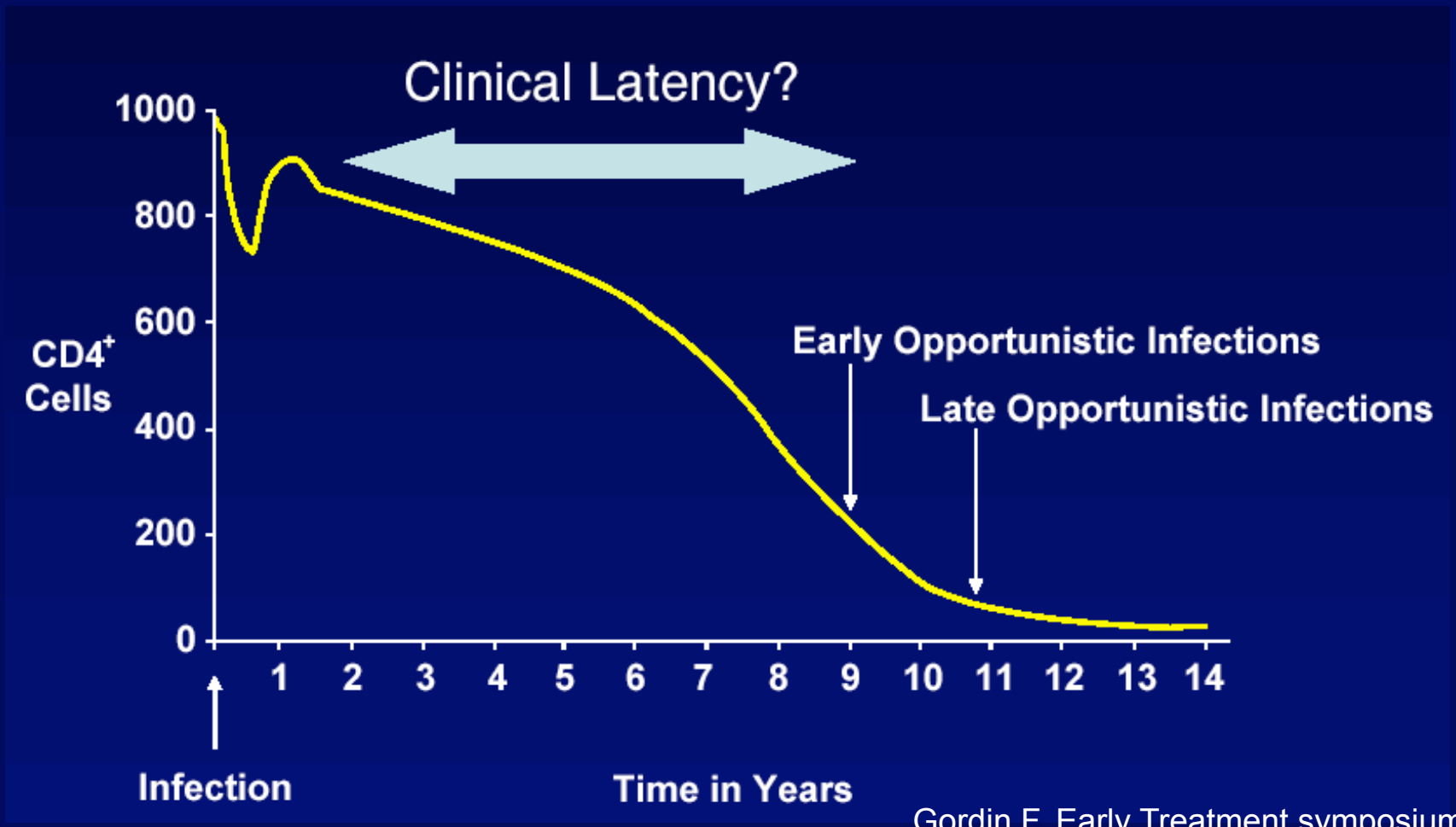
	Follow-up intervals	Incident cases/py	Incidence per 100py	Adjusted IRR * (95%CI)
Methods used for post-coital cleansing				
Overall	2,324	24/1566.4	1.53	
Cloth-alone	293	1/182.4	0.55	1.0
Cloth + washing	957	7/676.3	1.04	1.7 (0.20 4.55)
Washing-alone	1,074	16/707.7	2.26	3.7 (0.48 29.07)

Chi-sq for trend=3.62 , p=0.0554

Increasing degree of wetness (*assessed by self-reported washing*) was associated with a *borderline significant trend of increasing* risk of HIV-acquisition

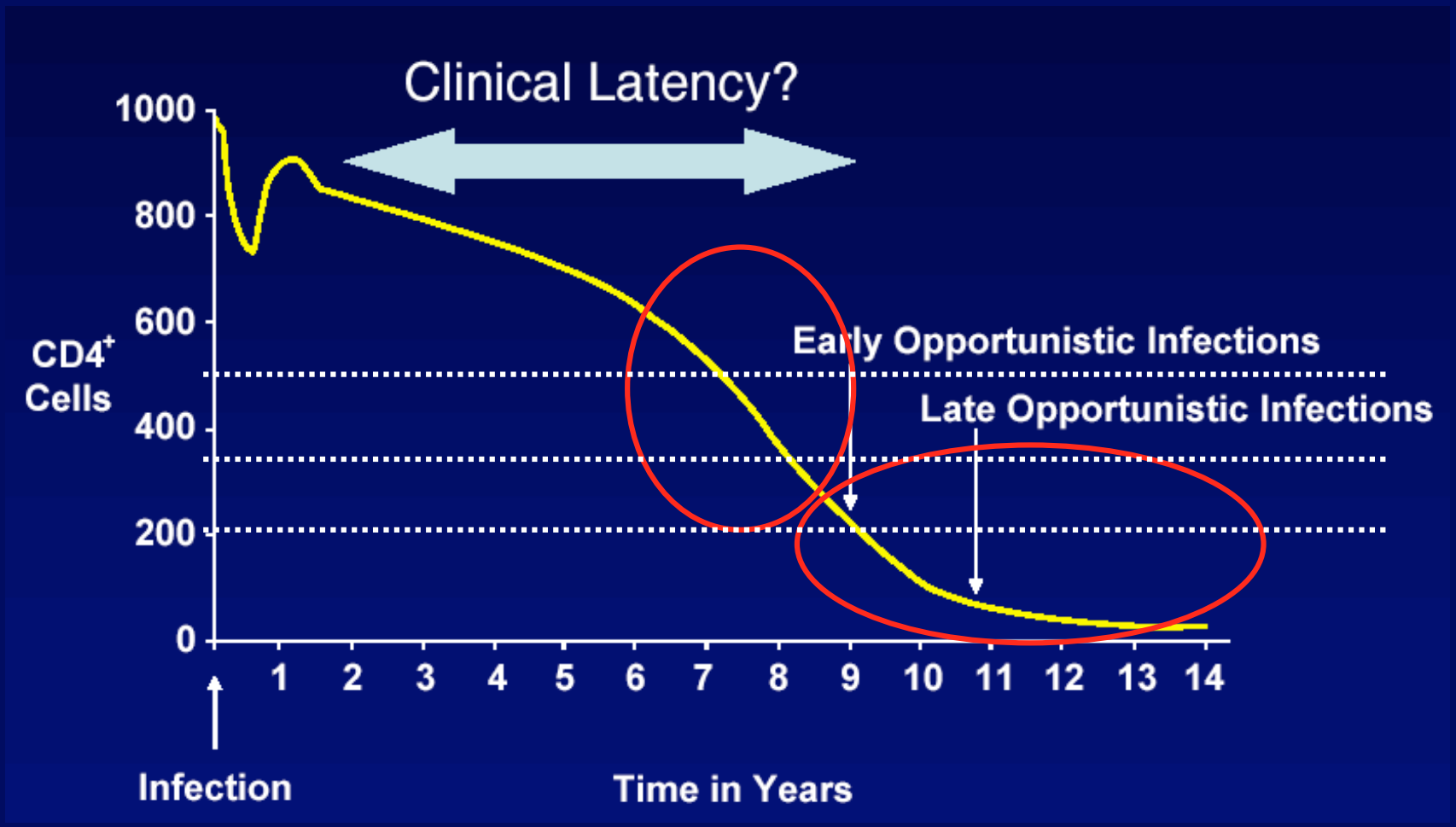
Makumbi FE et al. Abs WEAC1LB

Natural history - without treatment



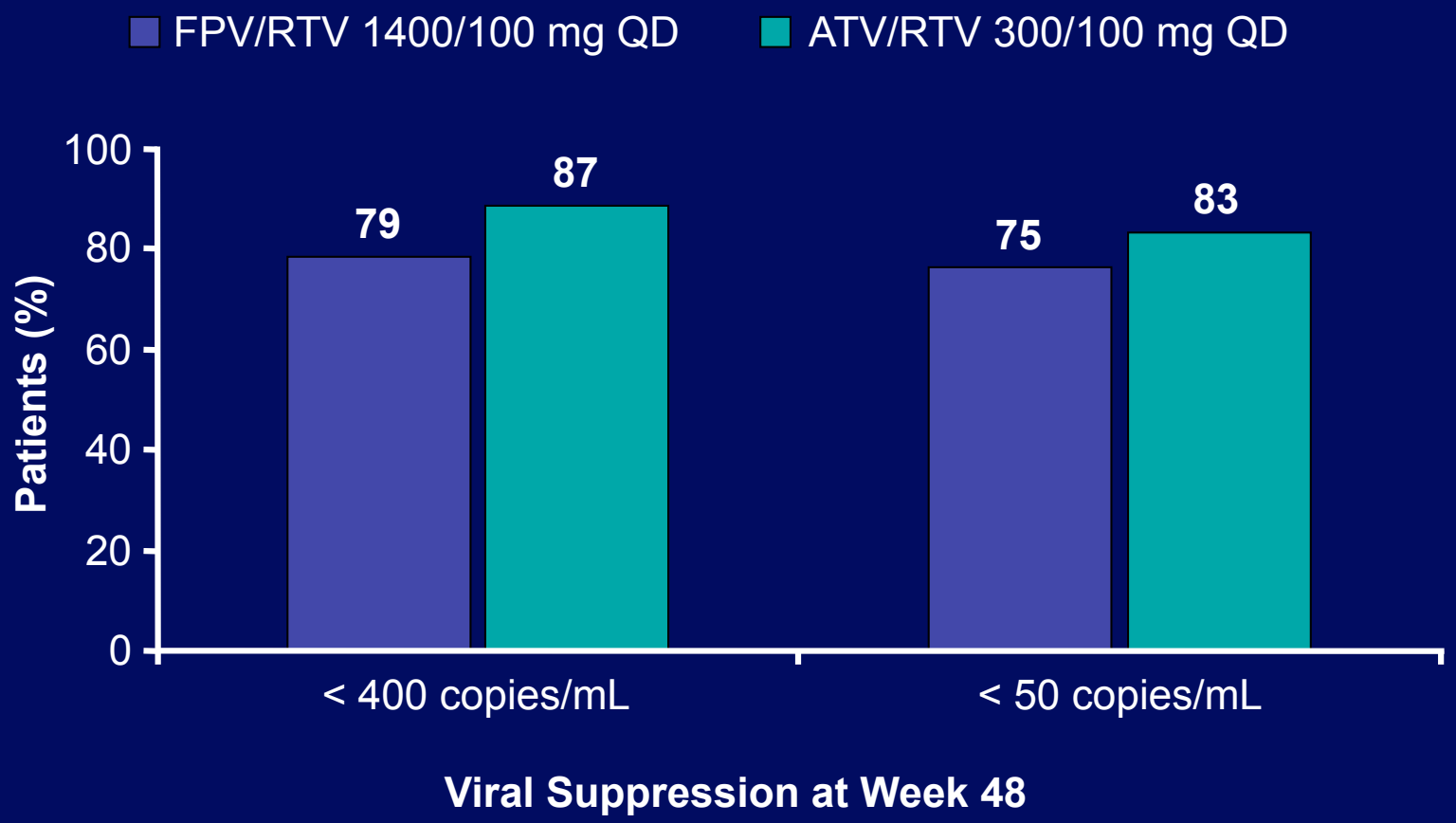
Gordin F. Early Treatment symposium.

Natural history - without treatment



FOS/r vs ATV/r (ALERT): 48wk naïve (ITT)

Only 50 pts per arm



Smith K, et al. Abs WEPEB023

SQV/r vs LPV/r (Gemini): Planned interim 24wk naïve (ITT)

- Same viral load response through trial
- Both ~81% <400 c/mL and 69% < 50 c/mL
- Viral failure higher in SQV/r arm: 10 pts (6%) vs 3 pts (1.8%)
- Resistance higher in SQV/r arm: 2 pts vs 0
- Lipid results slightly better for SQV/r (mainly TG)

Walmsley S, et al. Abstract TUPEB069.