18th Annual Conference of the British HIV Association (BHIVA)



Professor Fiona Mulcahy

St James's Hospital, Dublin, Ireland

18-20 April 2012, The International Convention Centre, Birmingham

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	COMPETING INTEREST OF FINANCIAL VALUE £1,000:								
Speaker Name	Statement								
Prof Fiona Mulcahy:	Professor Mulcahy has received grants and research support from MSD, Abbott, BMS, VIVVE, GSK, and Jannsen. She has also undertaken speaker, advisory board and consultancy work for MSD, Abbott, GSK, BMS, Jannsen and Gilead								
Date	April 2012								

18-20 April 2012, The International Convention Centre, Birmingham





10 Top Papers 2011-2012

Prof Fiona Mulcahy







Science's Choice for Breakthrough of the Year for 2011!!!!

"Bruce Alberts" editor in chief of Science" Science 2011:334;1604



Prevention of HIV infection with early antiretroviral therapy

Cohen M et al N.Eng J MED 2011:365;493-505



Prevention of HIV infection with early antiretroviral therapy Cohen M et al N. Eng J MED 2011:365;493-505

HPTN052: STUDY DESIGN

- 1763 stable, healthy, sexually active, serodiscordant couples
- 890 HIV-positive men and 873 HIV-positive women from sub-Saharan Africa (n = 954), Asia (n = 531), Latin America (n = 276) and the USA (n = 2)
- CD4 cell count: 350–550 cells/mm³

Randomization

Immediate ART (886 couples)

Primary transmission endpoint

Virally linked transmission events

Primary clinical endpoint

WHO Stage 4 clinical events, pulmonary tuberculosis, severe bacterial infection and/or death

WHO = World Health Organization





HPTN052: EARLY ART PREVENTS HIV TRANSMISSION TO SEXUAL PARTNERS

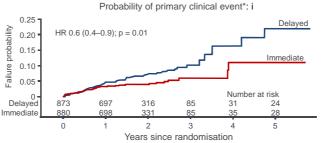


- 28/39 transmission events were linked
 - One in the ART immediate arm and 27 in the ART delayed arm (p < 0.001)
 - 23/28 (82%) transmissions in sub-Saharan Africa
 - 18/28 (64%) transmissions from infected participants with CD4 cell count > 350
 - 18/28 (64%) transmissions from female to male partners
- Viral suppression in treated individuals
 - Immediate arm: after 1 year, 90% of total had viral suppression
 - Delayed arm: after 1 year, 93% of total had viral suppression



HPTN052: PRIMARY CLINICAL EVENTS

- Median follow-up: 1.7 years
- 105 individuals experienced at least one primary clinical endpoint
 - 40 immediate arm: incidence 2.4/100 PY (95% CI: 1.7-3.3)
 - 65 delayed arm: iincidence 4.0/100 PY (95% CI: 3.1-5.0)



*Death, WHO Stage 4 clinical event, pulmonary tuberculosis or severe bacterial infection PY = person-years; CI = confidence interval; HR = hazard ratio



Implications

- Patient information
- Transmission prevention
- PEP guidelines
- Pregnancy options

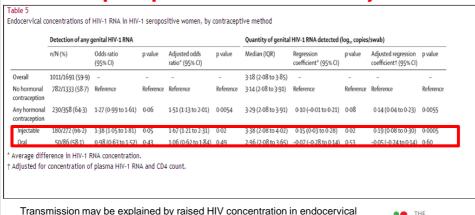


2



Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study **Prospective study of 3790** Hormonal contraception heterosexual, HIV-1 serodiscordant ■ No hormonal couples from seven African countries1 aHR 1.98 0 person-years) Injectable contraception was Rate of HIV-1 acquisition (1.06 - 3.68)p = 0.03more commonly used than oral pills 6.61 Analysis controlled for age, pregnancy, condom use and HIV plasma concentrations aHR 1.97 (1.12 - 3.45)3.78 Subgroup analysis showed p = 0.02 100 - Significantly increased HIV risk with 2.61 injectable contraceptive use ber 2 1.51 Non-significant increase with oral contraceptive use 0 Female Male HIV-negative HIV-negative GUIDE aHR = adjusted hazard ratio . Heffron R et al. Lancet 2012:12;19-26

Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study



Transmission may be explained by raised HIV concentration in endocervical secretions

. Heffron R et al. Lancet 2012:12;19-26







The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL



When to Start Antiretroviral Therapy in HIV-Associated Tuberculosis

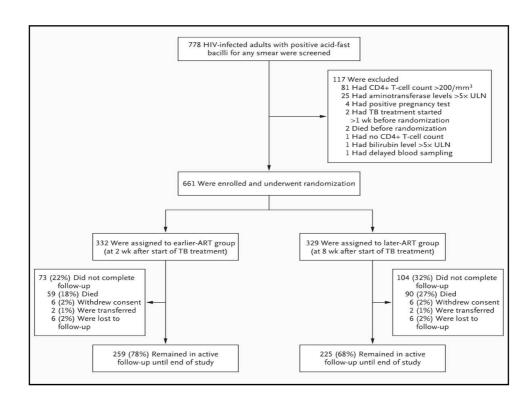
M. Estée Török, M.D., Ph.D., and Jeremy J. Farrar, M.D., Ph.D.

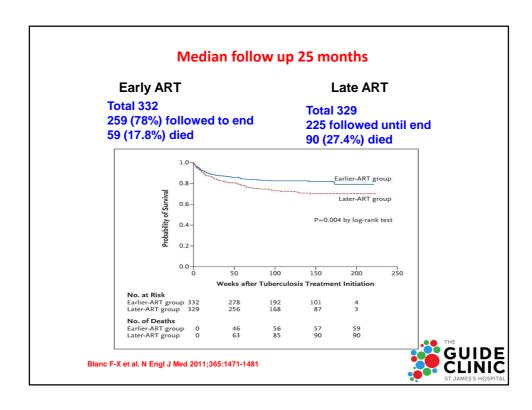


Earlier versus Later start of Antiretroviral Therapy in HIV- infected Adults with Tuberculosis Blanc Fx et al N Eng J Med 2011:365;1471-80

- 661 pts randomised to early ART (D4T/ 3TC/EFV) @ 2 vs 8 weeks post TB Rx initiation
- Median CD4 25x10⁶/ml
- Median HIV VL 5.64 log
- TB Rx Inah/rif/PYZ/Eth x 2 months, followed by rif/Inah x4 months.
- Prophylaxis with co-trimoxazole and fluconazole (CD4<200)







Results

- **Survival Rate** Earlier-ART group vs later-ART group (P=0.004 by the logrank test) **Death rate** was 8.28 / 100 pys (95% confidence interval [CI], 6.42 to 10.69) in the earlier-ART group vs 13.77/100 pys (95% CI, 11.20 to 16.93) in the later-ART group (P=0.002).
- In the multivariate analysis, the **adjusted hazard ratio for death** in the earlier-ART group, vs the later-ART group, was **0.62** (95% CI, 0.44 to 0.86; P=0.006).
- Tuberculosis-associated IRIS was significantly increased 110 events in the earlier-ART group,, vs 45 events in the later-ART group (hazard ratio, 2.51; 95% CI, 1.78 to 3.59; P<0.001).
- Six deaths were directly related to tuberculosis-associated IRIS, all occurring in the earlier-ART group.

Implications

- Benefit of early initiation of ART in patients with higher CD4+ T-cell counts ??
- Benefit in patients other than those with pulmonary tuberculosis, ??
- IRIS in patients with pulmonary tuberculosis is rarely lifethreatening. But In patients with more severe forms of disease, such as tuberculous meningitis, mortality is much higher and intracranial IRIS may prove fatal.



Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)-associated Tuberculous meningitis.

Torok ME, Yen NT, Chau TT, et al Clin Infect Dis 2011;52:1374-1383

- Randomized, double-blind, placebo-controlled trial
- 253 Vietnamese patients with tuberculous meningitis,
- ART was given within 1 week or was deferred until 8 weeks after presentation.
- Results:
 - no reduction in mortality
 - increased frequency of severe adverse events in the group that received ART within 1 week after presentation.





The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

JULY 7, 2011

VOL. 365 NO. 1

New Regimens to Prevent Tuberculosis in Adults with HIV Infection

Neil A. Martinson, M.B., B.Ch., M.P.H., Grace L. Barnes, B.S.N., M.P.H., Lawrence H. Moulton, Ph.D., Reginah Msandiwa, R.N., Harry Hausler, M.D., Ph.D., Malathi Ram, Ph.D., James A. McIntyre, M.B., B.Ch., Glenda E. Gray, M.B., B.Ch., and Richard E. Chaisson, M.D.



```
•1148 pts ( S AFRICA)

•Median CD4 484

•>18 yrs

•5mm+ tuberculin skin test

Exclusion factors:

•active TB

•TB Rx >2/12

•ART

•CD4 < 200

Four regimens:

once-weekly INH 900 mgs-RPT 900mgs DOT x12/52

twice-weekly INH 900mgs-RIF 600mgs DOT x 12/52

daily self-supervised INH 300mgs x 6/12

daily self-supervised INH 300mgs indefinitely

Median follow-up duration was approximately 4 years.
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- The incidence rates of TB were 1.4–2.0 per 100 person-years, without significant differences between the four regimens.
- Treatment completion was greater for the two rifamycin-containing regimens, and grade 3 or 4 adverse effects were more common for INH taken indefinitely



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

DECEMBER 8, 2011

VOL. 365 NO. 23

Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

Timothy R. Sterling, M.D., M. Elsa Villarino, M.D., M.P.H., Andrey S. Borisov, M.D., M.P.H., Nong Shang, Ph.D., Fred Gordin, M.D., Erin Bliven-Sizemore, M.P.H., Judith Hackman, R.N., Carol Dukes Hamilton, M.D., Dick Menzies, M.D., Amy Kerrigan, R.N., M.S.N., Stephen E. Weis, D.O., Marc Weiner, M.D., Diane Wing, R.N., Marcus B. Conde, M.D., Lorna Bozeman, M.S., C. Robert Horsburgh, Jr., M.D., Richard E. Chaisson, M.D., for the TB Trials Consortium PREVENT TB Study Team*



What Regimen should we use?



Centers for Disease Control and Prevention

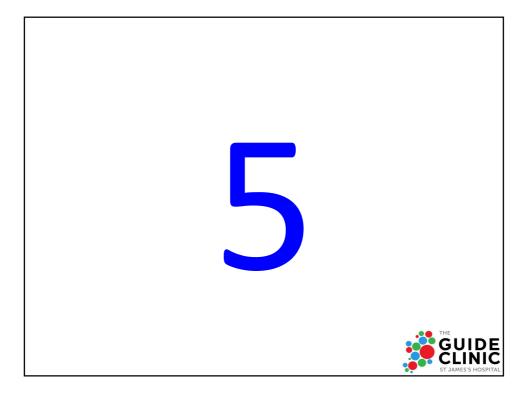
CDC 24/7: Saving Lives. Protecting People. Saving Money through Prevention.

Table 1. Latent TB Infection Treatment Regimens

Drugs	Duration	Interval	Minimum doses
Isoniazid	9 months	Daily	270
		Twice weekly*	76
Isoniazid	6 months	Daily	180
		Twice weekly*	52
Isoniazid and Rifapentine	3 months	Once weekly*	12
Rifampin	4 months	Daily	120

^{*}Use Directly Observed Therapy (DOT)





Efficacy of Quadravalent HPV vaccine against HPV infection and Disease in males

Giuliano AR et al N Eng J Med 2011 :364;401-11



HPV vaccine against Anal HPV Infection and Anal Intraepithelial Neoplasia

Palefsky et al N Eng J Med 2011:365;1576-85

- 602 MSMs enrolled
 - 299 vaccinated with qHPV
 - 299 placebo
- Age 16 to 26 years
- 5 or fewer lifetime sexual partners
- Insertive or receptive anal intercourse or oral sex within the past year.

Exclusion criteria:

- History or presence of clinically detectable anogenital warts or lesions suggesting other STI.
- HIV positive



Serum specimens for HPV serologic testing:

Obtained on study day 1 and month 7.

Detailed anal examination:

Day 1, months 7, 12, 18, 24, 30 and 36.

Each visit:

Dacron swabs – anal cytologic analysis HPV DNA – PCR assays Digital rectal examination and standard anoscopy



RESULTS

71.8% completed the 36 months follow- up period.

2/3 included in the pre-protocol efficacy population.

- Subjects (Pre-Protocol Efficacy)
 - were seronegative on day 1
 - PCR-negative for both swab and biopsy specimens from day 1 through month 7 for the relevant vaccine HPV type (or types)
 - did not have any protocol violations
 - received all 3 vaccinations within 1 year
 - had 1 or more follow-up visits after month 7
- Case counting commenced at month 7
- 194 qHPV recipients and 208 placebo were eligible for the pre- protocol efficacy analysis of HPV – 6, 11, 16 or 18 – related AIN end point.
- HPV- DNA positive:

27.4 % HPV 6 or 11 16.4% HPV 16 11.3% HPV 18



End Point		qHPV Vaco	cine (N=299))		Placebo	Observed Efficacy (95% CI)		
	No. Included in Analysis	No. of Affected Partici- pants	Person-Yr at Risk	Events per 100 Person-Yr at Risk	No. Included in Analysis	No. of Affected Partici- pants	Person-Yr at Risk	Events per 100 Person-Yr at Risk	
AIN due to any HPV type	275	74	569.0	13.0	276	103	588.4	17.5	25.7 (-1.1 to 45.6)
HPV-6, 11, 16, or 18	2/5	38	607.1	6.3	276	11	611.9	12.6	50.3 (25.7 to 67.2)
HPV-16 or 18	275	12	662.7	1.8	276	27	668.3	4.0	55.2 (8.5 to 79.3)
AIN due to a specific HPV type									
HPV-6	275	18	644.8	2.8	276	47	645.3	7.3	61.7 (32.8 to 79.1)
HPV-11	275	13	651.2	2.0	276	25	660.5	3.8	47.3 (-7.1 to 75.2)
HPV-16	275	8	668.7	1.2	276	18	678.6	2.7	54.9 (-9.0 to 83.0)
HPV-18	275	5	671.9	0.7	276	11	684.5	1.6	53.7 (-44.6 to 87.4
By lesion type									
AIN grade 1	275	31	619.3	5.0	276	62	624.1	9.9	49.6 (21.2 to 68.4)
Condyloma acuminatum	275	13	651.3	2.0	276	31	664.2	4.7	57.2 (15.9 to 79.5)
Flat lesion	275	27	636.0	4.2	276	48	641.3	7.5	43.3 (7.3 to 66.0)
AIN grade 2 or 3	275	18	660.1	2.7	276	39	655.2	6.0	54.2 (18.0 to 75.3)
Grade 2	275	11	668.0	1.6	276	29	671.5	4.3	61.9 (21.4 to 82.8)
Grade 3	275	10	665.9	1.5	276	19	672.8	2.8	46.8 (-20.2 to 77.9
Anal cancer	275	0	678.4	0.0	276	0	694.8	0.0	NA

* The intention-to-treat population consisted of study participants who received at least one dose of the study drug. A participant may have been counted more than once if multiple lesions in different categories developed. NA denotes not applicable.



Efficacy against HPV 6/11/16/18 Anal Intraepithelial Neoplasia (AIN)

Young Men (16 – 26 years) Per Protocol Efficacy Population ~3 years of Follow Up

	qHPV N = 299				Placebo N = 299					
Endpoint	n	# Cases	PY at risk	IR/100 PY at Risk	n	# Cases	PY at Risk	IR/100 PY at Risk	Efficacy %	95% CI
HPV 6/11/16/18- related AIN/Anal Cancer	194	5	381.1	1.3	208	24	411.6	5.8	77.5	39.6, 93.3
AIN1	194	4	383.1	1.0	208	16	413.8	3.9	73.0	16.3, 93.4
AIN2 or Worse	194	3	383.9	0.8	208	13	417.2	3.1	74.9	8.8, 95.4

Evaluation of the Efficacy of qHPV against AIN was studied in Men having Sex with Men (MSM) to ensure adequate end points during the period of follow up

Ref: Palefsky, J. M. et al. HPV Vaccine against Anal HPV Infection and Anal Intraepithelial Neoplasia. N Engl J Med 2011;365:1576-85.

Efficacy against HPV 6/11/16/18 Anal Intraepithelial Neoplasia (AIN)

Young Men (16 – 26 years) Per Protocol Efficacy Population ~3 years of Follow Up

	ı	qHPV N = 299		Placebo N = 299					
n	# Case	PY at risk	IR/100 PY at Risk	n	# Cases	PY at Risk	IR/100 PY at Risk	Efficacy %	95% CI
194	5	381.1	1.3	208	24	411.6	5.8	77.5	39.6, 93.3
194	4	383.1	1.0	208	16	413.8	3.9	73.0	16.3, 93.4
194	- 3	383.9	0.8	208	13	417.2	3.1	74.9	8.8, 95.4
	194	n Case: 194 5 194 4	N = 299 # PY at risk 194 5 381.1 194 4 383.1	N = 299 R/100 PY at risk Risk	N = 299 R/100 PY at risk Risk n Risk n	N = 299 N = 299 N = 299 N = 18/100 PY at risk Risk n Cases 194 5 381.1 1.3 208 24 194 4 383.1 1.0 208 16	N = 299 N = 299	N = 299 N = 299 N = 299 N = 299 IR/100 PY at Risk n Cases Risk Risk 194 5 381.1 1.3 208 24 411.6 5.8 194 4 383.1 1.0 208 16 413.8 3.9	N = 299 N = 299 N = 299

Multiple Infections occurred frequently

At least 3 cases likely to be not due to HPV 6/11/15

Ref: Palefsky, J. M. et al. HPV Vaccine against Anal HPV Infection and Anal Intraepithelial Neoplasia. N Engl J Med 2011;365:1576-85

Efficacy against HPV 6/11/16/18 Persistent Infection (Anal)

Young Men (16 – 26 years) Per Protocol Efficacy Population ~3 years of Follow Up

			HPV =299)			Pla (N:			
Endpoint	n	# of Cases	PY At Risk	IR per 100 PY at Risk	n	# of Cases	PY at Risk	IR per 100 PY at Risk	Efficacy (%) (95% CI)
HPV 6/11/16/18	193	2	385.6	0.5	208	39	381.2	10.2	94.9 (80.4, 99.4)

Evaluation of the Efficacy of qHPV against Persistent Infection (Anal) was studied in Men having Sex with Men (MSM) to ensure adequate end points during the period of follow up

Ref: Palefsky, J. M. et al. HPV Vaccine against Anal HPV Infection and Anal Intraepithelial Neoplasia. N Engl J Med 2011;365:1576-85.

Implications

- Study shows efficacy of the qHPV against HPV- 6, 11, 16 or 18related AIN grade 1,2 or 3, against persistent anal infection with
 each of the four HPV strains, and against anal detection at any time
 of DNA of each of the 4 HPV types, in both pre- protocol efficacy and
 the intention –to- treat population.
- The proportion of participants who reported serious adverse events was relatively low and was similar in both groups.
- Does this apply to our HIV+ pts???
 - age of the participants,
 - short follow-up time,
 - limited sexual activity of participants.



6

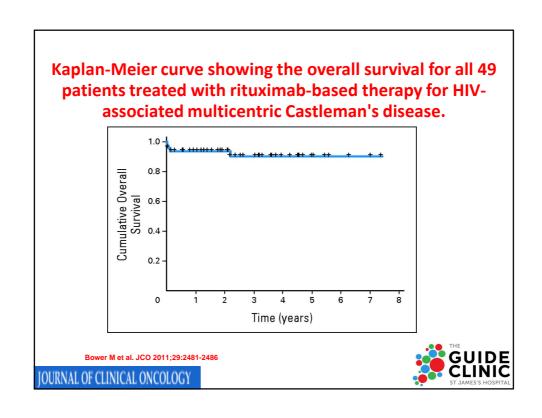


Clinical features and outcome in HIVassociated Multicentric Castlemans Disease

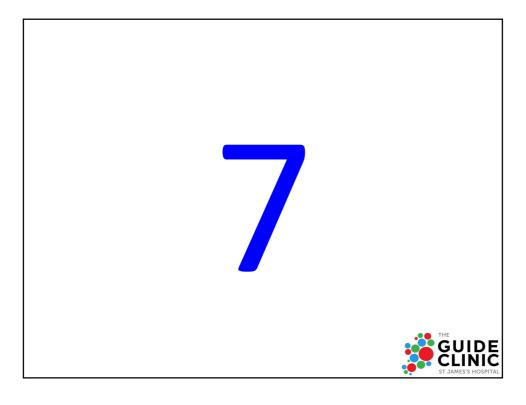
Bower M et al J Clin Oncol 2011:29;2481-5

- 61 pts with MCD
- 53 (87%) male, median age 42 yrs
- Median interval HIV and MCD DX 2.4 yrs(0-24)
- Median follow up 4.2 yrs
- 49 pts RX Rituximab +/- etoposide
 - 2yr survival 94%(CI 87-100%) vs 42% (14-70%) pre rituximab
 - 5yr survival 90%(CI 81-100%) vs 33% (6-60%) pre rituximab
 - P<.001
 - 8/46 pts with clinical remission relapsed





•	ns Disease	al criteria defining a	
criteria	% of patients	criteria	% of patients
fever	98	cough	61
C-reactive protein > 20 mg/L in the absence of any other aetiology	92	Nasal obstruction	40
Peripheral lymphadenopathy	100	Xerostomia	40
splenomegaly	95	Rash	62
oedema	18	Neuro features	66
thrombocytopenia	33	hypoalbuminaemia	70
Pleural effusion	18	Jaundice	14
Acsites	8	Autoimmune hemolytic anemia	43 THE



Host Genomics and HCV treatment response

Clark PJ , Thompson A J Gastroenterol Hepatol 2012:2,212-22

- Human genome >3 billion nucleotide base pairs with 90% identical between individuals
- Most common genetic variation is a single nucleotide polymorphism (SNP)
- Genome wide ass studies (GWAS) now widely available
 - Major limitations
 - Necessitates v large well characterised cohort
 - Do not include rare variants
 - High no of ass tests required



Genotype1 HCV and Peg-ifn/RBV treatment response

IDeAL Study

- 1137/1671 pts pharmacogenomic analysis included in analysis
- SNP rs12979860 biallele (C/T) with 3 genotypes CC,CT,TT
- SNP rs12979860/IL28B CC genotype ass with2-3 increase in SVR in 3 ethnic groups
- Also ass with RVR and EVR
- Freq of IL28B allele lower in AA 64% vs 89% Caucasian pts.
- 6 other SNPs on a common haplotype also ass with SVR
- Other studies G allele of rs8099917 ass with non response to treatment, both tag a common haplotype

- Spontaneous clearance increased with favourable IL28B allele
 CC 64% vs CT24% vsTT6%
- More likely to present with jaundice
- Poor IL28B alleles ass with more severe steatosis and LDL-C levels, elevated ALT
- HIV does not modulate the association
- Response rates to IFN RX post transplant improve where donor or recipient carry the good response variant!! The effect is additive!

Non-Genotype -1HCV

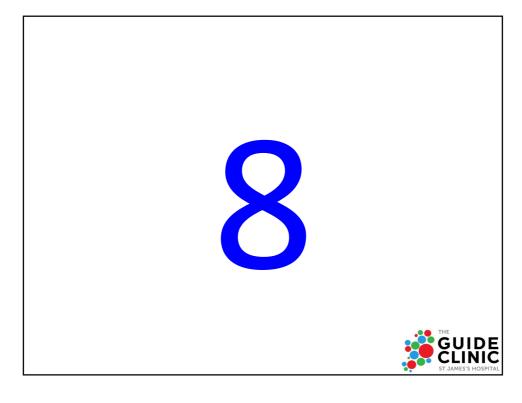
- No significant ass between genotype and SVR in Genotype 2/3 HCV
- Possibly in genotype 4 /6 HCV



Implications

- IL28B most important re Neg Predictive Value (NPV)
- In poor responders delay for DAAs?
- Treat seroconverters with poor allele with IFN/RBV?
- Choose optimum transplant donor organs?
- Other alleles may prove more important





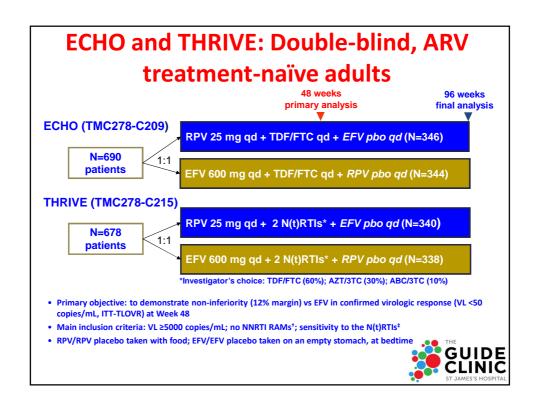
Rilpivirine versus Efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected withHIV-1 (THRIVE)

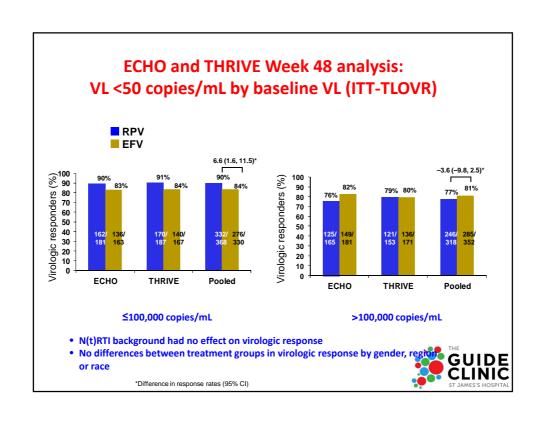
Cohen C et al Lancet 2011:378;229-36

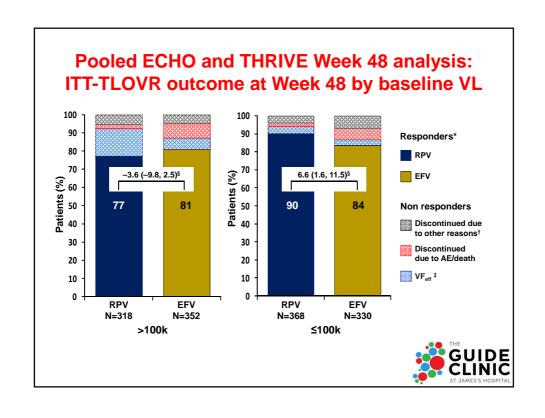
Rilpivirine versus Efavirenz with Tenofovir and Emtricitabine in treatment- naive adults infected withHIV-1 (ECHO)

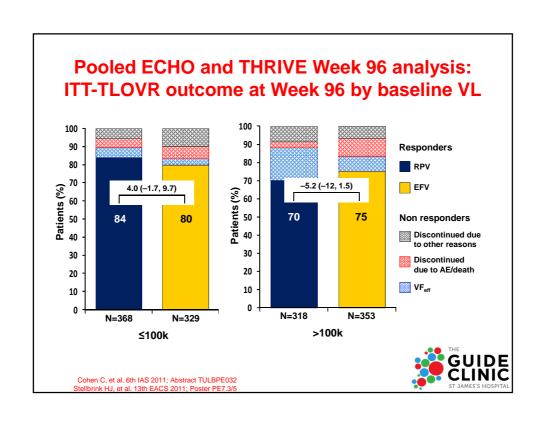
Molina JM et al Lancet 2011:378;238-46











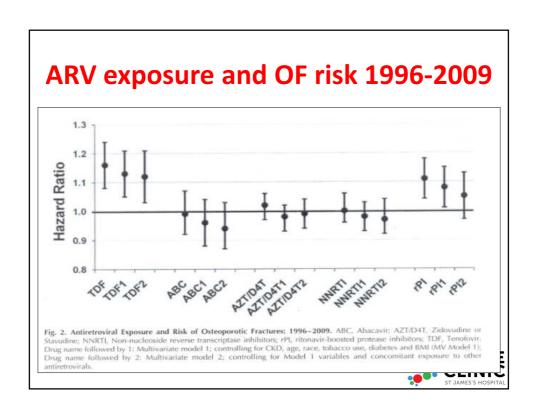


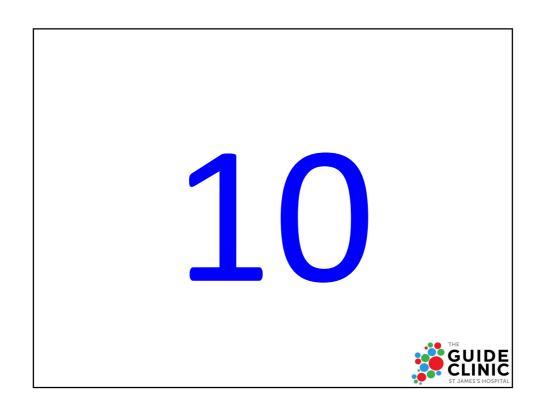


Osteoporotic fracture risk associated with cumulative exposure to Tenofovir and other antiretroviral agents Bedimo R et al AIDS 2012,26:

- 56 660 HIV pts
- · Risk of OF was examined by
 - Univariate analysis : UV
 - Multivariate analysis :MV1 (controlling for race,age,tobacco use, diabetes,BMI,HepC)
 - MV2 (controlling for MV1 variables + concomitant ARV exposure)







Association of hiv infection with spontaneous and iatrogenic preterm delivery: effect of haart

Marta Lopez^a, Francesc Figueras^a, Sandra Hernandez^a, Montserrat Lonca^b, Raul García^a, Montse Palacio^a and Oriol Coll^a

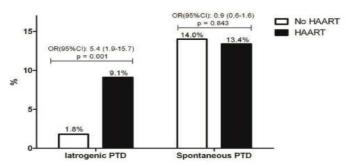
AIDS 2012 Jan 2;26(1):37-43

Single Center Study

- 1557 women analyzed (519 infected and 1038 non-infected)
- Excluded Hx of &risk factor for PTD, active IVDU, multiple geststion
- latrogenic preterm delivery: delivery < 37 weeks due to the following reasons: preeclampsia, intrauterine growth restriction, fetal distress or intrauterine fetal death
- Spontaneous preterm delvery: delivery < 37 weeks including premature rupture of membranes

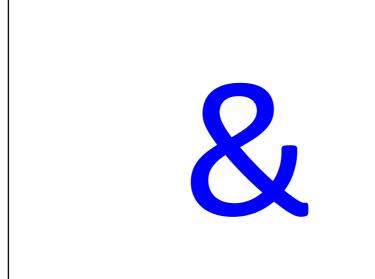
 Incidence of preterm delivery: 19.7% in HIV+ group vs 8.5% in controls (OR 2.6 95%CI 1.9-3.6;p<0.001)

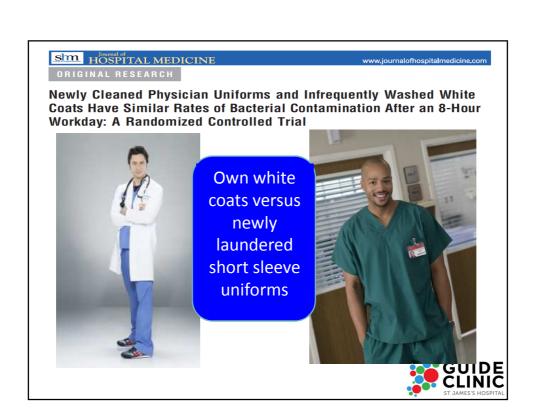
Incidence of each type of prematurity by HAART use



- significant association between use of HAART in the second half of pregnancy and iatrogenic preterm delivery (OR 6.2 CI1.4-26.8 p=0.015)
- no association between spontaneous preterm delivery and use of HAART

Lopez et al. AIDS 2011





Rate of bacterial colonisation of newly laundered uniforms

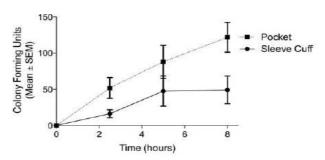


FIGURE 2. Time course of bacterial contamination after donning newly laundered uniforms.





No differences in:

- •in cfu from white coats vs newly laundered uniforms, P=0.61
- •in no. MRSA contaminated
- in bacterial or MRSA wrist contamination



