

Metabolic Complications

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Lower Incidence of Lipodystrophy With ABC/3TC vs d4T/ddl

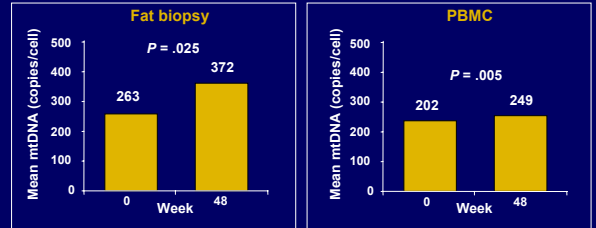
- FIRST study: randomized, prospective trial
 - ABC/3TC vs d4T/ddl backbones
 - Subgroup enrolled in metabolic substudy
- Increases in body cell mass and fat through Month 12 in both arms
- Between Months 12 and 32, reductions in total and regional fat in d4T/ddl arm but not in ABC/3TC arm

Rate of Change From Week 0-32*	d4T/ddl	ABC/3TC
Total body fat (kg/month)	-0.08	0.08
Hip circumference (cm/month)	-0.18	0.10
Mid-arm skinfold fat area (cm ² /month)	-0.21	0.05
Waist skinfold fat area (cm ² /month)	-0.62	0.62

* All $P < .05$

Shlay et al. Abstract ThOrB1360.

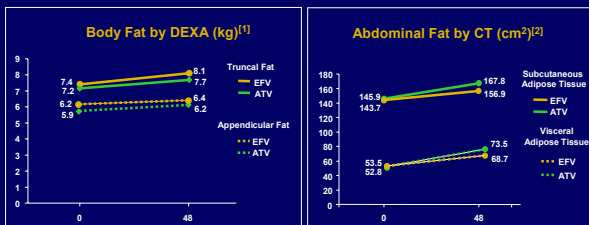
Recovery in mtDNA Following Switch to NRTI-Sparing Regimen



- When stratified for previous NRTI:
 - Increases in fat mtDNA only significant with switch from d4T (not AZT)
 - Increases in PBMC mtDNA only significant with switch from AZT (not d4T)

Boyd et al. Abstract WePpB2064.

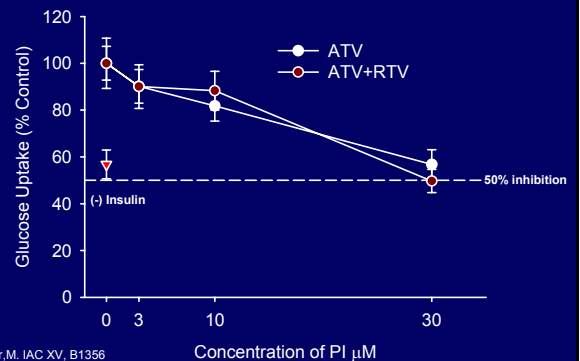
BMS-034: Total Body Fat Changes (DEXA) After 48 Weeks of Atazanavir-Based Therapy



- Also in vitro study: No difference in glucose uptake between ATV vs ATV + RTV (< 3 μM concentration)^[2]

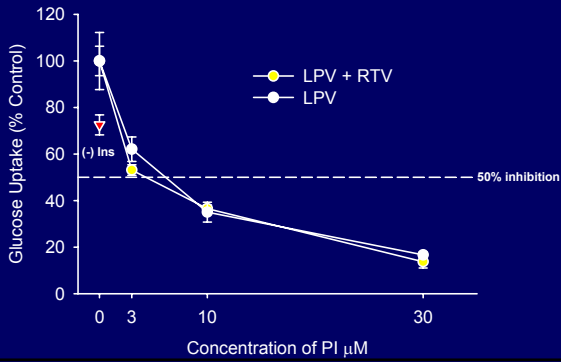
1. Noor et al. Abstract WePpB5874. 2. Noor et al. Abstract ThOrB1356.

Effect of ATV+RTV (2 μM) on Glucose Uptake in Human Primary Adipocytes

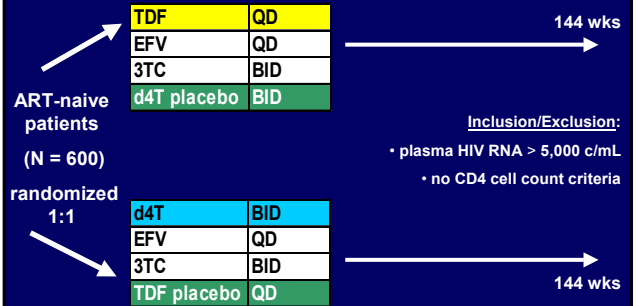


Noor, M. IAC XV, B1356

Effect of LPV+RTV (2 μM) on Glucose Uptake in Human Primary Adipocytes

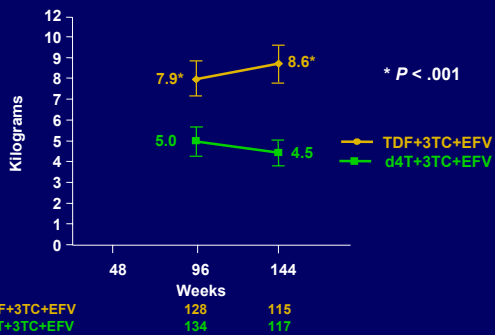


Study 903 – Week 144 Study Design



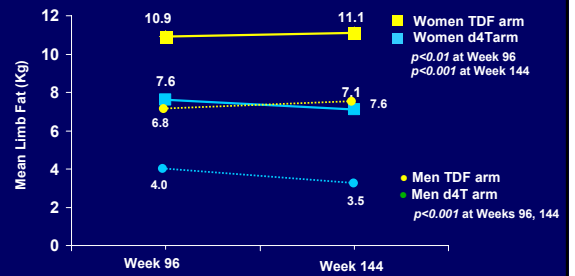
Gallant JE. XV Int AIDS Conf, July 2004, Bangkok, #4538

GS 903 Study: Mean (95% CI) Total Limb Fat at Week 144



Gallant et al. Abstract TuPeB4538.

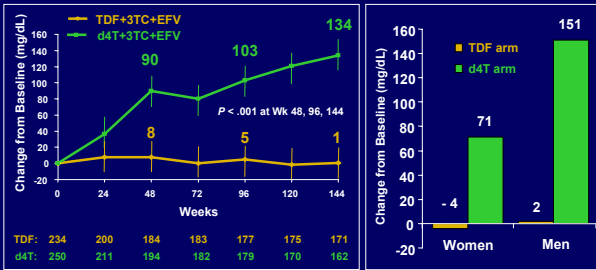
Study 903 – Week 144 Limb Fat Changes*



Ruiter A de. XV Int AIDS Conf, July 2004, Bangkok, #1083

GS 903 Study: Greater Effect of Stavudine on Triglycerides

- Increased TG elevations in TDF vs d4T,^[1] and in men vs women on d4T^[2]

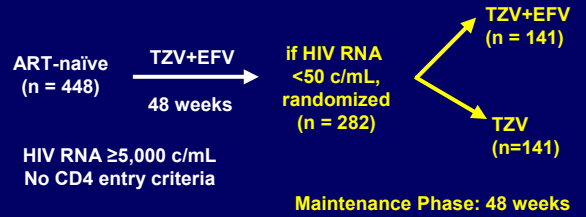


1. Gallant et al. Abstract TuPeB4538. 2. De Ruiter et al. Abstract MoOrB1083.

ESS40013

Study Design

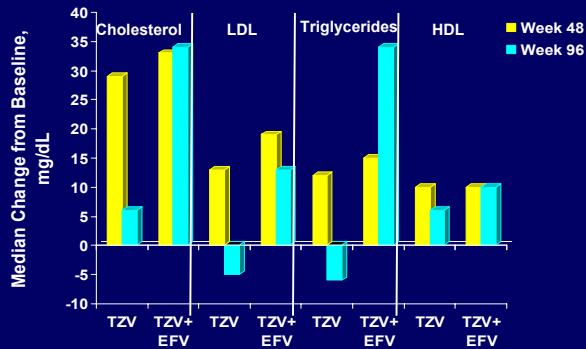
Phase IV, 96-week, randomized, multicenter (40 US sites) study



Markowitz M, et al. XV IAC 2004: Oral LBoRb14.

ESS40013

Fasting Lipid Parameters



Markowitz M, et al. XV IAC 2004: Oral LBoRb14.

2NN Study : Lipid Extension

N=320 (Of 833 patients who completed 48 week study), followed on continued therapy for mean of 84 weeks (range 48=132):

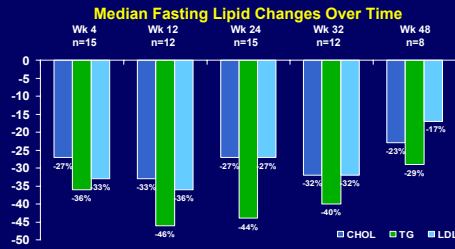
Mean Increase in lipid levels (mmol/L)

	HDL-c		LDL-c		TC		TG	
	W 48	post trial	W 48	post trial	W 48	post trial	W 48	post trial
NVP	0.40	0.21	0.54	0.97	1.00	1.46	0.05	0.61
EFV	0.31	0.19	0.79	0.97	1.28	1.52	0.42	0.86
NVP+EFV	0.65	0.33	0.66	0.73	1.58	1.51	0.63	1.17

Conclusion: Sustained significant lipid rises to a median of 84 weeks with differences between groups less marked as compared to 48 weeks

van Leth, F. IAC XV, WePpB2065, 2004

Improvement in Lipids after Substitution of PI or NNRTI to Tenofovir



- Substitution to TDF
 - Improved lipids abnormalities
 - Maintained viral suppression; no discontinuations
 - Treatment option for HAART-associated dyslipidemias

Ruane P. XV Int AIDS Conf, July 2004, Bangkok, #4583.

Improvement in Lipids Following Switch to NNRTI and non-Thymidine Analog

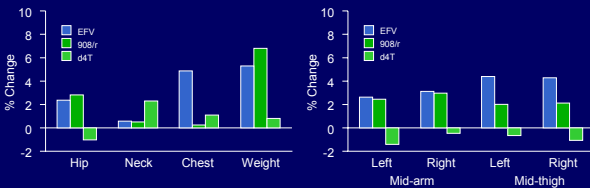
- Patients with HIV <50 c/mL and on d4T/AZT+NNRTI+EFV and with either CH or TG levels above 300 mg/dl (n=36)
- Randomized to substitute EFV with NVP and d4T or AZT with a different non-TA NNRTI (switch group) or to continue the ongoing treatment (control)

Change from BL at Week 48 (mg/dL)	Switch Group	Control
Triglycerides	-144 (p=0.0012)	+42 (p=NS)
Cholesterol	-24 (p=0.008)	-7 (p=NS)

1. Maggiolo RK. XV Int AIDS Conf, July 2004, Bangkok, #5865.

CLASS Study (ESS40001) EFV vs 908/r vs d4T + (ABC+3TC bid) Lipid and Anthropometric 96 Week Analysis

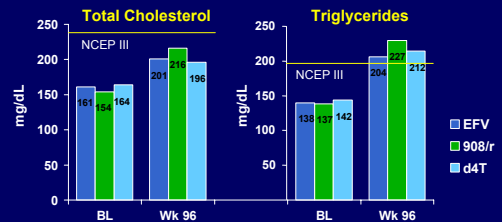
- ABC+3TC+d4T arm led to fat loss in the hip, mid-arm and mid thigh



Sathasivam, K. XV Int AIDS Conf, July 2004, Bangkok, #5944

CLASS Study (ESS40001) EFV vs 908/r vs d4T + (ABC+3TC BID) Lipid and Anthropometric 96 Week Analysis

- Significant increase in median change in total cholesterol from baseline to week 96 for the EFV and 908/r arms compared to the d4T arm (p < 0.001)
- Antihyperlipidemics initiated in the following:
 - EFV (6%), 908/r (12%), d4T (4%)



Sathasivam, K. XV Int AIDS Conf, July 2004, Bangkok, #5944

Subclinical Atherosclerosis: Increased CIMT and CAC: Prospective 48 wk

Mean CIMT (mm)	PI Group (n = 33)	Nevirapine Group (n = 22)
Baseline	0.97	1.04
Year 1	1.15	1.14
Increase	0.18	0.10

Patients With CAC Score	PI Group (%)	NNRTI Group (%)	Relative Risk Ratio* (95% CI)
> 10	52	26	2.32 (1.24-3.19)
> 100	22	7	9.56 (2.80-12.9)

*Multivariate analysis

Ierone, G, IAC XV, Abstract TbOrB1355, 2004

Coronary Calcium Scores (2)

Other factors associated with increased CAC:

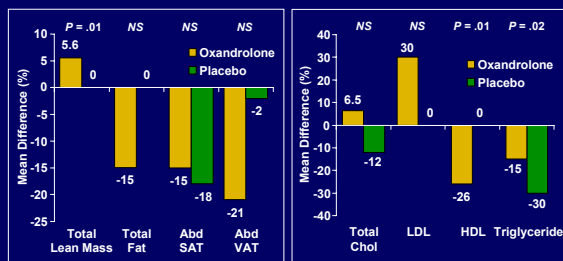
- Age
- Hypertension
- Years living with HIV/AIDS

Brachial artery reactivity not significantly different between the 3 groups

Ierone, G, IAC XV, Abstract TbOrB1355, 2004

Exercise ± Oxandrolone in Patients on HAART

- 32 patients completed 12 weeks of follow-up; groups very different at baseline
- No change in LDL or HDL from exercise alone; worsening with oxandrolone



Smith et al. Abstract MoOrB1059.



Other Complications

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Renal Safety of Tenofovir DF

- Several studies of renal safety¹⁻³
- Follow-up ranging from 48 weeks to 3 years
- Very little evidence of progressive renal dysfunction in pts with normal renal function at baseline
- Some very slight decreases in renal function by very sensitive measure, despite no change in creatinine clearance²

1. Lewis et al. Abstract TuPeB4599.
2. Staszewski et al. Abstract WePeB5917.
3. Mauss et al. Abstract WePeB5941.

Study 903 – Week 144 Serum Creatinine and Phosphorus

	Women		Men	
	TDF arm (n=78)	d4T arm (n=73)	TDF arm (n=218)	d4T arm (n=223)
Graded Serum Creatinine (mg/dL)				
1 (≥0.5 increase from baseline)	3%	4%	4%	2%
2 (2.1-3.0)	0%	0%	<1%	0%
3 (3.1-6.0)	0%	0%	0%	<1%
4 (>6.0)	0%	0%	0%	0%
Graded Serum Phosphorus (mg/dL)				
1 (2.0-2.2)	3%	1%	5%	4%
2 (1.5-1.9)	1%	0%	4%	3%
3 (1.0-1.4)	1%	0%	0%	<1%
4 (<1.0)	0%	0%	0%	0%

Ruiter A de. *XV Int AIDS Conf*, July 2004, Bangkok, #1083

Renal Studies with TDF – Retrospective, Non-Comparative

Ref	No. pts	Duration (weeks)	SCr (mg/dL)	CrCL (mL/min)	P
Scott ¹	437	24	+ 0.1	-2.3	NS
Horberg ²	238	52	mean +0.1 median +0.02		0.03 NS
Jaegel-Guedes ³ **	206	72	+0.11	-15	0.001

- 5.5% patients pre-existing renal disease
- TDF dose not adjusted for renal insufficiency
- One patient required dialysis
- 47% patients on other nephrotoxic agents
- 5 patients >0.5 mg/dL ↑ SCr
- 3 patients developed renal failure
 - Burkett's lymphoma with pre-existing renal disease (n=1)
 - Concurrent nephrotoxic agents (n=2)

1 Scott JP. *XV Int AIDS Conf*, July 2004, Bangkok, #4632; 2 Horberg MA. *ibid*, #2066; 3 Jaegel-Guedes E. *ibid*, #5937.

Other Complications

Gynecomastia

- Largely related to hypogonadism^[1]
 - After controlling for hypogonadism, no associations with antiretroviral therapy
- Rate similar to that of general population

Preeclampsia

- HIV infection independent risk factor for preeclampsia and infant death^[2]
- Appears related to chronic maternal use of antiretrovirals, ie, before pregnancy

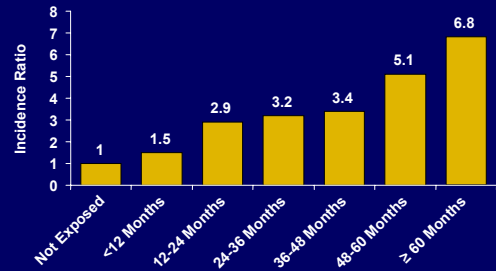
Osteonecrosis

- Significant relationship between duration of exposure and osteonecrosis^[3]
- Also associated with low CD4+ cell count

Note: No evidence that these are drug-related toxicities

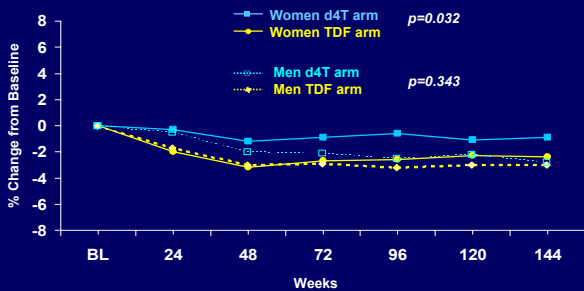
1. Biglia et al. Abstract ThOrB1357. 2. Suy et al. Abstract ThOrB1359.
3. Mary-Krause et al. Abstract ThOrB1358.

Longer Duration of HAART Associated With Increased Incidence of Osteonecrosis



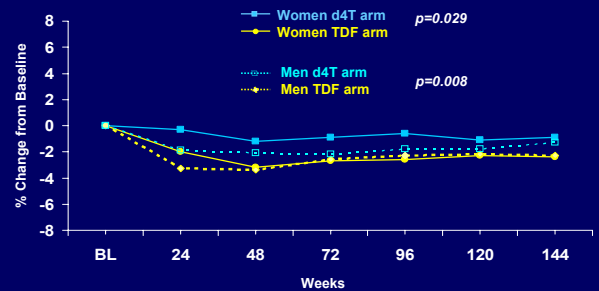
Mary-Krause et al. Abstract ThOrB1358.

Study 903 – Week 144 Mean % Change in Hip BMD



Ruiter A de. XV Int AIDS Conf, July 2004, Bangkok, #1083

Study 903 – Week 144 Mean % Change in Spine BMD



Ruiter A de. XV Int AIDS Conf, July 2004, Bangkok, #1083

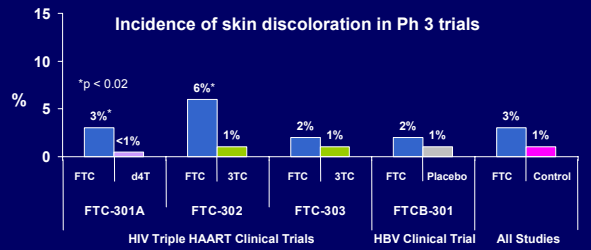
Study 903 – Week 144
Bone Fractures Summary

	TDF+3TC+EFV (n=299)	d4T+3TC+EFV (n=301)
Fractures	5 (1%)	11 (4%)

- All fractures were associated with trauma except a vertebral compression fracture on the d4T arm
- No fractures in women

Incidence of FTC Skin Discoloration in Ph 3 Trials

- Occurred mainly on palms and soles
- Mild, 29/33 (88%); moderate, 4/33 (12%) of cases
- Caucasians <1%, Hispanics 3%, Asians 4%, Blacks 8%



Mondou E. XV Int AIDS Conf, July 2004, Bangkok, #5916

Characteristics of Skin Discoloration in Emtricitabine-treated Adults

- HIV Trials, incidence 29/814 (4%)
 - Median time to onset was 88 days (range 10 to 490 days)
 - Resolution occurred in 5/29 patients (17%) while continuing study drug; ongoing cases remained mild or moderate
 - No patients discontinued treatment due to skin discoloration
- HBV Study, incidence 4/167 (2%)
 - Median time to onset was approximately 70 days (range 12 to 131 days)
 - Resolution occurred in 2 patients after discontinuing emtricitabine
- No association with any dermatologic or general systemic condition

Mondou E. XV Int AIDS Conf, July 2004, Bangkok, #5916



Viral Hepatitis and Opportunistic Infections

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Effect of HCV Coinfection on Survival

Data from VA and 2 clinical cohorts^[1]

- In VA, increasing impact of coinfection on survival over time
- In clinical cohorts, HCV associated with increased mortality; HR = 1.38 ($P < .01$)
- HR decreased in pts with CD4+ < 50, but stable at approximately 1.92 in higher CD4+ cell count strata

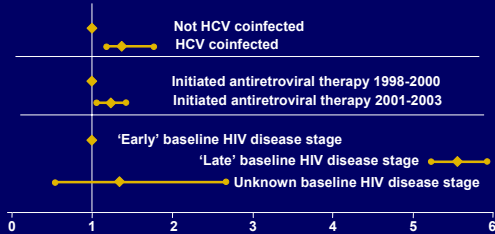
CDC study^[2]

- Patients treated with HAART, 1996-2003. Median FU: 23 months
- Increased mortality in HCV+ patients
- However, *no difference in survival* for HCV+ vs HCV- after correcting for alcohol use, IDU, HBV

1. Fultz et al. Abstract MoPeB3318.
2. Sullivan et al. Abstract WeOB1325.

Blunted CD4+ Cell Count Response to HAART in HCV/HIV-Coinfected Patients

Estimated OR for achieving mean CD4+ count after 3-12 months of HAART



Cowling et al. Abstract MoPeB3300.

Use of Lopinavir/Ritonavir in Coinfected Patients

Analysis of 819 patients in LPV/r studies

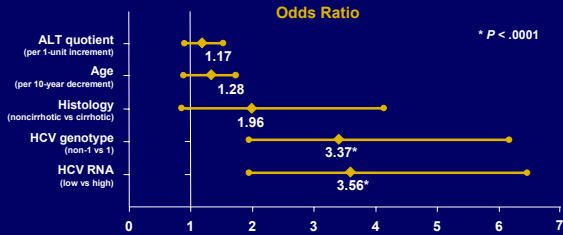
- HBV/HCV+ pts (n = 132) more likely to have grade 3/4 AST/ALT elevation
 - 13% vs 3%; RR = 4.1
- Effect not specific to LPV/r
 - In M98-863, trend toward fewer grade 3/4 AST/ALT in LPV/r vs NFV pts

Retrospective chart review, Toronto

- 202 HBV- and/or HCV-coinfected pts initiating NNRTI- or PI-based HAART
- ALT measured at baseline and after starting HAART (n = 103)
- 21% ever had grade 3/4 ALT elevation during follow-up
- Significant predictors by multivariate analysis:
 - Age (OR, 1.45 per 10 yrs; $P = .04$)
 - Current LPV/r (3.18; $P = .001$)

Da Silva et al. MoPeB3285, Chihrin et al. MoPeB3281.

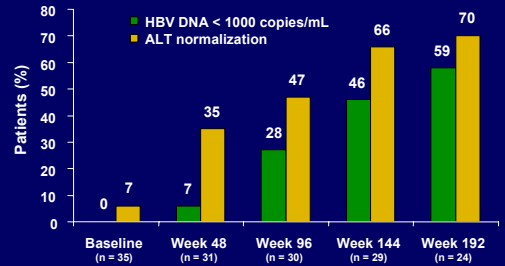
APRICOT: Predictors of HCV Response to Peginterferon/Ribavirin



- Week-12 nonresponse predicted lack of SVR to PEG/IFN^[1]
- Predictors of response were HCV-related, not HIV-related^[2]
 - Baseline CD4+, VL, use of ART, type of ART *not* significant predictors

1. Rodriguez-Torres et al. Abstract MoPeB3304.
2. Cooper et al. Abstract MoPeB3329.

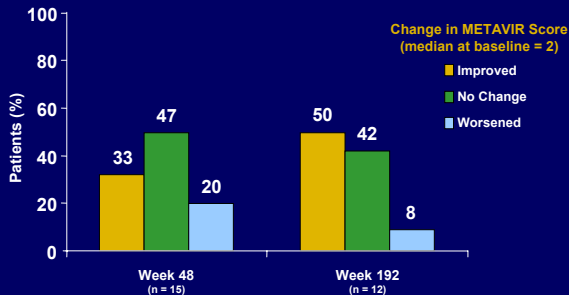
4-Year Follow-up of Pilot Study of Adefovir for Lamivudine-Resistant HBV Coinfection



- No emergence of K65R resistance in HIV after 4 years
- No emergence of adefovir-resistant HBV

Benhamou et al. Abstract WeOrA1329.

Adefovir for Lamivudine-Resistant HBV Coinfection: Improvement in Fibrosis



Benhamou et al. Abstract WeOrA1329.

Management of OIs

Treatment of toxoplasmosis

- 2 patient series suggesting efficacy of TMP/SMX^[1,2]

Prognostic value of extrapulmonary TB

- Extrapulmonary TB not associated with increased risk of HIV progression in South Africa^[3]
 - Most extrapulmonary TB was lymphatic
- Should not be used as criterion for starting antiretroviral therapy in patients with CD4+ > 200

1. Foltzer et al. Abstract MoPeB3234. 2. Mootsikapun et al. Abstract MoPeB3235.
3. Grant et al. Abstract MoPeC3392.

PAP Screening for Anal Neoplasia

- SFGH: Prospective biannual screening of 417 men
- Initial Pap screening has high sensitivity (95%) but low specificity (30%)
 - All positive tests would therefore require follow-up by high-resolution anoscopy
- 54% of individuals screened positive
- 1% prevalence of biopsy-proven anal cancer
- Appropriate treatment of dysplasia and benefits of early treatment remain unknown

Lee et al. Abstract ThO1B1407.

