

CROI 2005 Update: Pharmacogenomics, Drug Interactions, Metabolic Complications, Viral Hepatitis Coinfection

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2 million years of lives saved, US, 1989-2003 (Walensky, Abstract 143)

Year	Intervention	Pts x1000	Survival Gain (mos)	Total gain (yrs x 1000)
1989-92	PCP prophylaxis	113	2	18
1993-96	MAC prophylaxis	162	4.6	35
1997-98	ART 1 (new drugs)	79	40	265
1998-99	ART 2 (combo Rx)	53	105	504
2000-02	ART 3 (simplify)	78	111	723
2003	ART 4 (reduce tox)	27	179	409
Total				2101

2 million years of lives saved, US, 1989-2003 (Walensky, Abstract 143)

Disease/Intervention	Per Person Survival Gain (mos)
Cancer (all)	10
ICAD/CABG	20
Lymphoma/BMT	80
AIDS/HAART	180

Switching off t-RTIs for Lipoatrophy

Moyle, Abstract 44

Inclusion criteria: patients on D4T (71) or AZT (34), age 42, VL <50, CD4 nadir 130, currently 500, with moderate to severe lipoatrophy

Switched to TNF or ABC (open label), measure fat by DEXA (peripheral) or abdominal fat (by CT)

Significant and equal benefit to improvement in limb fat in both arms (0.4 – 0.5 kg) at 48 weeks

Virologic suppression similarly maintained in both groups

**Fewer TDF treated patients initiated lipid lowering rx
6 discontinuations in ABC arm versus one discontinuation in TDF arm due to toxicity**

Switching off t-NRTIs for Lipoatrophy

Murphy, ACTG 5110, Abstract 45

Patients on ART, VL < 200, 76% on D4T, median age 46, clinical evidence of lipoatrophy

Open label switch off t-NRTI to ABC, LPV/r + NVP, or continue tNRTI

Results at 24 weeks:

Group (n)	change thigh fat by CT (cm ²)	abd fat by CT (cm ²)	VL <200
ABC (40)	-0.2	+9.2	92%
LPVr/ + NVP (37)	+8.4	+16.6	93%
continue tNRTI	-3.2	-8.8	100%

Switching to EFV/LPV based ART for LA (Tebas, ACTG 5116)

62 patients suppressed on ARV for 18 mos, VL <200, randomized to continuing 2N + NNRTI versus switch to efavirenz/lopinavir

After 48 weeks, NRTI sparing arm had increased limb fat (+562 g) versus decreased limb fat (-246 g) in NRTI arm by DEXA scan

Change in lipids in NRTI sparing arm were significantly worse than in NRTI arm (TG +85 mg/mL versus +11 mg/mL; TC +19 mg/mL versus -7 mg/mL)

No changes in fasting glucose, insulin, truncal fat or bone density

Study not powered to show differences among NRTIs used in NRTI arm

Fish Oil (Maxepa) for ARV-induced hypertriglyceridemia (De Truchis, Abstract 39)

Prospective, double blind study, n = 122,
Patients on ARV with fasting TG > 2000 after dietary counseling
Randomized to 2 g fish oil capsules TID vs. placebo
Mean TG 4500; patients with TG > 10,000 excluded

Results at week 8:

	<u>TG</u>	<u>TG change (%)</u>	<u>% TG Normalized</u>
Maxepa	3,400	-25%	22.4%
Placebo	4,800	+1%	6.5%

No change in HDL in either arm.

Switch to r/ATZ from current ART, effect on lipids (Martinez, Abstract 850)

Patients with baseline TG > 500 or chol > 200 or LDL >130 for 3 mos; subgroup of Spanish HIV patients on atazanavir expanded access study (n=255)

Baseline characteristics: mean age 40, 40% with HIV VL < 400; CD4 380; 30% with multiple coronary risk factors, 70% of patients on PI or r/PI

Data at 6 mos:

% VL < 500	58%
TG change	-18%
TC change	-10%
LDL change	-10%

Approximately 1/3 of patients d/c'd lipid lowering therapy inadvertent secondary to r/ATZ in 14 pts (5.5%) but led to drug discontinuation in only 3 (1.2%)

Switch from PI or r/PI to unboosted ATZ in patients with hyperlipidemia and suppressed VL (Sension, Abstract 858)

246 patients, VL < 50, CD4 460, nadir CD4 410, 40% on r/PI, 20% on Kaletra, stable ARV regimen for 3 mos, no prior PI rebound, LDL > 130

Randomized to continue PI or r/PI or switch to unboosted ATZ

Effects at 12 weeks comparing “switch arm” with “continuation arm:”

LDL	-15.2
TC	-17.4
TG	-34.8

LDL < 130 14% atazanavir arm versus 33% continuation arm

– 2 % virologic failure in each arm; 48 week data pending

DAD Study: Long Term F/U of Cardiac Complications (Abstracts 42 and 866)

Observational study, 23,000 patients Europe, Australia, US, mean ART exposure 4.46 years demonstrated continued increased risk of MI with ART; compared MI rates with age/sex matched HIV neg pts

	rate of MI (per 1000 patient - years)
no ART	1.39
any ART	2.53
ART > 6 years	6.07

by multivariate analysis, hyperlipidemia only partially explained increased risk

RR men versus women HIV positive 2.04

Other RR: prior CAD 9.0; smokin 5.0, FH 2.5

however, overall risk of MI has decreased over time possibly related to use of different ARV regimens and due to treatment of lipids

Tenofovir vs. Adefovir for HIV/HBV Coinfection

ACTG 5127 (Abstract 124, Peters)

Patient inclusion: HBV DNA >100,000, HIV RNA < 10,000
52 patients, 92% male, mean age 41, 56% Caucasian, 33% AA;
75% had baseline HIV RNA < 50, mean baseline HBV DNA
1,000,000,000

Randomized to adefovir 10 mg qd versus TDF 300 mg qd,
median f/u 75 weeks

Results at 75 weeks:	HBV DNA reduction (log)
TDF	4.4
ADF	3.2

TDF arm associated with superior response, but study not
powered to assess superiority of TDF

High Risk of Fibrosis Progression in HIV/HCV Coinfected Patients with Minimal Fibrosis on Initial Biopsy (Sulkowski, Abstract 121)

Patients studied: 67 coinfecting patients, with sequential biopsies, average time between biopsies 2.83 years

Blinded fibrosis scores (Ishtak criteria, F0 – F6)

Baseline characteristics: mean age 44, 75% male, 86% AA, 27% active ETOH, 86 % on ART, 31 % with elevated ALT; mean baseline fibrosis score 0.8

Results:

Increased fibrosis score ≥ 2 in 28%

Increased fibrosis score associated with baseline HIV RNA > 10K and elevated AST at baseline

A similar study with paired biopsies showed hepatic steatosis did not increase risk of fibrosis, but was highly associated with D4T use

Risk of Progressive Renal Dysfunction on Tenofovir (Abstracts 818, 820)

In MACS cohort, 564 patients on HAART were assessed; HAART use associated with increased risk of GFR < 60 (5%); tenofovir doubled risk of GFR < 60 as compared with other ART. In Hopkins Cohort, 344 pts initiated TDF based ART, and 314 patients initiated non TDF based HAART; TDF arm had 10% decrease in GFR over 3 mos versus 6 % decrease in GFR with non TDF based ART

In Hopkins study, decreased creatinine clearance associated with longer treatment with TDF, lower CD4, baseline renal insufficiency and diabetes

Long term use of TDF may lead to long term risk of nephrotoxicity, possibly in association with high dosing (borderline baseline GFR) or use of concurrent drugs which increase TDF levels (ritonavir, kaletra)

PK Interaction: omeprazole and ritonavir/atazanavir (Agarwala, Abstract 658)

Ritonavir 100 mg/ atazanavir 400 mg dosed 2 hours after omeprazole 40 mg in 48 volunteers

Atazanavir AUC decreased by 75%

C_{max} and C_{min} also decreased by 70 – 75%

Giving cola with omeprazole did not improve PK interaction

Increasing atazanavir dose to 400 mg did not improve PK interaction

Genetic Polymorphisms in P450 2B6 Predict Efavirenz Metabolism (Haas, Abstract 81)

Efavirenz AUC's measured in 340 efavirenz recipients in ACTG 388
49% Caucasian, 31% Black, 19% Hispanic
Overall, T polymorphisms associated with higher efavirenz AUCs:

<u>Genotype</u>	<u>EFV 24 hour AUC (mcg-hr/L)</u>
GG	49
GT	58
TT	101

Although genetic polymorphisms associated with higher EFV exposure, these higher levels were not associated with different virologic response rates

Risk of Efavirenz CNS Toxicity Correlates with CYP2B6 polymorphisms (R-Novoa, Abstract 652)

Studied association between efavirenz levels, signs of neurotoxicity and CYP 2B6 polymorphisms in 111 patients (from Spain) starting efavirenz based ART

Results:

Polymorphism (%)	EFV toxic levels	Signs of CNS toxicity
GG (50%)	0%	4%
GT (44%)	20%	32%
TT (7%)	40%	30%

containing polymorphisms not predictive of virologic response but correlated with high levels and symptoms of CNS toxicity

Risk of Nevirapine Hepatotoxicity associated with Drug Metabolism Genes (Ritchie, Abstract 832)

Nested case control study, 445 patients starting first NNRTI
20 cases, 50 controls, 23% female, 77% male, 19% AA, 81%
Caucasian, mean age 39

T-allele in MDR-1 gene associated with decreased risk of NVP
hepatotoxicity (OR 0.45)

CYP2B6 GT or TT polymorphism plus MDR1 allele predicted risk of
nevirapine hepatotoxicity in 70%