Mild and Severe Adverse Effects of Antiretroviral Treatment

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¿Which one of the following statements about this reaction is true?

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e) **A patient receiving abacavir for more than one year had his reatment interrupted when he could not obtain medication. He hould not restart abacavir because re-challenge is known to be associated with a fulminate reaction.**
f) **I do not know, I'm coming to learn.**

The Undesired Consequences of Antiretroviral Therapy

- Hypersensitivity Reactions
- Gastrointestinal
- Pancreatitis
- Neuromuscular
- Bone
- Renal
- Hematological
- Lipodystrophy
- Lipid Disorders

Hypersensitivity Reactions

- Acute allergic reactions
  - Virtually any antiretroviral
  - Nevirapine – linked to Steven-Johnson Syndrome
  - Etc., etc.
- Idiosyncratic reaction of abacavir
  - 3-4% incidence
  - Linked to HLA B 5701 haplotype
  - Pts should either be screened for HLA B 5701, or counseled and closely followed

Gastrointestinal Effects

- **Nausea & vomiting:**
- **Diarrhea**

Pancreatitis

- Didanosine ~ 3% risk.
- Baseline amylase and lipase before initiation of therapy.
- Clinical vignette – 36 yr old woman with aids starts didanosine, lamivudine and boosted indinavir. She responds with a fall in viral load to non-detectable range and rise in CD4 counts. Three months later she is admitted with severe pancreatitis. The likely cause?

Pancreatitis

- Alcohol abuse?
- Trauma?
- Biliary tract stone in ampulla?
- Ascaris in pancreatic duct?
- Hypercalcemia?
- Hyperlipidemia?
- Didanosine? The prime suspect……..

Neuro-Muscular Adverse Effects

- Challenging management problem because of HIV – induced CNS, muscular and peripheral nervous system disease.
- Challenging because of co-morbid diseases – psychiatric disease, substance abuse, liver disease, diabetes, among others.
- Challenging because of interaction with other medications.

Central Nervous System Effect of Efavirenz

- Dizziness
- Headache
- Confusion, stupor, impaired concentration, agitation, amnesia,
- Depersonalization, hallucinations
- Insomnia, abnormal or vivid dreams

Peripheral Neuropathy

- Zalcitidine ddC
- Stavudine D4T
- Didanosine DDI
- Zidovudine AZT
- Protease Inhibitors

Distal Sensory Polyneuropathy (DSP)

- Most common peripheral neuropathic complication (> 30% of patients with moderate to severe immunosuppression)[1]
- Symptoms (usually start distally, in feet)[2,3]
  - Numbness, paresthesias, dysesthesias, spontaneous pain, burning pain, deep pain, lightning pains, stimulus-evoked pain
  - Reduced pinprick, temperature, vibration, proprioceptive sensations
- Important to distinguish cause (HIV infection or antiretroviral therapy)

1. Herrmann D, et al. In: Roos K, ed. Principles of neurologic infectious diseases. Columbus, Ohio: McGraw-Hill; 2005. p. 103-112. 2. Cornblath DR, et al. Neurology. 1988;38:794-796. 3. Tagliati M, et al. Arch Neurol. 1999;56:84-89.

Antiretroviral-DSP

- Symptoms typically occur in first weeks or months of initiating dideoxy-NRTI therapy (d-drugs, ddI, d4T, ddC)
  - Virtually indistinguishable from HIV-DSP
    - Higher levels of pain, abrupt onset, and rapid progression
    - Elevated serum lactate levels often found[1]
- D-drugs associated with 15% to 30% incidence of sensory neuropathy in HIV-infected patients
- Use of ddI + d4T associated with increased risk over either agent alone
- PI-associated DSP also seen
  - IDV neurotoxic to dorsal root ganglia, possibly via inhibition of release of macrophage-derived growth factors[2]

1. Brew BJ, et al. AIDS. 2003;17:1094-1096. 2. Markus R, et al. Lancet. 1998;352:1906-1907.

Pharmacologic Agents for HIV-DSP

Class	Drugs/Effects
Antidepressants	• Amitriptyline – Useful with concurrent insomnia • Nortriptyline – Least cardiac effects • Desipramine – Least anticholinergic effects
Anticonvulsants	• Gabapentin – Generally well tolerated • Lamotrigine – Must be slowly titrated

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ZDV-Related Myopathy

- Virtually indistinguishable from HIV myopathy
- Light microscopy of affected muscle shows
  - Absence of inflammatory infiltrate
  - Endomysial collection of T lymphocytes
  - Scattered muscle fiber necrosis
  - Variable muscle fiber atrophy
- Associated with longer duration of use, higher doses, lower CD4+ cell count, presence of existing myopathy
- Develops within 9-12 months of initiating therapy

Osteonecrosis & Osteoporosis

- Both well documented in patients with HIV infection and among patients receiving ART.
- Brown et al, Abst 966, 15th CROI – Bone mineral density loss of ~ 2.5% over 96 wks in pts randomized to combivir plus either lopinavir/ritonavir or efavirenz.
- Alendronate + vitamin D + calcium increased bone mineralization vs Vit D + Ca alone..
- Exercise, calcium supplementation and possibly specific therapy may be indicated; osteonecrosis may require joint replacement.
- Conclusion? More data needed.

Renal Effects

- **Indinavir: crystallization and ureteral colic**
- **Tenofovir: decrease in GFR, Fanconi syndrome**

Serum glucose of 90 mg/dl and persistent urine glucose dipstick readings of >500 mg/dl. What adjustment in antiretroviral therapy is indicated?

Fanconi Syndrome

- Manifestations
  - Hypokalemia
  - Metabolic acidosis
  - Hypophosphatemia
  - Glucosuria
- A proximal tubular function.
- Onset after initiation of tenofovir avr 9.6 months (range 1-25 months)
- Resolves with discontinuation of tenofovir.

Is Tenofovir Absolutely Contra-indicated In Persons with Renal Insufficiency?

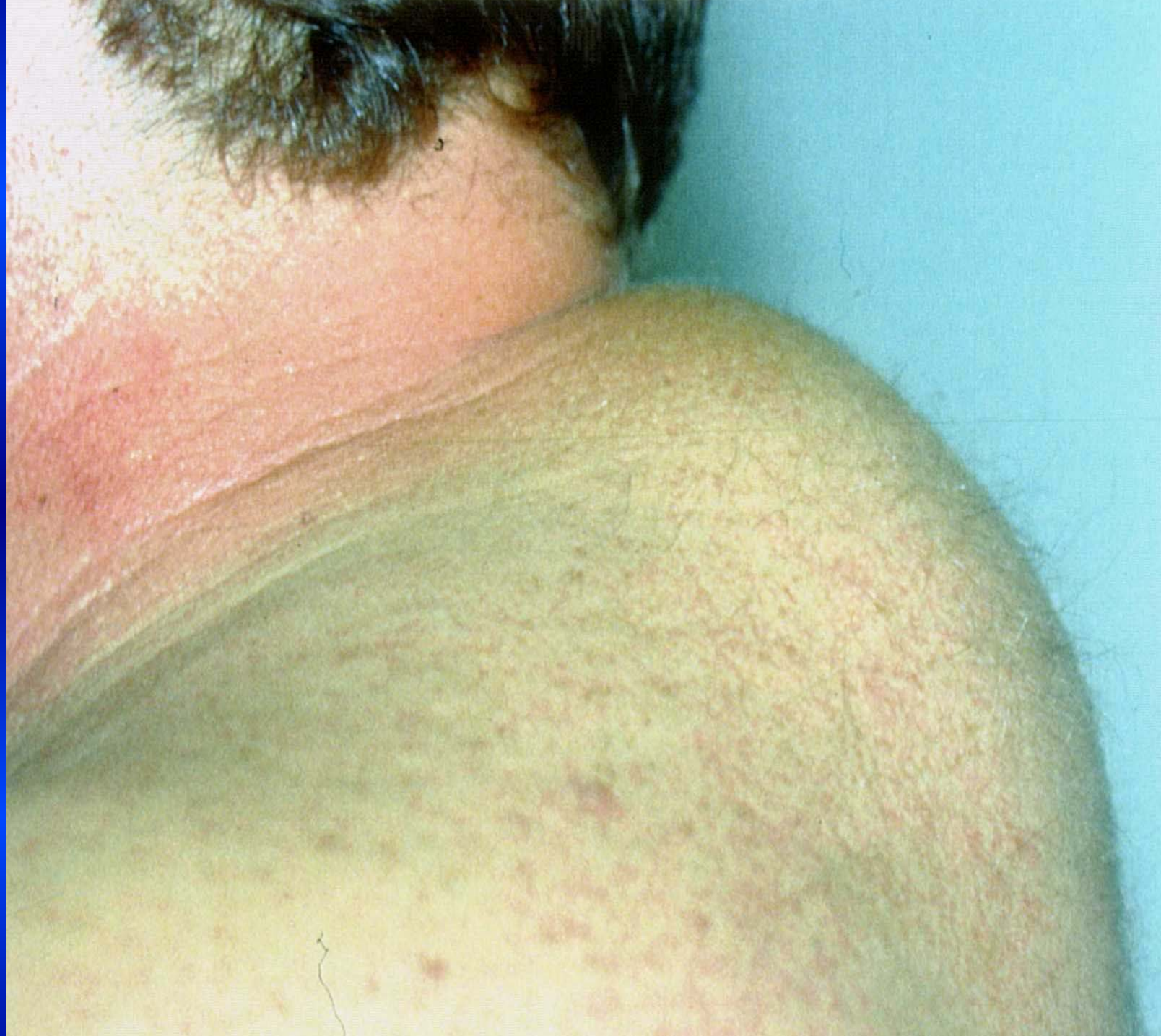
- Heffelfinger et al. Abst 779, 13th CROI– tenofovir an independent risk factor for acute renal failure in 9535 pts on ART.
- Zimmermann et al. CID 2006 – Tenofovir associated acute renal failure – 5 pts and 22 pts from medical literature

Hematological Effects

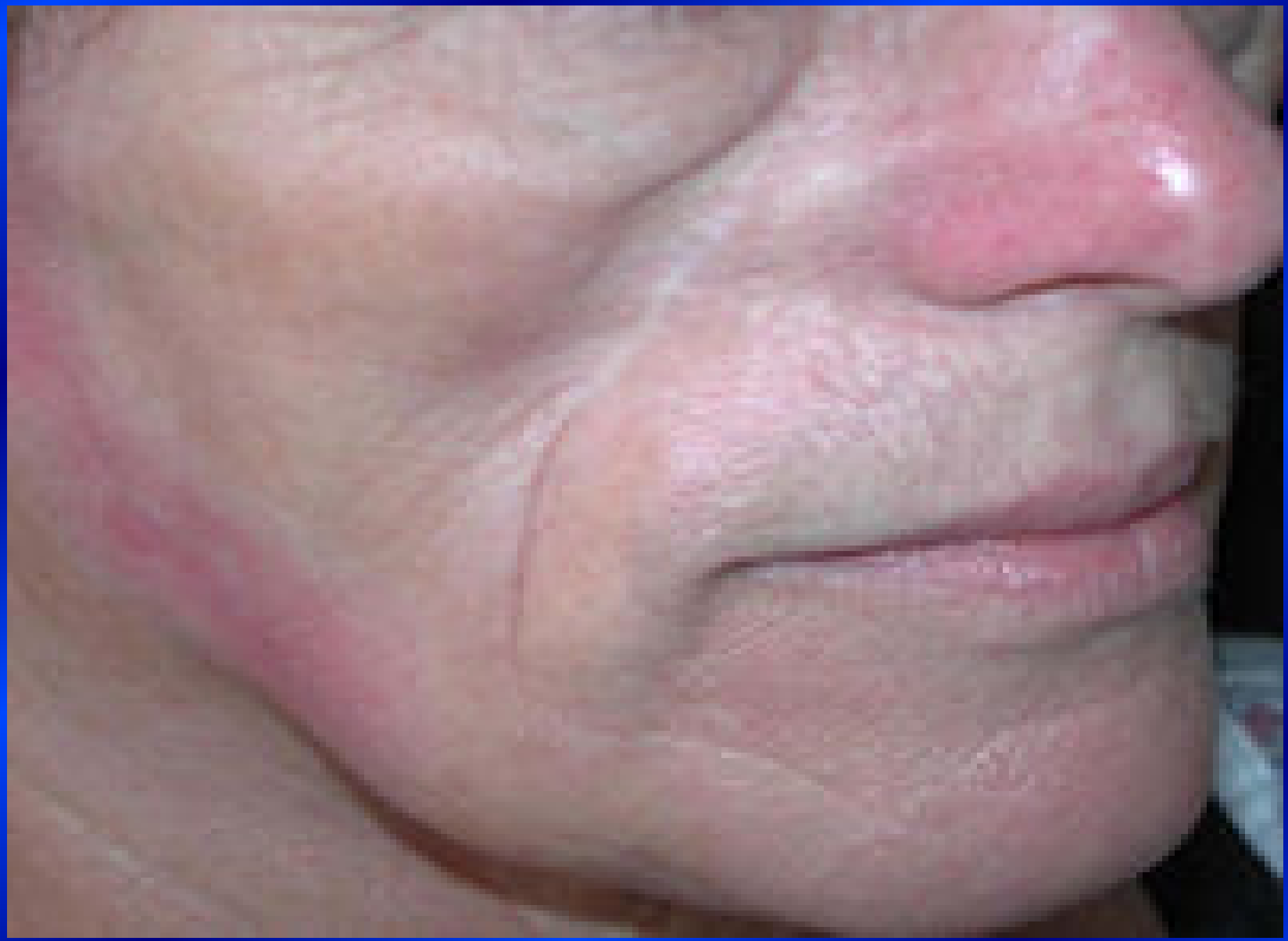
- **Macrocytosis: NRTIs, esp. combivir**
- **Anemia: Combivir (zidovudine as first given in doses of 200 mg q 4 h was associated with transfusion dependency)**

Lipodystrophy

- Hypothetical basis is mitochondrial dysfunction of NRTIs, unknown with the Pis.
- Complex syndrome without a universally accepted definition
  - Lipoatrophy of face and subcutaneous fat on extremities
  - Dorsicervical fat pad development
  - Mesenteric fat accumulation
  - Occasionally trunkal fat accumulation



Lipo-atrophy

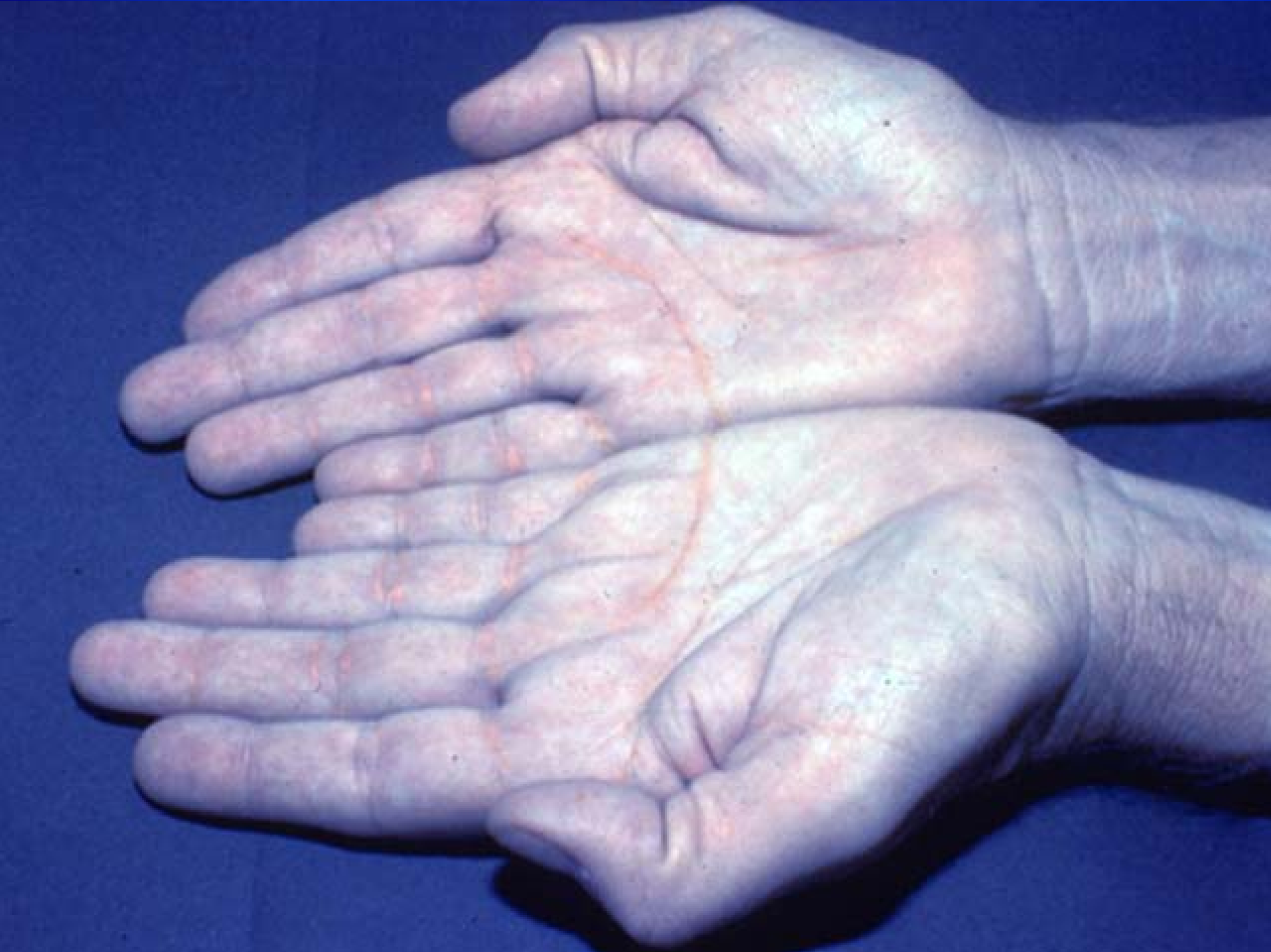


Management of Lipodystrophy?

- Lipoatrophy – 3 studies have shown benefit in switching NRTIs
  - Martin et al, AIDS, 2004 – MITOX randomized study demonstrated improvement in limb fat with switch from thymidine analogues to abacavir
  - Moyle et al, AIDS, 2006 – RAVE nonrandomized study of switch to abacavir or tenofovir with improvement
  - McComsey et al CID, 2004 – TARHEEL study of switch from stavudine to abacavir or zidoudine showed greater gain in limb fat.
- No such improvement in lipohypertrophy

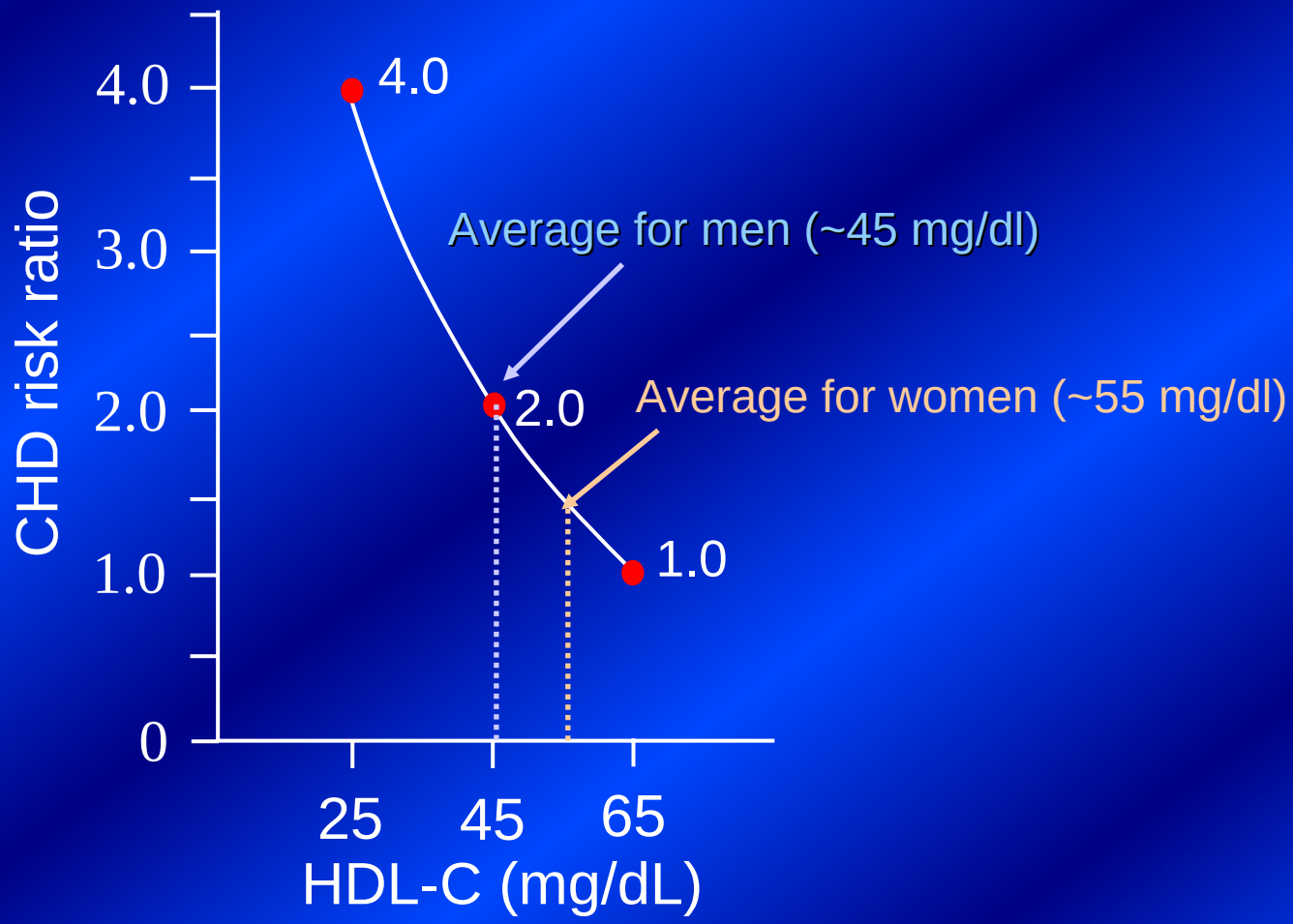
Lipid Disorders

- Hypertriglyceridemia
- Hypercholesterolemia

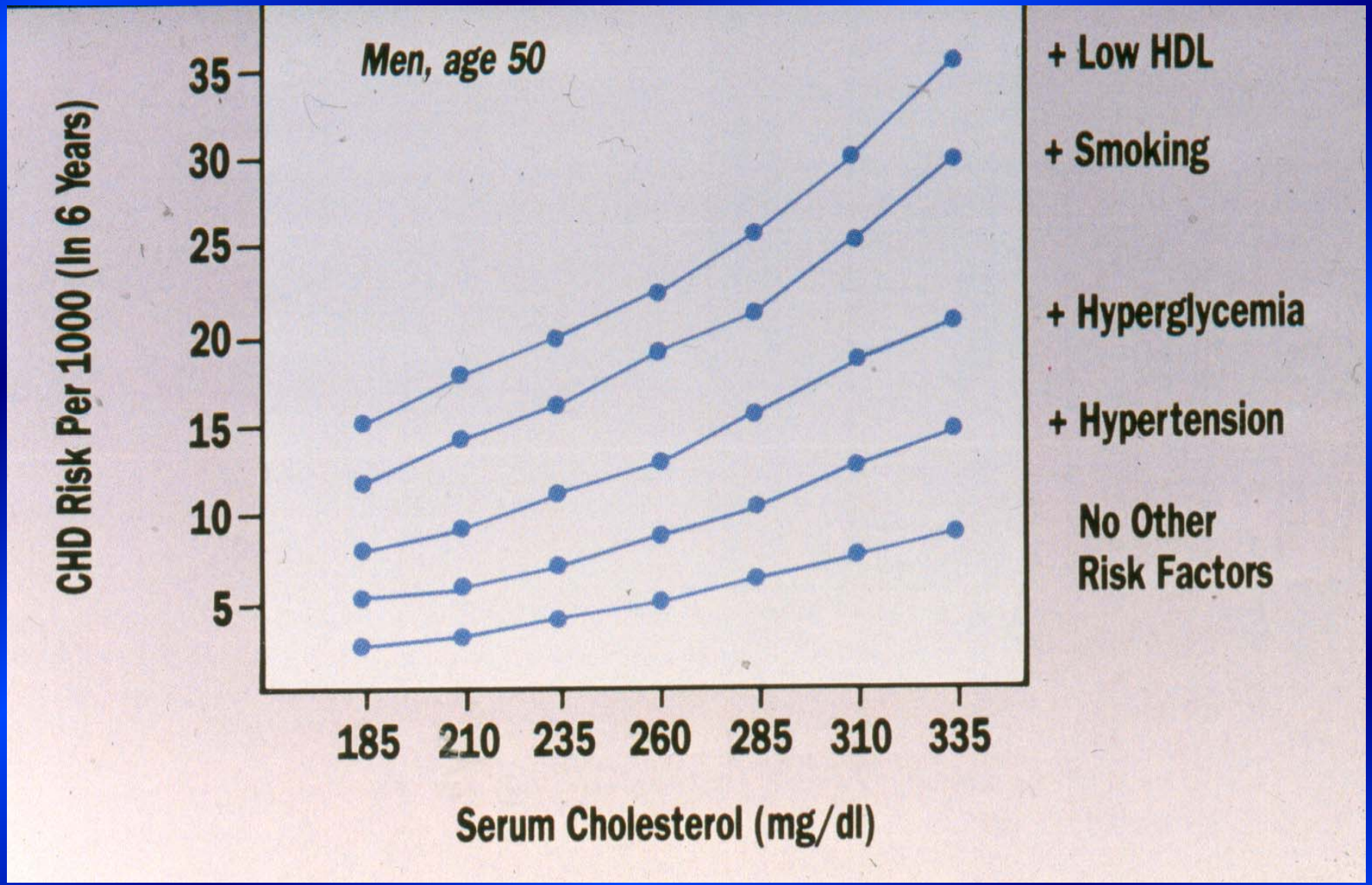


CHD Risk According to HDL-C Levels

Framingham Study

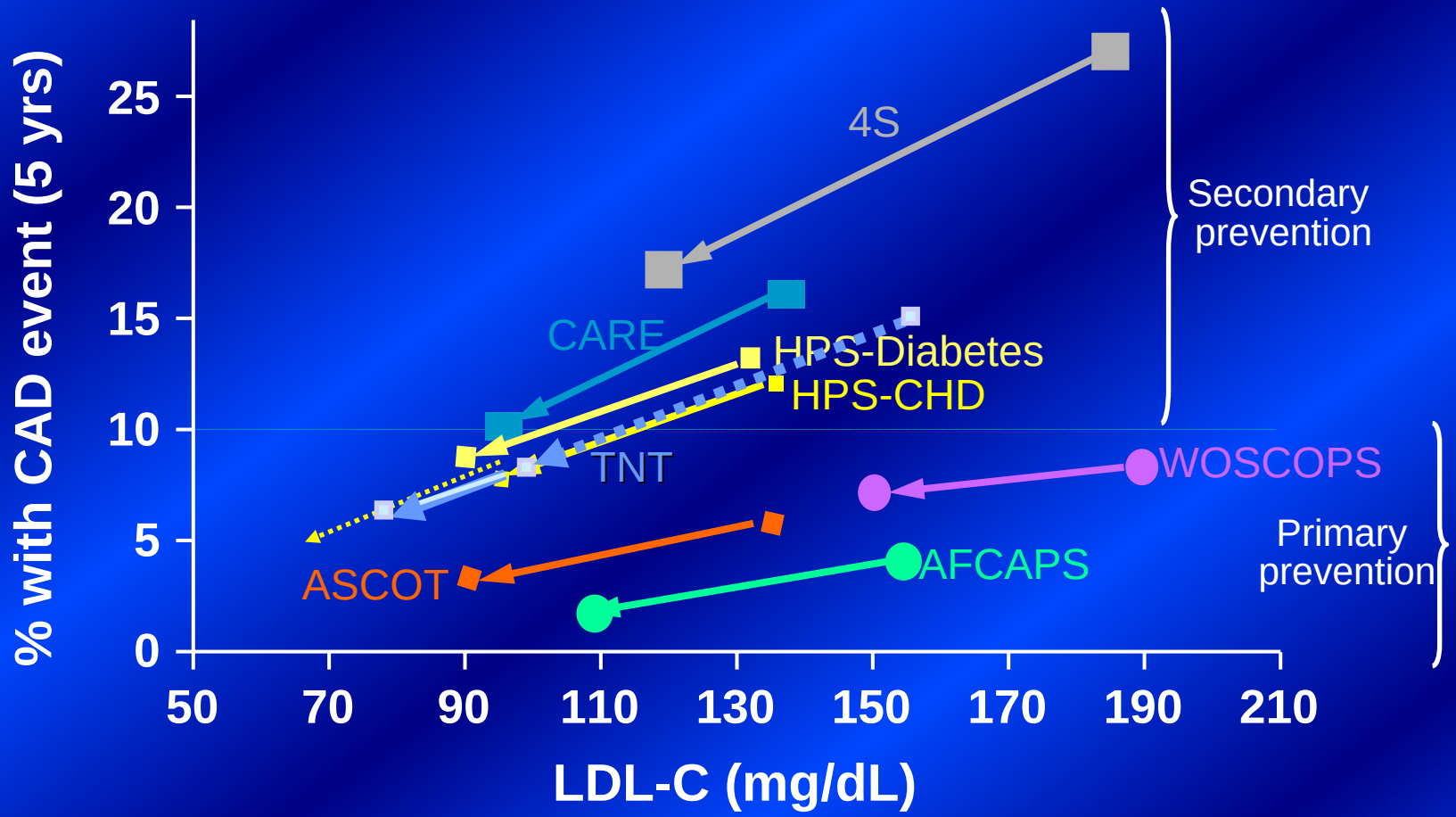


Crucial Importance of the Additive Effect of Multiple Risk Factors



Relationship between LDL-C lowering and CHD event reduction: ATP III Update (2004)

The Major Statin Intervention Trials



Note: each study lowered LDL-C by about 30%

Conclusions

- Expect further evidence of adverse effects of Highly Effective Antiretroviral Therapy HEART).
- Over time, the availability of HAART will mean that we spend increasing effort in the management of these complications.

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