

# Complications of Antiretroviral Therapy

**This slide deck is presented as a writing sample only and is not for reproduction, distribution, or any other purpose. Text is owned by the copyright holder (Turner White Communications Inc).**

# Management of ART Toxicity

- Mild adverse effects
  - Continue therapy
  - Patient education; reassurance
- Severe or intolerable adverse effects
  - Single-drug substitution, same class
  - Simultaneous discontinuation of all drugs
  - Staggered discontinuation
    - First NNRTIs
    - NRTIs 5–7 days later

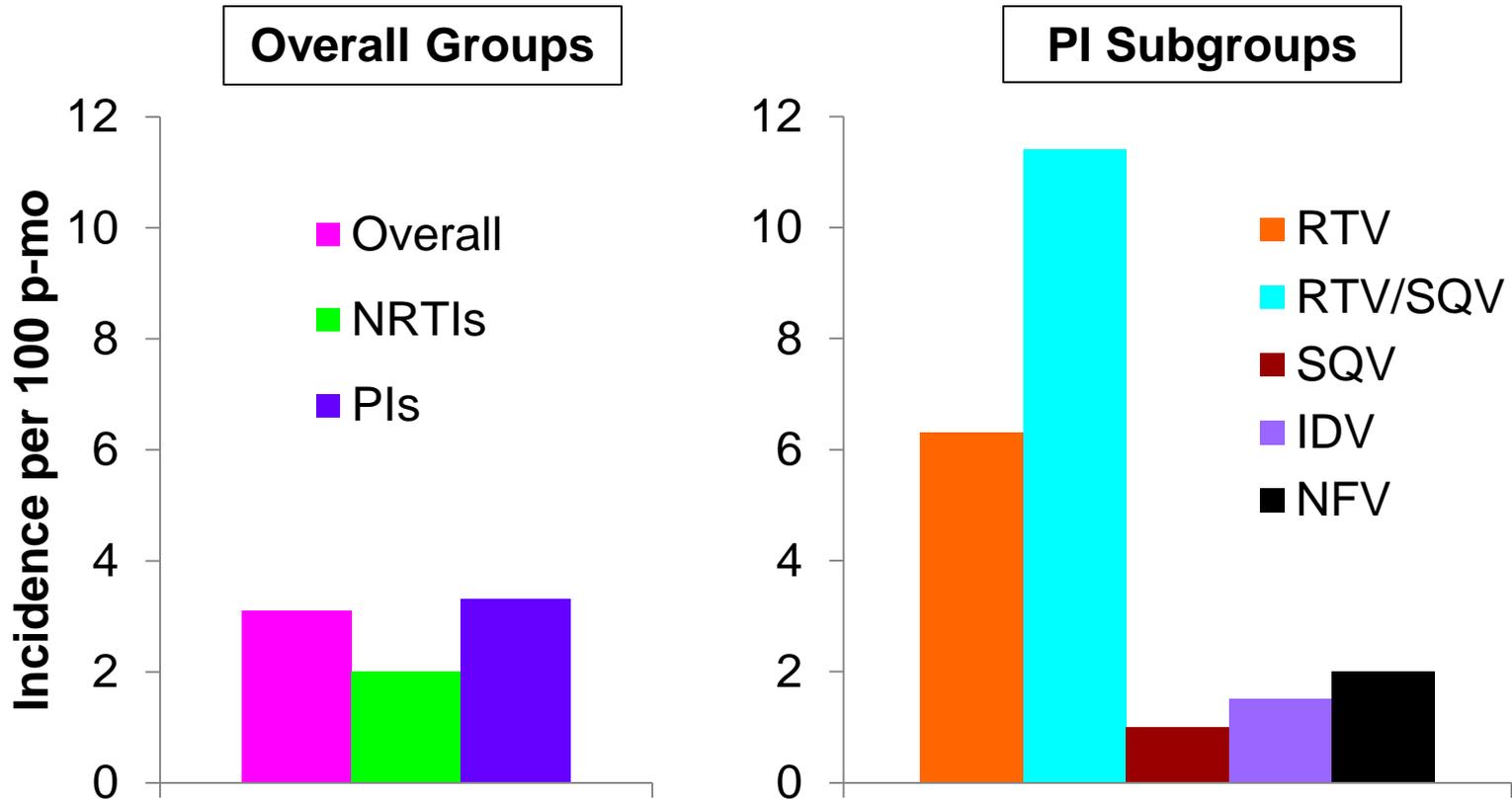
# Common Toxicities of NRTIs

- Mitochondrial toxicity (all; esp. stavudine)
  - Lipoatrophy
  - Hepatic steatosis; lactic acidosis
  - Peripheral neuropathy
- Bone marrow suppression (zidovudine)
- Myopathy, myositis (zidovudine)
- Pancreatitis (didanosine)
- Renal impairment (tenofovir)
- Hypersensitivity reaction (abacavir)

# Common Toxicities of PIs

- Fat accumulation (all agents)
- Dyslipidemia (all)
- Hepatotoxicity (all)
- Hyperglycemia (all)
- Increased bleeding in hemophilia (all)
- Osteopenia/osteoporosis (all)
- ECG changes (atazanavir)
- Hyperbilirubinemia (atazanavir, indinavir)
- Nephrolithiasis/urolithiasis (indinavir)
- Skin changes (indinavir)

# Severe Hepatotoxicity by ART Regimen



P-mo = person-months.

Adapted from Sulkowski MS, et al. *JAMA*. 2000;283:74-80.

# Common Toxicities of NNRTIs

- Rash (all agents)
  - May include severe morbidity and mortality
- CNS effects (efavirenz)
- Teratogenicity (efavirenz)
  - Pregnancy category D; neural tube defects
- Hepatotoxicity (all; especially nevirapine)
  - Use nevirapine cautiously
  - Adequate CD4 counts; monitor liver function

# Common Toxicities of Fusion Inhibitor

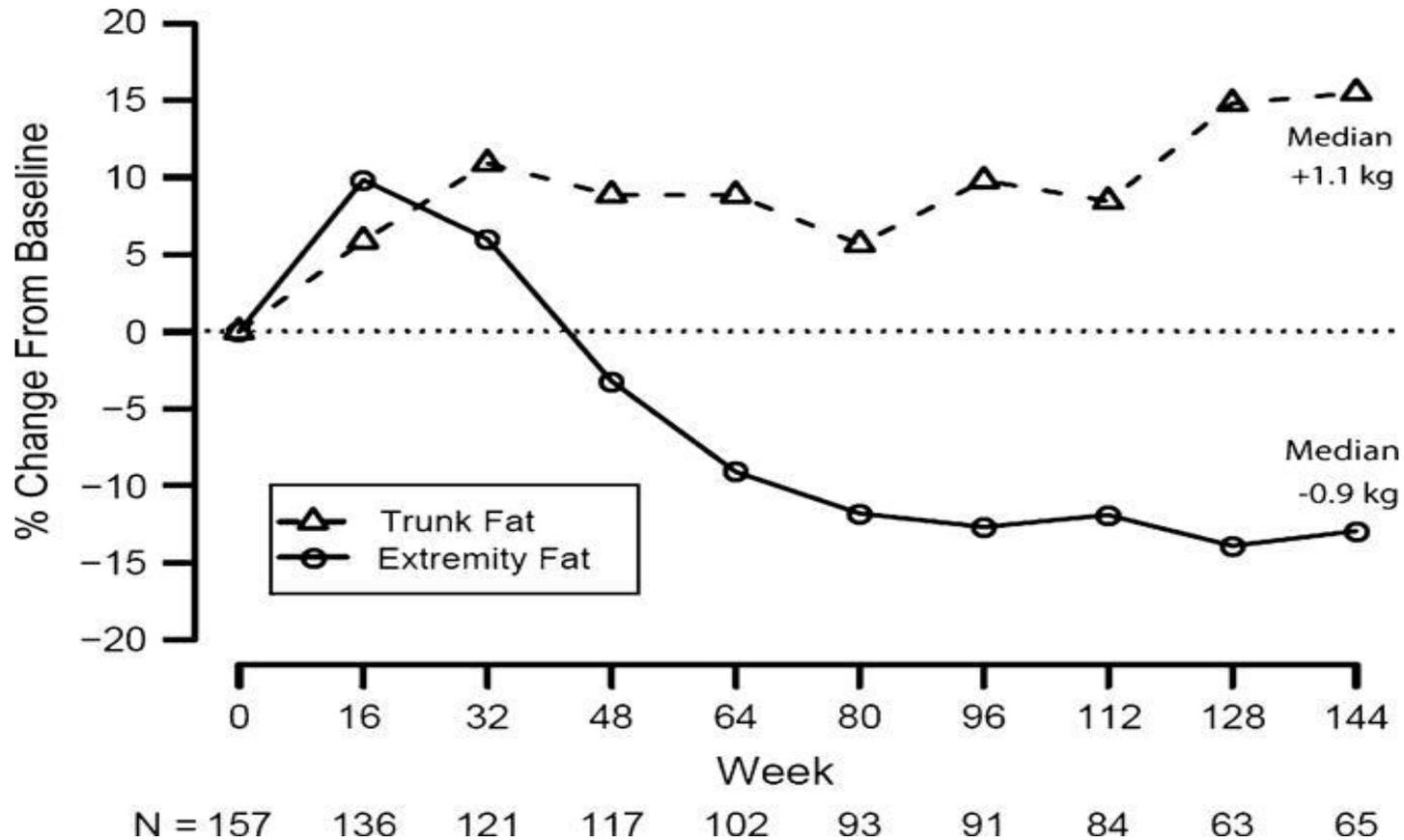
Enfuvirtide is the only approved agent

- No known systemic toxicity
- Injection-site reactions in nearly 100%
  - Redness
  - Itching
  - Swelling
  - Pain
  - Hard skin or lumps

# Long-term Complications of ART: Fat Maldistribution Syndromes

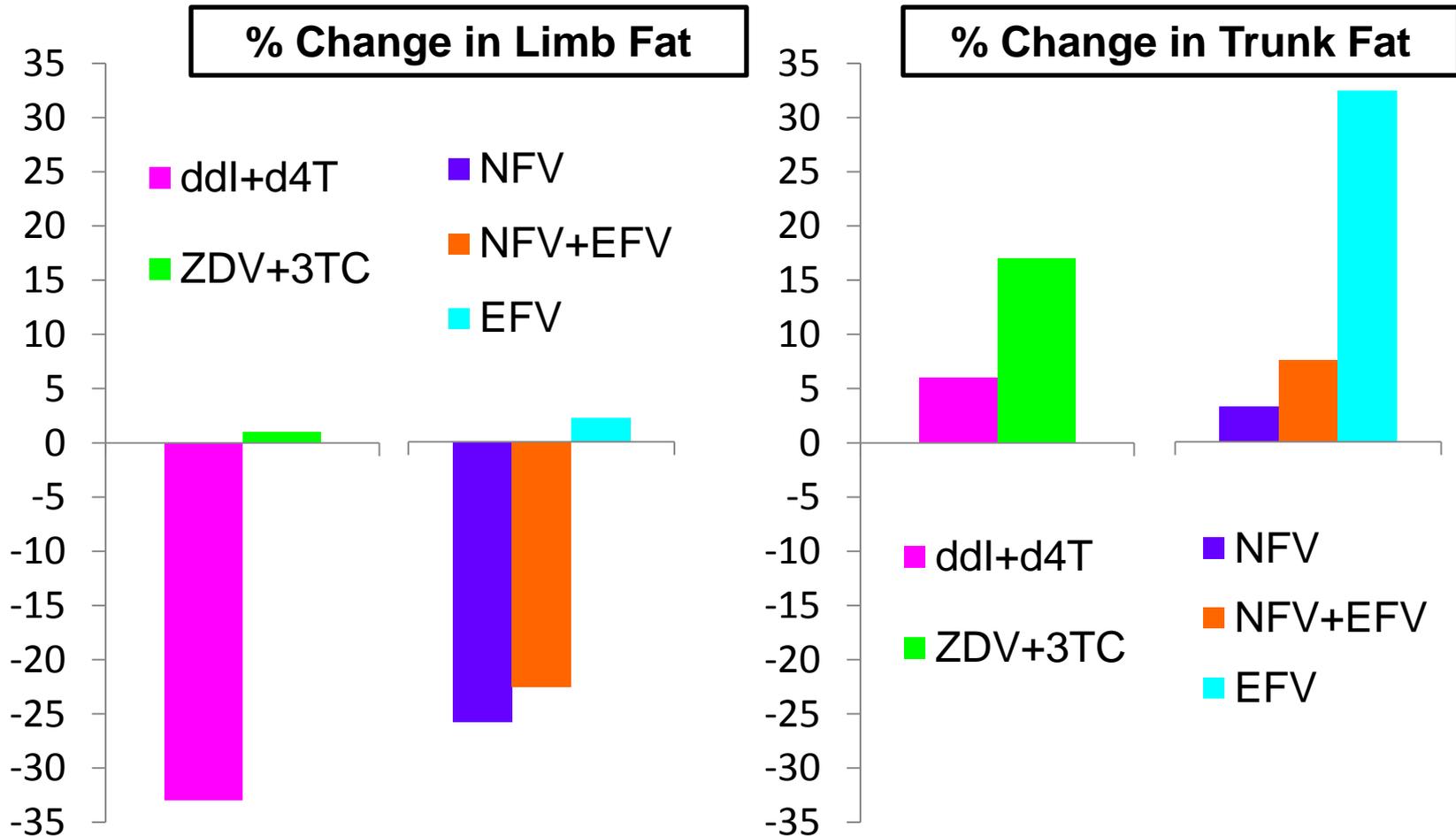
- Lipoatrophy
  - Most common morphologic abnormality
  - Due to mitochondrial toxicity of NRTIs
- Fat accumulation
  - Less common than lipoatrophy
  - Thought to be due to PI therapy

# Changes in Body Fat Indices with ART



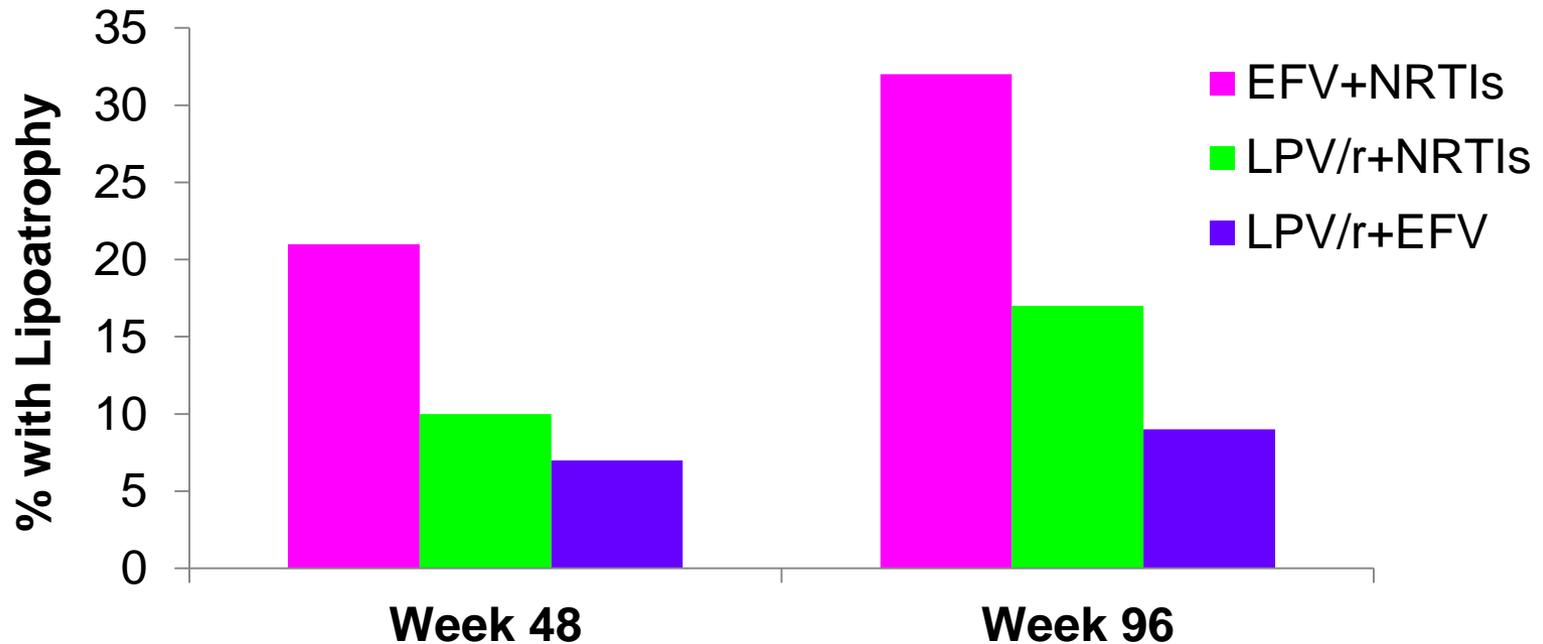
Reprinted from Dubé MP, et al. *J Acquir Immune Defic Syndr.* 2007;45:508-514.

# Lipoatrophy by ART Regimen: Changes at 144 Weeks



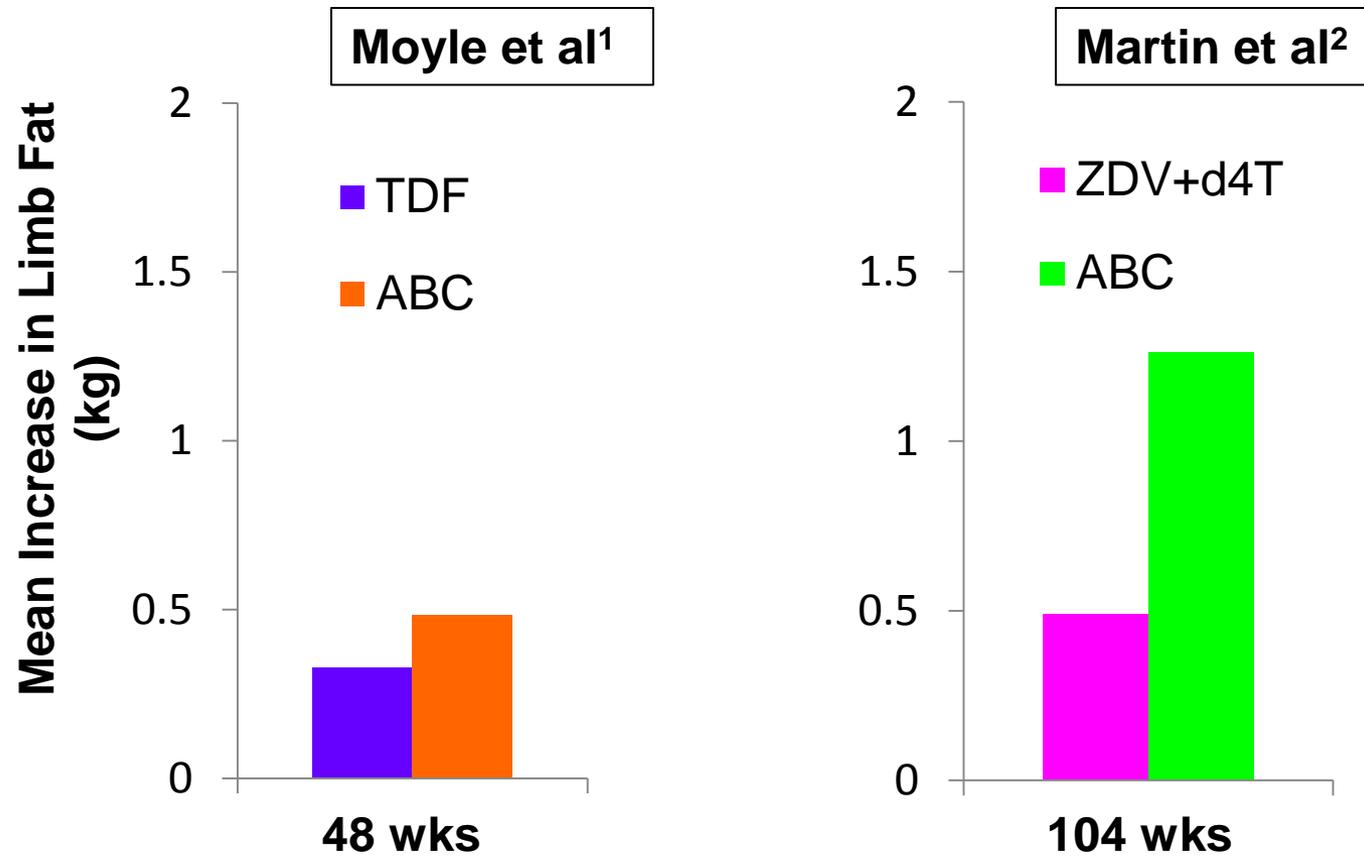
Adapted from Dubé MP, et al. *J Acquir Immune Defic Syndr.* 2007;45:508-514.

# Lipoatrophy by ART Regimen: NRTIs vs NRTI-Sparing Regimen



Reprinted from Haubrich R, et al. 14th Conference on Retroviruses and Opportunistic Infections; Feb. 25–28, 2007.

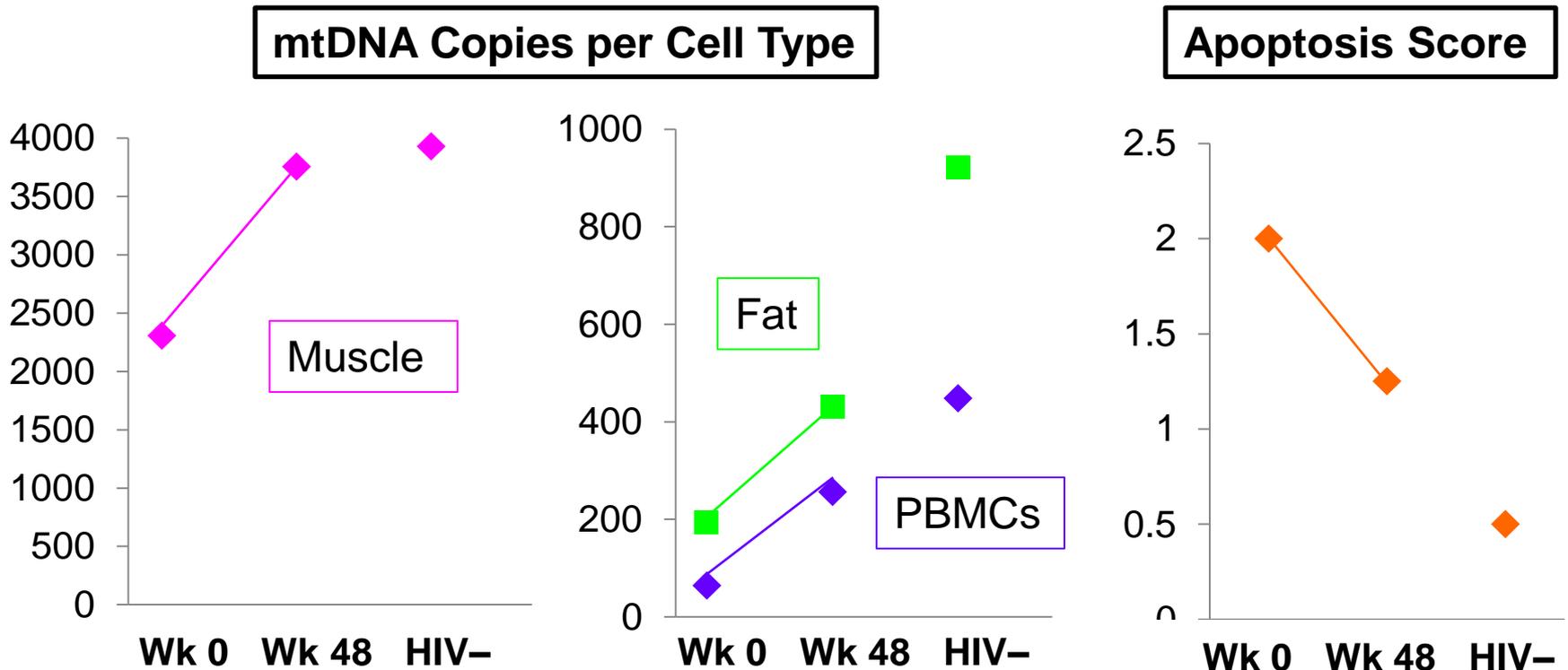
# Lipoatrophy by ART Regimen: Effect of Switching Stavudine



1. Adapted from Moyle GJ, et al. *AIDS*. 2006;20:2043-2050.

2. Adapted from Martin A, et al. *AIDS*. 2004;18:1029-1036.

# Mitochondrial Toxicity by ART Regimen: Effect of Switching Stavudine



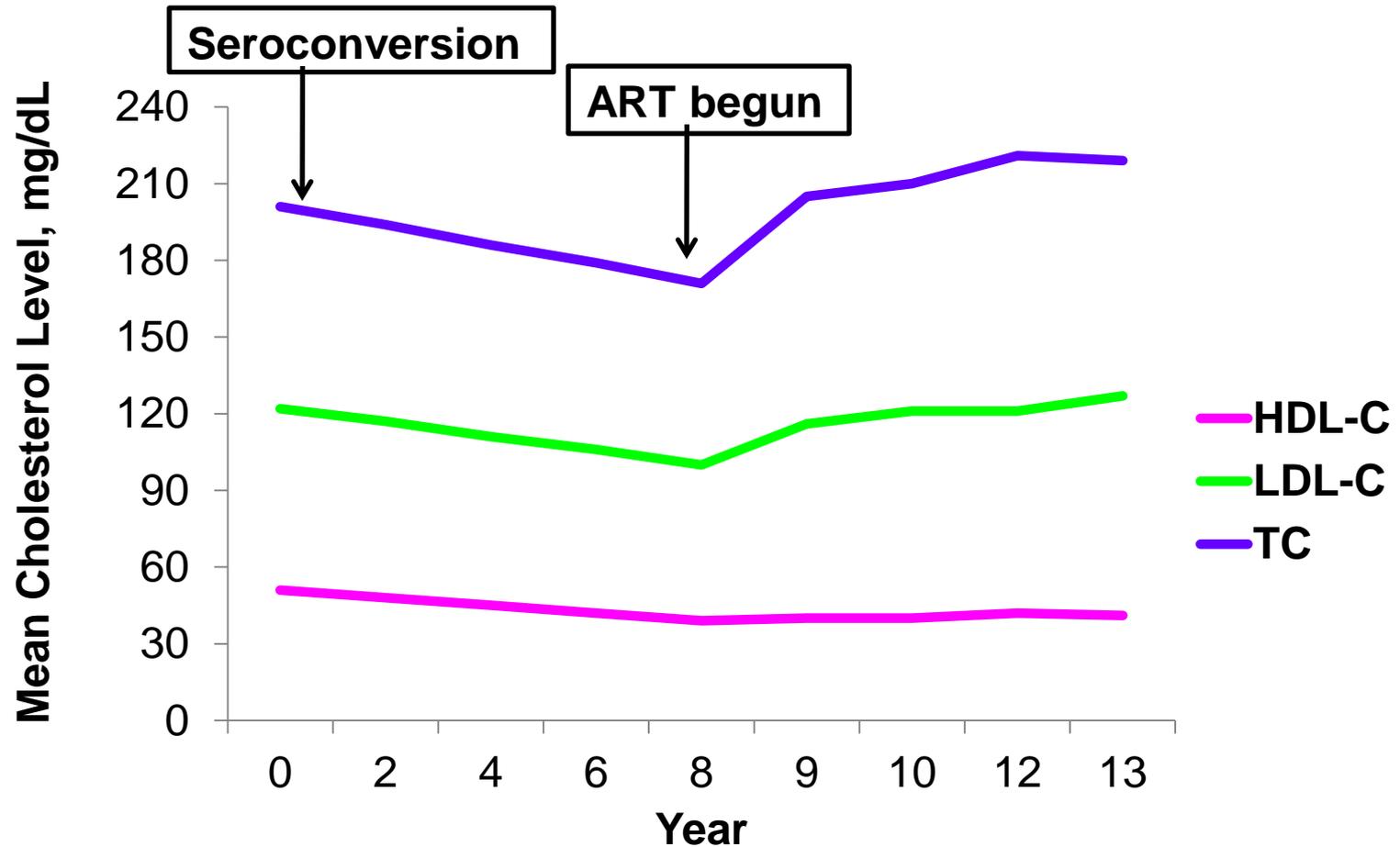
Adapted from McComsey GA, et al. *AIDS*. 2005;19:15-23.

# Long-term Complications of ART: Lipid Effects

Lipid effects include elevated TC, LDL-C, TGs

- PIs
  - Highest risk among ART classes
  - Especially ritonavir
- NRTIs
  - Highest risk with stavudine, then zidovudine
- NNRTIs
  - Highest risk with nevirapine and efavirenz
  - But also improvement in HDL-C

# Dyslipidemia Due to HIV and ART



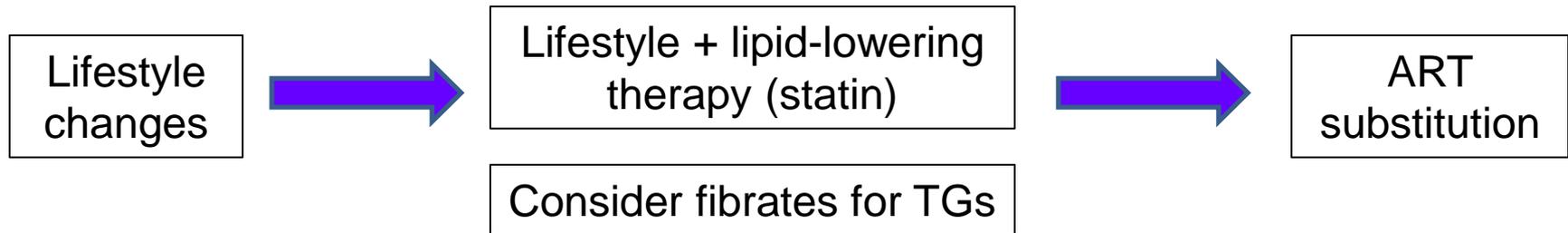
Adapted from Riddler SA, et al. *JAMA*. 2003;289:2978-2982.

# Lipid Effects of PIs

Drug	TG / VLDL-C	LDL-C	HDL-C
Ritonavir	↑↑↑	↑	↔
Lopinavir / ritonavir	↑↑	↑	↔/↑
Tipranavir / ritonavir	↑↑	↑	↔
Saquinavir / ritonavir	↑	↑	↑
Fosamprenavir / ritonavir	↑	↑	↑↑
Indinavir / ritonavir	↑↑	↑	↔
Darunavir / ritonavir	↑	↑/↔	↑?
Atazanavir / ritonavir	↑	↑/↔	↑
Nelfinavir	↔?	↑	↑↑
Atazanavir	↔	↔	↔/↑?
Indinavir	↔	↑	↔

# Management of Dyslipidemia

## Apply NCEP guidelines



## Challenges of lipid-lowering therapy

Multiple medications

Drug–drug interactions (statins, PIs)

Difficulty reaching NCEP goals despite therapy

# Lipid-Lowering Therapy: Drug–Drug Interactions with ART

Recommendation	Lipid-lowering Treatment
Low potential for interaction	Fibrates
	Pravastatin
	Fluvastatin
	Fish oil
	Niacin*
Start lowest dose; use cautiously	Atorvastatin
	Rosuvastatin
Contraindicated with PIs	Lovastatin
	Simvastatin

\* In rare cases, can induce insulin resistance.

# Long-term Complications of ART: Insulin Resistance and Diabetes

- Risk factors
  - Reduction in insulin sensitivity with PIs
  - Long-term exposure to NRTIs
  - HCV coinfection; traditional risk factors
- Management
  - Fasting glucose level before ART
  - Routine glucose monitoring; possible GTT
  - IGT or diabetes: consider switch to NNRTIs

# Insulin Resistance by ART Regimen

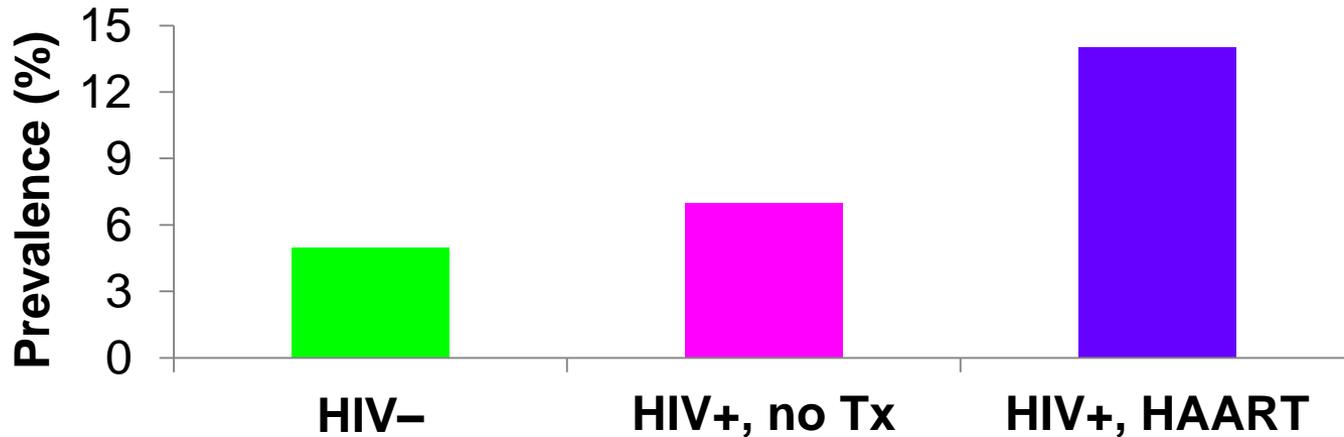
Group (per 1-yr increase in ART)	Difference in QUICKI	OR, insulin >15 $\mu$ U/mL
HIV-	0	1
HIV+	-0.27 (-0.49 to -0.05)*	1.59 (1.07-2.35)*
PI	0.00 (-0.04 to 0.04)	1.06 (0.99-1.14)
Indinavir	-0.05 (-0.12 to 0.02)	1.14 (1.02-1.26)*
NNRTI	0.01 (-0.05 to 0.07)	0.95 (0.84-1.06)
NRTI	-0.04 (-0.07 to -0.01)*	1.08 (1.02-1.13)*
Stavudine	-0.11 (-0.17 to -0.05)*	1.22 (1.11-1.35)*
Lamivudine	-0.06 (-0.12 to 0.00)*	1.12 (1.02-1.24)*

QUICKI = quantitative insulin sensitivity check index; OR = odds ratio.

\*  $P < 0.05$ .

Adapted from Brown TT, et al. *AIDS*. 2005;19:1375-1383.

# Diabetes by ART Regimen



Group	Prevalence *	Incidence †	Adjusted RR
HIV-	1	1.4 (0.8–2.6)	1
HIV+, no Tx	2.21 (1.12–4.38)	1.7 (0.6–4.5)	NA
HIV+, HAART	4.64 (3.03–7.10)	4.7 (3.2–7.1)	4.11 (1.85–9.16)

RR = rate ratio adjusted for age and body mass index; NA = not applicable.

\* Prevalence ratio based on 1278 men; adjusted for age and body mass index.

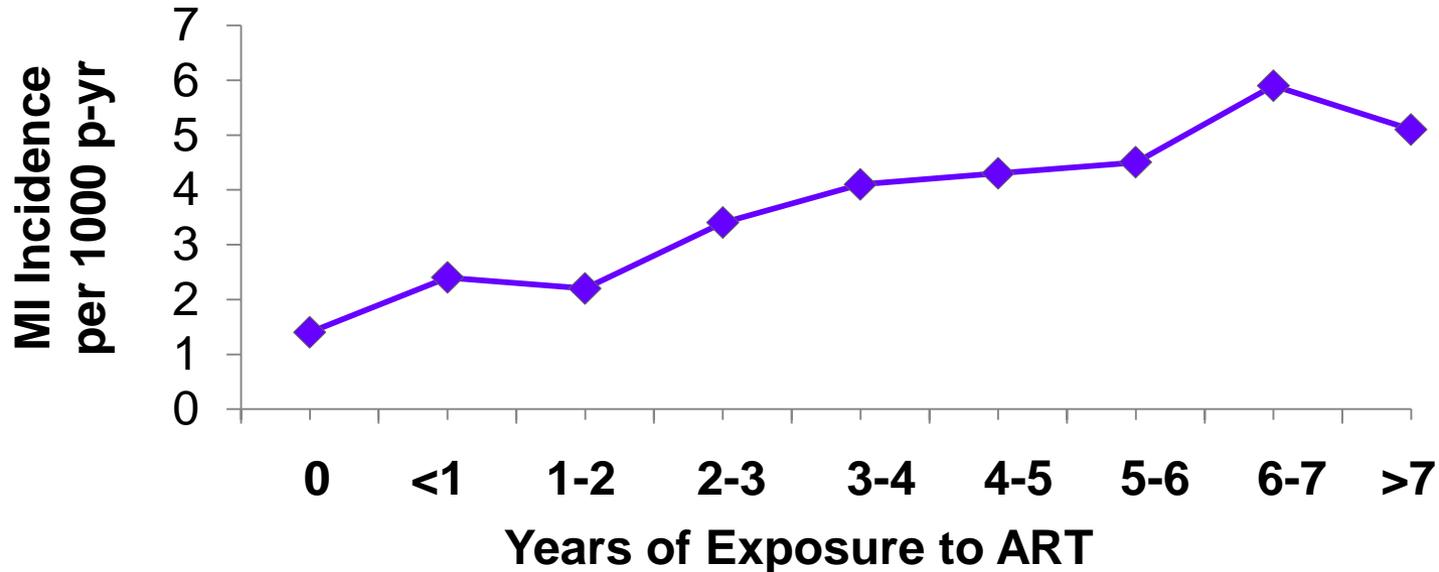
† Incidence rate per 100 person-years, based on 680 men.

Adapted from Brown TT, et al. *Arch Intern Med.* 2005;165:1179-1184.

# Long-term Complications of ART: Cardiovascular Risk

- Risk factors
  - Dyslipidemia
  - Insulin resistance
  - Lipodystrophy
  - Endothelial dysfunction
  - Smoking
  - Duration of ART
  - PIs seem to be mainly responsible
- Management: continue therapy

# Myocardial Infarction by ART Regimen



Group	Adjusted RR*	95% CI
All ART	1.16	1.09–1.23
PIs	1.16	1.10–1.23
NNRTIs	1.05	0.98–1.13

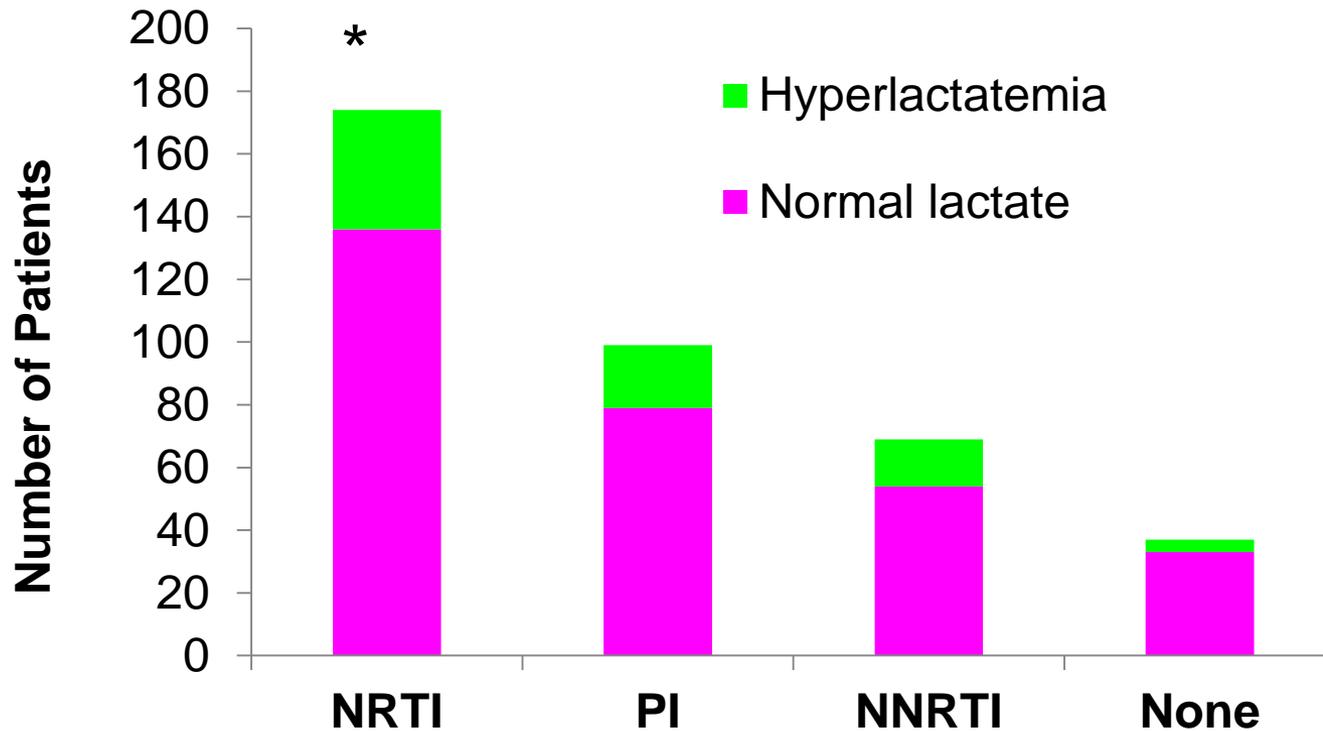
p-yr = person-years; RR = relative rate per year of exposure.

Adapted from Friis-Moller N, et al. *N Engl J Med.* 2007;356:1723-1735.

# Long-term Complications of ART: Lactic Acidosis

- Asymptomatic hyperlactatemia
  - Mildly elevated blood lactate
  - Does not predict lactic acidosis
- Symptomatic hyperlactatemia
  - Nonspecific symptoms
- Lactic acidosis syndrome
  - Severe symptomatic hyperlactatemia
  - Metabolic acidosis, hepatomegaly, steatosis
  - Rare but often fatal
  - Stop NRTI treatment

# Hyperlactatemia by ART Regimen



\*  $P = 0.03$ .

Adapted from Vrouenraets SM, et al. *Antivir Ther.* 2002;7:239-244.

# Hyperlactatemia Risk Factors

Significant Risk Factor	OR	95% CI	P
ALT (per 10 U/L) *	1.13	1.001–1.3	0.03
<b>NRTI treatment *</b>	<b>3.0</b>	<b>1.0–9.27</b>	<b>0.05</b>
Stavudine (n = 56) †	2.8	1.4–5.7	0.004
Stavudine/lamivudine (n = 40) †	2.2	1.0–4.8	0.05

OR = odds ratio; CI = confidence interval; ALT = alanine aminotransferase.

\* Multiple logistic regression analysis.

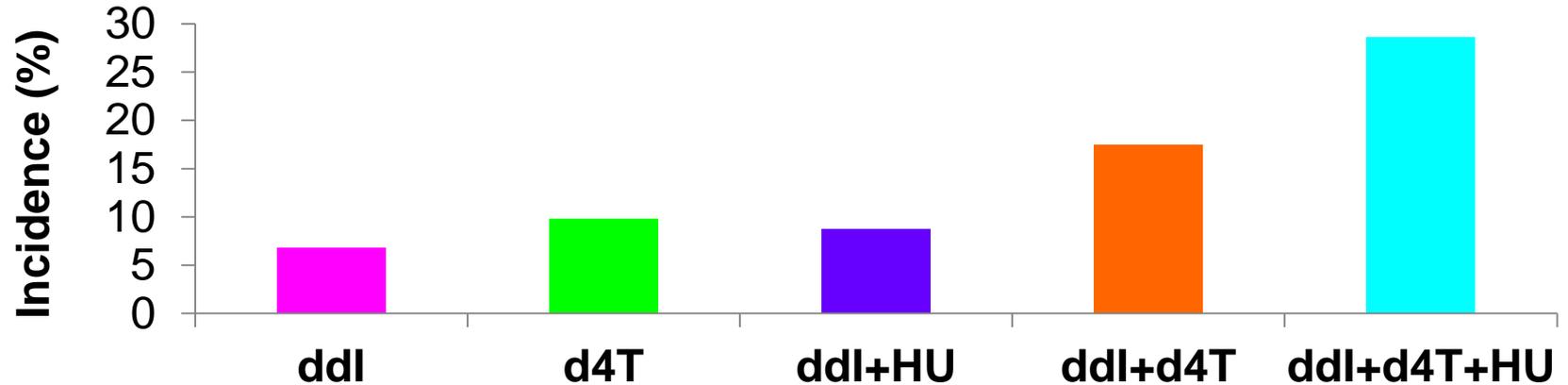
† Unadjusted univariate analysis.

Adapted from Vrouenraets SM, et al. *Antivir Ther.* 2002;7:239-244.

# Long-term Complications of ART: Distal Sensory Peripheral Neuropathy

- Characteristics
  - HIV-related causes
  - NRTIs (esp. stavudine + didanosine)
  - Risk is higher with advanced HIV
  - Pain, numbness, loss of sensation
- Management
  - Discontinue NRTIs
  - Adjunctive treatments for persistent pain

# Peripheral Neuropathy by ART Regimen



Regimen	HR	95% CI	P
d4T	1.39	0.84–2.32	0.20
ddl+HU	2.35	0.69–8.07	0.18
ddl+d4T	3.50	1.81–6.77	0.001
ddl+d4T+HU	7.80	3.92–15.5	0.0001

HU = hydroxyurea; HR = hazard ratio.

Adapted from Moore RD, et al. *AIDS*. 2000;14:273-278.

# Summary: Common Adverse Effects

## NRTIs

Mitochondrial toxicity  
Lipoatrophy  
Hepatic steatosis  
Lactic acidosis  
Peripheral neuropathy  
Bone marrow suppression  
Myopathy  
Pancreatitis  
Renal impairment  
Hypersensitivity

## PIs

Lipodystrophy  
Dyslipidemia  
Hepatotoxicity  
Hyperglycemia  
Hemophilia bleeding  
Osteoporosis  
ECG changes  
Hyperbilirubinemia  
Urologic stones  
Skin changes

## NNRTIs

Rash  
CNS effects  
Teratogenicity  
Hepatotoxicity

## Fusion inhibitor (enfuvirtide)

Injection-site reactions

# Summary:

## Management of Adverse Effects

- Adjunctive strategies:
  - Choose agents carefully
  - Optimize lifestyle
- Pharmacologic strategies:
  - Mild effects: continue therapy
  - Moderate effects: single-drug substitution
  - Severe effects: discontinuation