

Chronic Complications of HIV ICAP Webinar Grand Rounds



21 October 2010



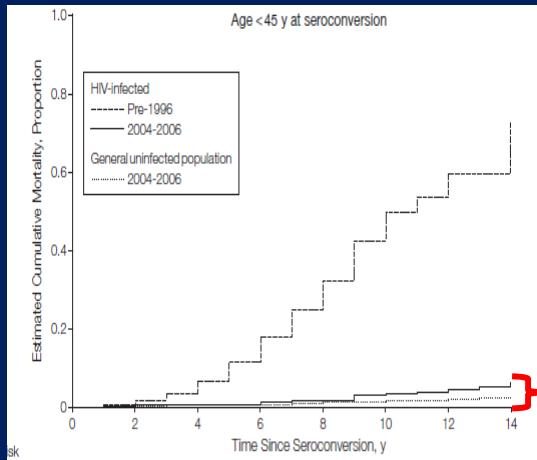
Objectives

1. Overview of select chronic complications of HIV
2. Impact of HIV and HAART therapy on outcomes for non-AIDS illnesses
3. Management of HIV chronic complications in RLS



What is the Excess Mortality due to HIV?

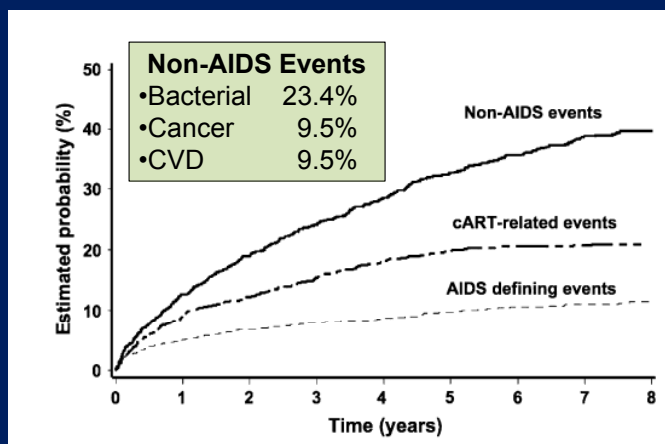
- **CASCADE Study**¹
 - 16,534 HIV patients
 - 23 European cohorts
 - Followed ~6 years
- Mortality w/ ART
- Excess Mortality with ART **BUT** still greater than the general population



3 Bhaskaran, et al. JAMA 2009



Incidence of Non-AIDS Clinical Events ANRS C08 Cohort Study

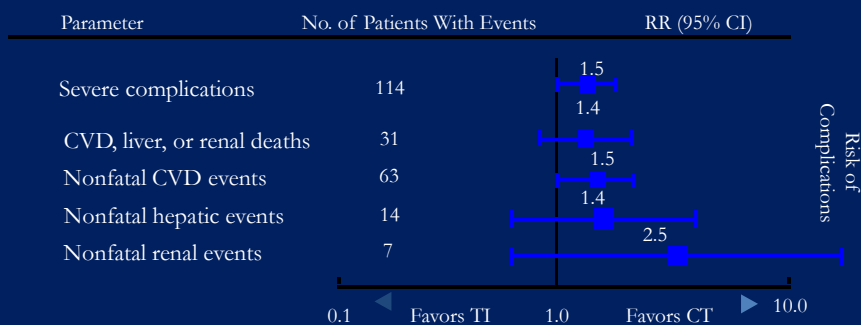


4 Ferry, et al. JAIDS 2009



SMART: HIV Progression With Continuous HAART vs Interruption

- Does interrupted therapy lower rate of major HAART toxicities?
- CD4-guided drug conservation strategy was associated with significantly greater disease progression or death, compared with continuous viral suppression: RR: 2.5 (95% CI: 1.8-3.6; $P < .001$)



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El-Sadr, et al. NEJM. 2006



Spectrum of HIV Complications

Nervous System

- cognitive function
- neuropathy

Pulmonary

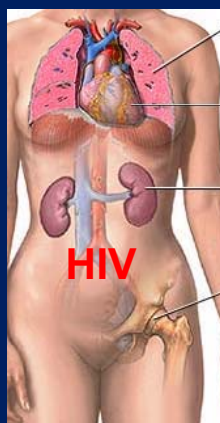
- pulmonary htn
- pulmonary fibrosis

GI

- diarrhea

Endocrine

- Vit D deficiency
- Thyroid
- Diabetes



Cardiovascular

- atherosclerosis
- vascular disease

Renal

- renal insufficiency

Skeletal/Muscle

- osteoporosis/penia
- fractures
- myopathy
- sarcopenia

Reproductive

- hypogonadism

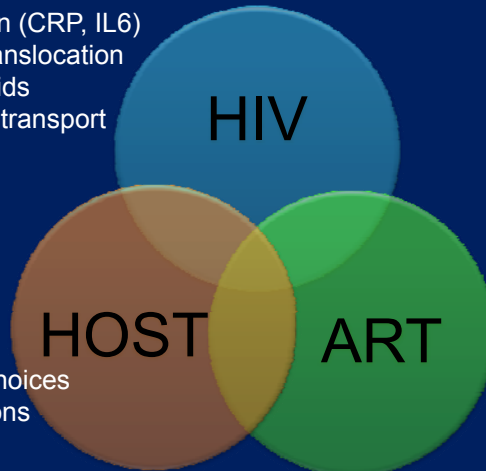
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What is the Mechanism for Disease?

- Inflammation (CRP, IL6)
- Microbial translocation
- Oxidized lipids
- Cholesterol transport

- Genetics
- Lifestyle choices
- Co-infections



- Direct
- Indirect



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Neuhaus JID June 2010

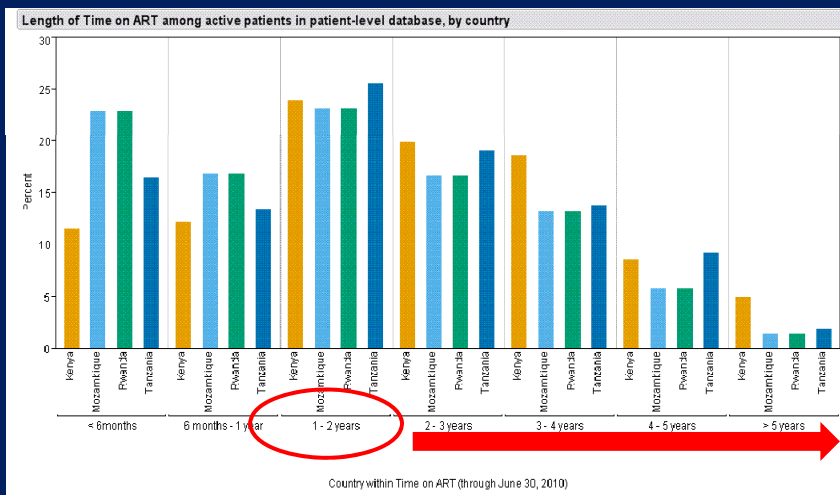
Limitations of Existing Research

- Research limitations
 - Observational studies
 - Time frame
- Contextual limitations
 - Different patient population
 - Different HAART regimens
 - Different length of treatment
 - Different management therapeutics of complications



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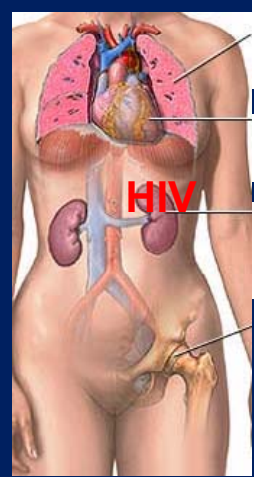
Percent on ART/Years at ICAP Sites



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Spectrum of HIV Complications



Cardiovascular
 • atherosclerosis
 • dyslipidemia

Renal
 • renal insufficiency

Metabolic
 • Bone Health
 • Lipodystrophy

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Cardiovascular Disease



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CVD in HIV-Infected Patients

Study	Population	N (HIV)	Primary Result	Control	Prospective	PI Effect
D.A.D	11 HIV cohorts	23,468	PI exposure → ↑ rate AMI	No	Yes	Yes
Mary Krause	French Hospital Database	34,976	PI exposure → ↑ rate AMI	No	No	Yes
Bozzette	VA Healthcare System	36,766	PI exposure → ↓ rate AMI/CVA	No	No	No
Currier	CA Medicaid	28,513	CHD ↑ in young HIV vs control	Yes	No	Yes
Klein	Kaiser	4159	CHD and AMI ↑ in HIV vs control	Yes	No	No
Triant	Partners HealthCare System	3851	AMI ↑ in HIV vs control	Yes	No	NA

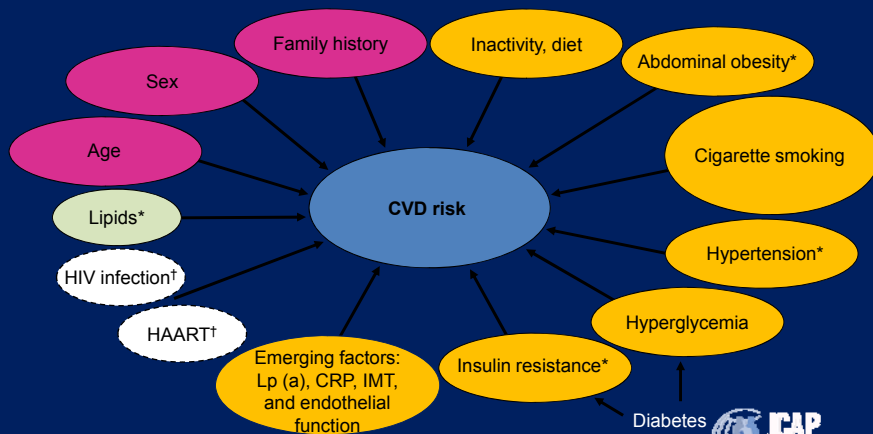
AMI, acute MI; CVA, cerebral vascular accident ; NA, not applicable.

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www.clinicalcareoptions.com



Metabolic Complications & Cardiovascular Risk Factors

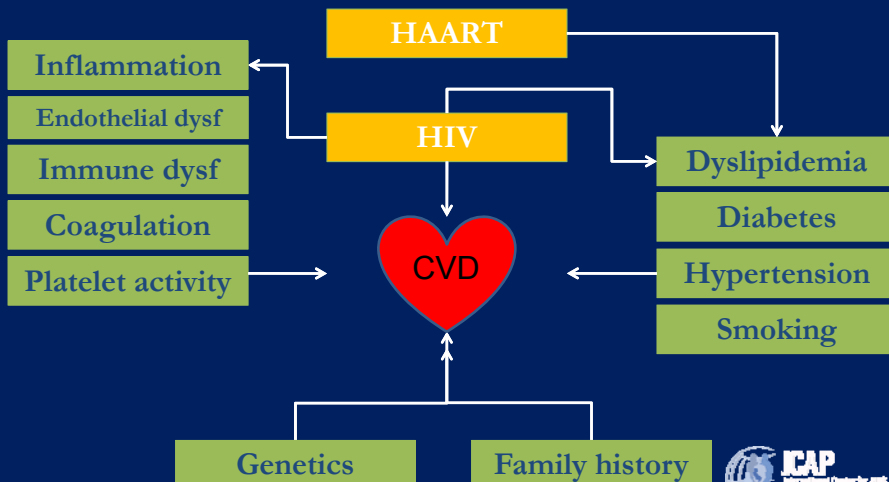


*Metabolic syndrome.
 †Precise contribution unclear.

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What is the Mechanism of HIV-related CVD?



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HIV and Markers of CVD

Lower CD4 counts ↑ CVD

- Even after controlling for CVD Risk Factors
 - Age, HTN, Diabetes, Dyslipidemia, smoking

CD4 count < 350 associated with ↑ arterial stiffness and abnormal ECG changes^{1, 2}

- Early initiation of HAART reduces risk of CVD²

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1. Ho, et al. AIDS 2010; 2. Carr, et al. AIDS 2009



HIV and Markers of CVD

Carotid intimal thickness

- Increased abnormalities in HIV+ treated patients¹⁻³
- Usually associated with traditional risk factors

Endothelial dysfunction

- HIV infection increase endothelial dysfunction, reversed with treatment⁴

ECG changes

- HIV infection associated with high prevalence of ECG abnormalities (in asymptomatic patients with no history of CVD)⁵

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1. Maggi, et al. AIDS 2000; 2. Talwani, et al. JAIDS 2002; 3. Hsue, et al. Circulation 2004; 4. Torriani F, et al. EACS 2005; 5. Carr, et al. AIDS 2009



Higher Incidence of CVD in HIV+ vs HIV- Patients

- 5000 HIV+ men followed for 10.5 years compared with 43,000 age-matched HIV- men
- HIV+ men had significantly higher rates of CVD ($P < .0001$) and MI ($P < .002$) vs HIV- men
- Trend for HIV-infected men on PI-based regimens to be at higher risk of CVD ($P = .11$) and MI ($P = .14$) vs those not taking PIs

Age-Adjusted Rates* From 1996-2004, Events per 1000 Person-Yrs (95% CI)	All HIV- Infected Patients	HIV-Infected Patients on Any PI	HIV-Infected Patients Not on PI	HIV- Uninfected Comparator Group
CVD	6.1 (4.9-7.3)	6.9 (5.3-8.6)	4.9 (3.1-6.8)	2.9 (2.7-3.1)
MI	3.8 (2.8-4.7)	4.4 (3.1-5.8)	2.9 (1.5-4.4)	2.2 (2.0-2.4)

*Rates adjusted to 1990 US population, 5-year age groups.

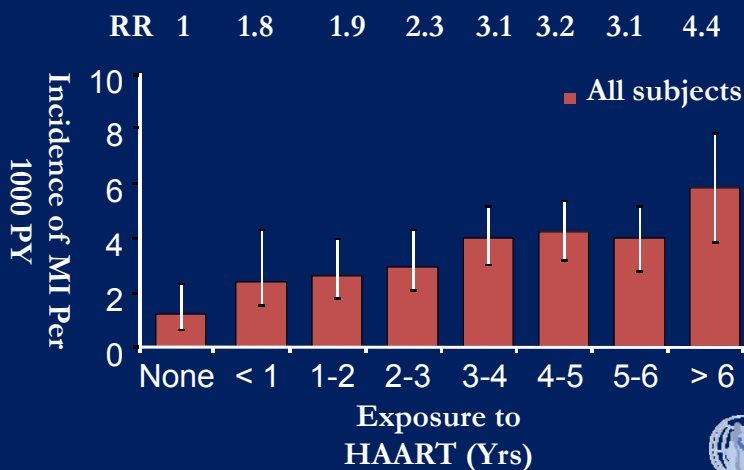


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Klein, et al. CROI 2007

D:A:D STUDY

Relationship Between Myocardial Infarction and HAART



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Fris-Moller, et al. NEJM, 2007

D:A:D Study Impact of PI and NNRTIs

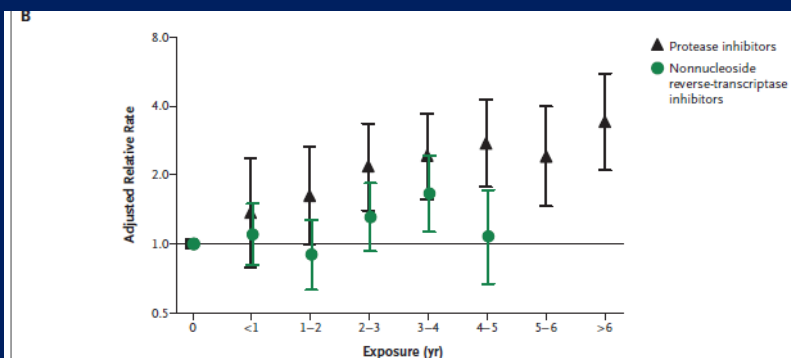


Figure 2. Risk of Myocardial Infarction According to Exposure to Protease Inhibitors and Nonnucleoside Reverse-Transcriptase Inhibitors.

Relative Rate of MI/year of drug exposure

PI 1.16% (CI 1.10-1.23)

NNRTI 1.05% (0.98-1.13)

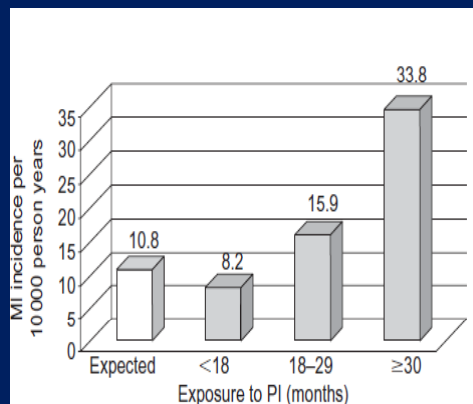
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Friis-Moller, et al. NEJM, 2007



MI Risk Increased with PI Use

- French Cohort Study evaluated MI diagnosis among men from 1996-1999
- Follow-up: 88,029 patient-years (n = 19,795 exposed to PIs)
- 60 MIs observed, 49 cases among men taking PIs
- Risk of MI ↑ with duration of PI exposure (* 18 mo)
- Relative hazard for MI with PI use: 2.56 (95% CI: 1.03-6.34)



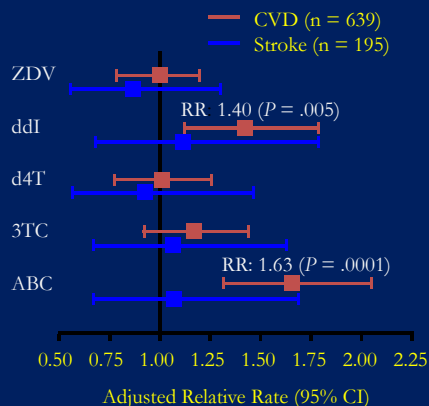
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Mary-Krause, et al. AIDS 2003.



ABC & DDI

- ABC, ddi (Current or recent < 6 months) associated with ↑ RR MI
 - 90% ↑ risk of MI with recent ABC
 - 49% ↑ risk of MI with recent ddi
 - Overall predicted rate of MI
 - Recent ddi: ~ 5/1000 PY
 - Recent ABC: ~ 6/1000 PY
 - Risk most prominent in individuals with underlying CVD risk factors
- ↑ risk no longer observed in patients who had discontinued ABC or ddi for > 6 months



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Sabin, et al. Lancet 2008



Cardiac Risk: Not so Simple¹



	RR per year exposure
PI	1.16 (CI 1.10-1.23) *lipids
NRTI	
ABC	1.90 (CI 1.47-2.45) * not cumulative
ddi	1.49 (CI 1.14-1.95)
NNRTI	not significant

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Smoking 2.83 (p<.001)



1. Aberg, et al. JID 2010; Worm, et al. JID 2010

Uncontrolled HIV Infection is Associated With Dyslipidemia

- Patients with untreated HIV¹⁻³
 - Low HDL-C
 - Low LDL-C (relatively high small dense LDL-C)
 - Elevated VLDL/TG

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1. Grunfeld , et al. Am J Med 1989; 2. Grunfeld C, et al, Am J Med 1991; 3. Mildvan D, et al. Lancet 1992



Effects of HAART on Dyslipidemia

- Effects of specific antiretroviral drugs difficult to determine based on their use in combinations
 - Limited data on monotherapy with selected antiretroviral agents
 - “Return to health” phenomenon¹
- Differences exist between and within classes
- Regimens may have beneficial effects on some lipid parameters and deleterious effects on others

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1. Riddler , et al. JAMA 2003



Effects of HAART on Lipids

- LDL-C tends to go up modestly with virtually all regimens
- **NNRTIs:** Increase HDL-C
 - EFV associated with greater LDL-C and TG increases than NVP, but these effects are likely outweighed by beneficial effects on HDL-C seen with both NNRTIs¹
- **NRTIs:** d4T and ZDV associated with adverse effects on lipids relative to TDF (and ABC)
- **PIs:** Majority increase TG and non-HDL-C, but HDL-C typically increases as well

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Fontas et al. JID 2004



HIV & Dyslipidemia in Africa

- Lipid levels significant lower than those of Europeans / Americans at baseline¹
- HAART still a risk factor in Africa²
 - d4T major culprit
- Limited access to lipid monitoring and lipid lowering therapies.
- Extreme poverty limits the ability of individuals to make choices about dietary intake and hinders healthy lifestyle patterns

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1. Adedeji, et al. Trop Geogr Med 1994; 2. Multimura, et al. JAIDS 2007



Conclusions

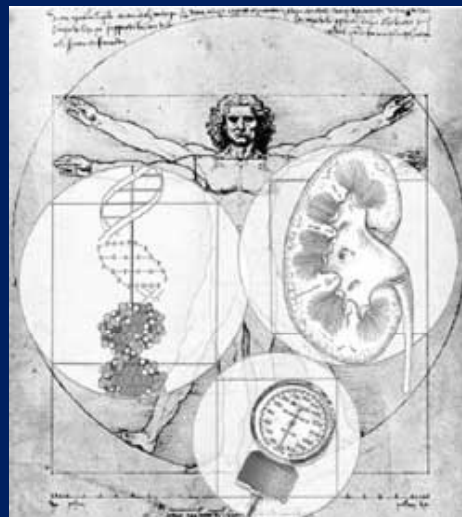
- Traditional risk factors (age, smoking, and hypertension) increase risk of CVD in individuals with or without HIV infection
- HIV disease confers its own increase in CVD risk
- There is evidence of an association between HAART use and a small increase in the absolute risk of CVD¹
- CVD risk should **not** influence the decision to initiate HAART in most cases
- Encouraging CVD risk reduction –smoking cessation, exercise & healthy diet should be integral to comprehensive approach to care.
- Secondary prevention: aspirin²

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1. The DAD Study Group, NEJM 2007; 2. Tornero, et al. JAIDS 2010

Kidney Disease



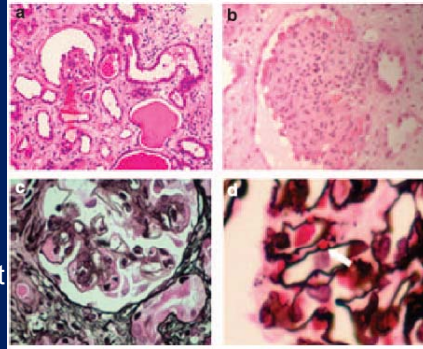
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HIV & Kidney Disease

HIV is associated with multiple causes of renal disease

- HIV-associated nephropathy:
(HIVAN) FSGS
- Drug-related renal impairment:
Cotrimoxazole, TDF, RTV
- Concurrent conditions: HBV, post



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Arendse, et al. Kidney Int 2010



HIVAN

- Occurs mostly in patients with low CD4 counts and advanced disease¹
- Occurs in the US, 2 -10 % of PLWHA, associated with a high VL² – Predominantly in African Americans
- Presents with nephrotic syndrome, and often normal BP. Rapid deterioration to end stage renal failure
- Biopsy: collapsing FSGS from virus induced podocyte injury
- Prevention & Treatment - Early detection of proteinuria and initiation of HAART

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1. Gupta, et al. CID 2005 2. Humpheys, et al. Kidney Int, 1994



HIVAN in Africa

- Under-diagnosed:
 - South Africa: 20% of cases of renal biopsies (all of whom had been mis-diagnosed with ATN)¹
 - Zambia: 34% (n=8546) of PLWHA starting HAART had renal insufficiency of which 26% were mod-severe²
 - Uganda: 8.4% of HIV-infected and 4.7% of HIV-negative individuals had mildly or moderately reduced GFR (P = 0.002)³

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1 . Mulenga, et al. AIDS 2008; 2. Arendse, et al. Kidney Int 2010; 3 Lucas, et al. JAIDS, 2010

HAART and Kidney Disease

DART Study: Low Rate of Severe Renal Impairment in Antiretroviral-Treated Patients in Resource-Limited Settings¹

- DART explored effect of HAART on renal function in Uganda.
- Baseline renal impairment was low, 1.9% to 3.1% of participants
- Development of chronic kidney disease was more common in patients receiving TDF (5.9% vs 2.1% to 3.1%; P = .004).
- But deleterious impact of TDF was small

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1. Reid, et al. XVI Intl AIDS Conf 2006

HIVAN in Africa Treatment

1. Screening for kidney disease
→ urine dipstick + serum creatinine of all patients at enrollment
2. Initiate HAART for all patients with proteinuria
Improved creatinine clearance in 21% of patients with renal impairment, UGANDA¹
3. Optimize BP and glucose control for patients with DM and HTN
4. ACE-inhibitors for patients with proteinuria

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1. Peters, et al. Kidney Int 2008



Metabolic Complications



Bone Health
&
Lipodystrophy

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HIV & Bone Disease

- Osteopenia/osteoporosis occur higher frequency in HIV patients than age-matched controls
 - Previous studies report HIV-related osteopenia in Europe /US prevalence of 40% to 50%
 - Gilead Study: treatment naïve patients baseline osteopenia 23-28%
- Causal factors of bone mineral density (BMD) decline in HIV cases largely unknown
 - HIV infection may increase risk of secondary causes
 - Low weight/wasting
 - Steroid use
 - Poor nutrition

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Mondy, et al. JAIDS 2005



HAART & Osteoporosis

- SMART sub-study: BMD declined less in interrupted therapy group ¹
- PIs are not associated osteoporosis¹
- TDF associated with □ bone mineral disease (BMD) ²
 - 602 randomized to TDF or d4T
 - TDF associated with significant hip and L- spine BMD compared to d4T

• SPINE	2.2%	vs. 1% decrease	(p<.001)
• HIP	2.8%	2.4%	(p< .064)
- Bone loss stabilizes over time

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1. Grund, et al. AIDS 2009 ; 2. Amorosa, et al. CID 2006; 3. Gallant, et al. NEJM 2004



HIV & Osteoporosis in Africa

- Other bone disorders are predominant
 - (secondary to malnutrition & TB)
- Osteoporosis not described in HIV populations in Africa –but merits further evaluation.
- Smoking cessation, weight bearing exercise and are feasible first line therapies

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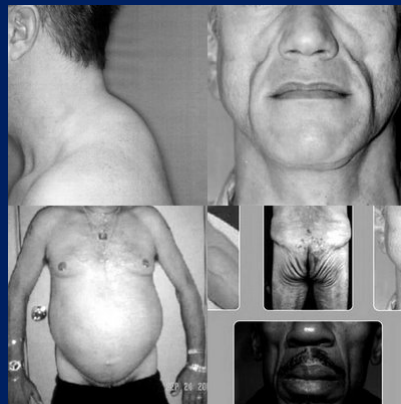
HIV-Associated Lipodystrophy

LipoAtrophy

- Loss of subcutaneous fat
- Face, trunk, extremities, and buttocks
- Strongly linked to the use of TA NRTIs (d4T, AZT)

LipoHypertrophy

- Central deposition of fat
- Intra-abdominal deposits, buffalo hump, and breast enlargement
- Women > men



<http://www.wellsphere.com/wellpage/symptoms-of-lipodystrophy>



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HIV-Associated Lipodystrophy

Variable prevalence 10-80%¹

Risk Factors²:

- Development of fat atrophy
 - Lower baseline body fat ($P < .001$)
 - Increased disease severity ($P = .006$)
 - Use of D4T ($P = .002$)

- Development of fat deposition
 - Female sex ($P < .001$)
 - Higher baseline body fat ($P = .005$)
 - Elevated triglyceride levels ($P < .001$)

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1. Mallon et al, AIDS 2003 2. Jacobson, et al. CID 2005

HAART and Lipodystrophy

- Thymidine analogues (d4T & AZT)¹ (lipoatrophy only)
- TDF and ABC are not associated with lipoatrophy²
- Impact of NNRTIs and PIs much less likely to affect body composition³

OTHER FACTORS

- Lower CD4 nadir⁴
- Genetic factors- polymorphisms in mitochondrial gene⁵

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1. Gallant, et al. 2004; 2. Podzamcer, et al. 2007; 3 Haubrich, et al. CROI 2007; 4. Lichenstein, et al. JAIDS 2003; 5. Hendrickson, et al. JAIDS 2009

Lipodystrophy & Stigma

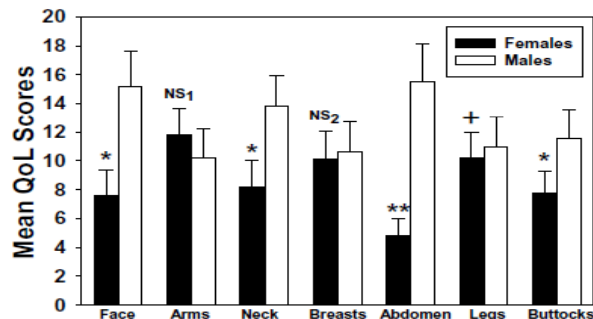


Figure 1
Quality of life and body changes by gender (n = 100; 60% females); Data expressed as median (interquartile range); on a summary scale of quality of life domain scores ranging from 4-20; *p < 0.05, **p < 0.001 versus male group; +p = 0.051, NS₁ p = 0.745; NS₂ p = 0.827.

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Mutimura, et al. AIDS Res and Therapy 2007



Management of Lipodystrophy

Prevention

Avoid d4T or AZT

Management

Modification of HAART

- Switch d4T or AZT to ABC or TDF¹

Surgical intervention

- Offered for cosmetic relief of facial lipodystrophy
- Limited randomized trials and no comparative studies of different approaches

Pharmacological interventions

- Have not been proven to be effective and may introduce new complications
 - Pioglitazone possibly beneficial in patients not taking d4T
 - increases in blood lipids and possible CVD

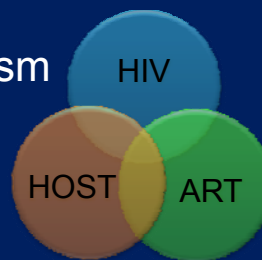
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1. Moyle, et al. CROI 2005



Summary

- ART has been successful in controlling HIV and restoring immune function
 - Mortality HIV patients approaching gen population
 - Non-AIDS illnesses increasing
 - Non-AIDS illnesses less common in Africa than US/Europe
- Multifactorial Mechanism



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Summary (2)

With patients surviving longer, necessary to think about how to mitigate complications

Consider for patients in chronic HIV care:

- Screening for DM, HTN, proteinuria
- Low cost primary prevention interventions:
 - CVD: Diet, Smoking cessation, weight management
- Changes in HAART regimens

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