Long Term Complications of ARV Treatment in HIV-Infected Children and Adolescents

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January 15th 2014, Addis Ababa

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Outline

- Why should be concerned about long term complications associated with ARV treatment
- Lipodystrophy
- Dyslipidemia
- Insulin resistance
- Cardiovascular health
- Bone Disease and Vitamin D

The GOOD, BAD and the UGLY

- Potent antiretroviral therapy (ART) has significantly reduced the morbidity and mortality of HIV-infected children
- The long-term benefits of ART are associated with metabolic complications, including lipodystrophy (LD), dyslipidemias, lactic acidosis, glucose intolerance, osteopenia and osteoporosis

Long term complications and HIV: are children at greatest risk?

- HIV-infected children begin lifetime therapy in infancy.
- CAD often results from exposure to risk factors that have their origins in childhood. (Nicklas Bogalusa Heart Study. 2002, Bao the Bogalusa Heart Study 1997).
- Osteoporosis risk is related to peak bone mass acquired during childhood and adolescence.
- What are consequences with respect to metabolic complications, bone abnormalities and CVD?

Lipodystrophy Syndrome

- Characterized by body fat abnormality and or metabolic disturbances associated with antiretroviral therapy
- May be associated with abnormalities of lipid regulation and glucose homeostasis
- Varying prevalence reported because of different definitions used and varying rates of drug use

Significance of Lipodystrophy

- Lipodystrophy can be a source of stigma (Slims Disease) and negatively affect ARV adherence (Duran S. AIDS 2001, Ammassari A. J AIDS 2002, Corless I. AIDS Patient Care STDS 2005, Mutimura . AIDS Res & Ther 2007).
- Lipodystrophy can be particularly problematic in adolescents (concerns about self image, self esteem) (Wedekind CA . Antivir Ther 2007)
- Lipodystrophy also associated with dyslipidemia, fatty liver, fatty muscle, and insulin resistance (Carter RJ. JAIDS 2006, Arpadi S. Arch Dis Child 2013)
    - Risk factors for CVD

Lipodystrophy is Common in HIV-infected Children on ART

- Prospective data from Thailand, prevalence of 9%, 47% and 65% respectively after 48, 96 and 144 weeks of NNRTI therapy (Aurpibul L . Antivir Ther 2007)
- Fat redistribution in children prevalence of 26% in the European Pediatric Lipodystrophy study (EPLG*, AIDS 2004)
  - Lipoatrophy 7.5% and 8.8% for lipohypertrophy
- Larger cross sectional study (n=426) from 3 European countries, (mean age 12.2, mean duration of ART 5.2 years) prevalence of fat abnormality was 57%
  - Lipoatrophy 28% and lipohypertrophy 27% (Alam N. J AIDS 2012)

*European Pediatric Lipodystrophy Group,

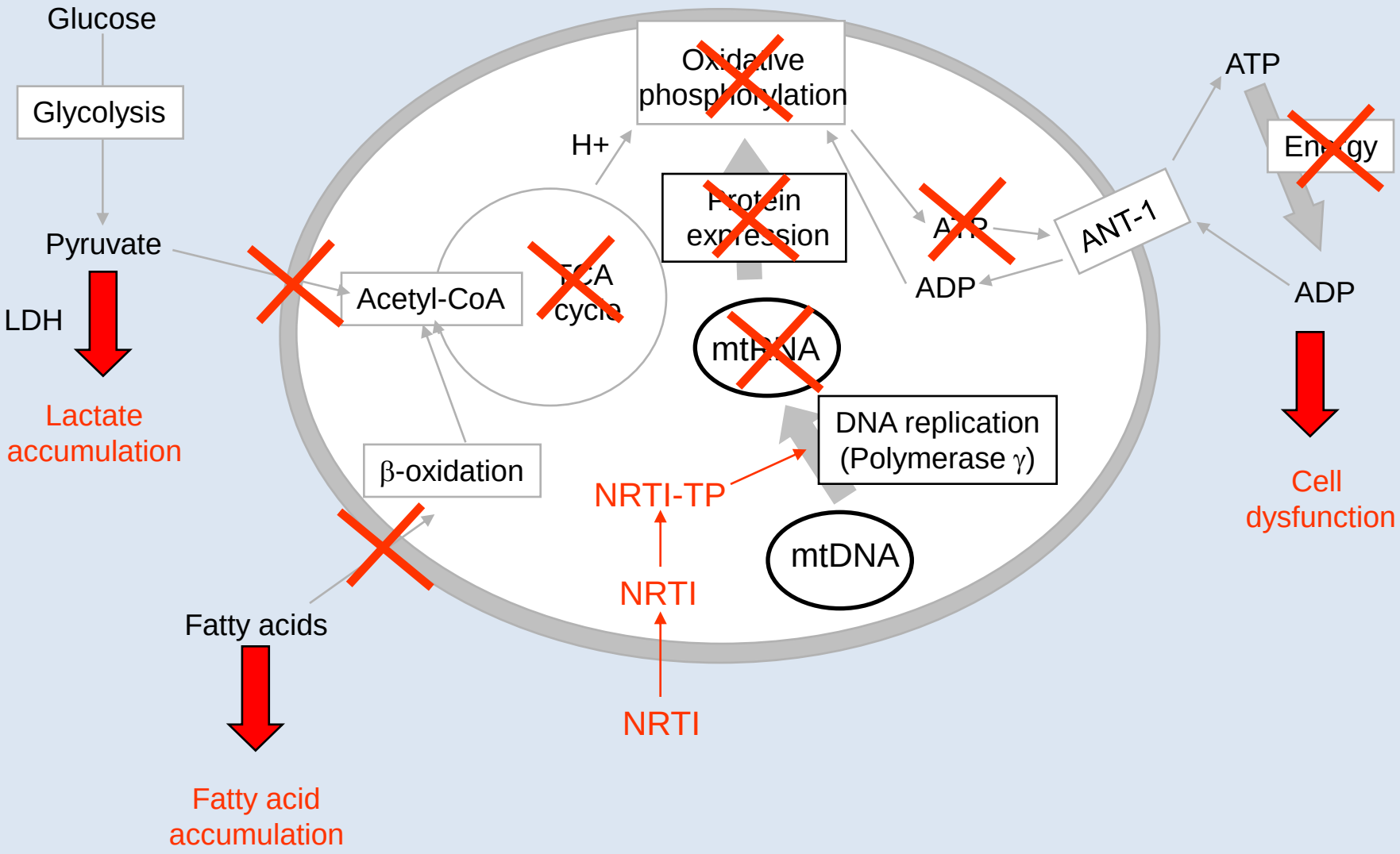
Lipodystrophy in African Children

- Among 364 Ugandan children, age 2-18 years (mean age 8 years) assessed by clinical exam (Piloya CROI 2010)
  - Lipodystrophy reported in 27%
- Prevalence of 30 % in 210 Tanzanian children age 1-18 years (Kinabo G. PIJD 2013)
  - 19% for lipoatrophy, 3.8% for lipohypertrophy, 7.1% for the mixed type)
- 100 children in the NEVEREST 2 study, mean age 5.1 (Arpadi S. Arch Dis Child 2013)
  - 8.3% with definite LD and 11.5% with possible LD
- Among 100 children age 3-12 years in SA, prevalence of visually obvious lipoatrophy was 36% (Innes S. BMC Peds 2012)
  - Half had severe form

Risk Factors for Lipodystrophy

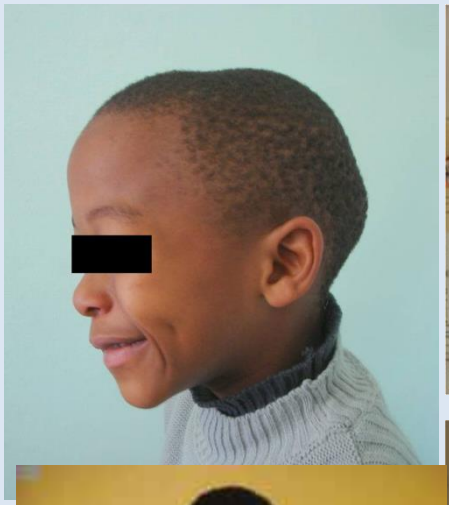
- RTIs, especially stavudine (d4T) and didanosine (ddI) appear causally implicated in lipoatrophy.
- PI often suspect in fat accumulation
- Increasing age, sexual maturation, and duration of ART exposure are associate with increase risk of lipodystrophy
- Low nadir CD4 count
- Genetic polymorphism of mitochondrial gene

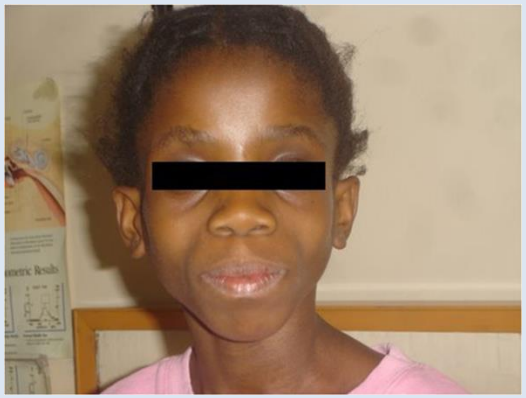
Effect of NRTIs on Mitochondria

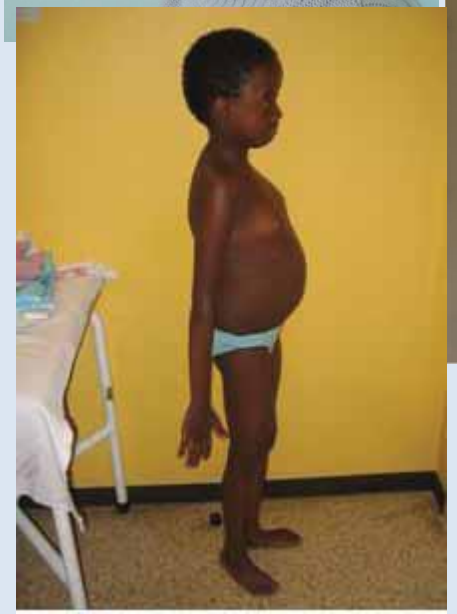


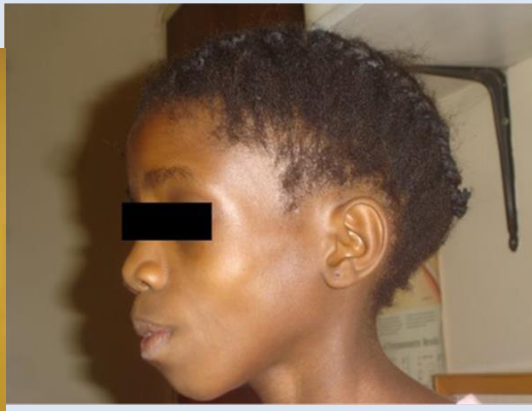
Signs of Lipoatrophy

- Sunken cheeks or prominent zygoma
- Skinny arms or legs with prominent veins, muscles and bones
- Loose buttock skin folds, prominent muscles, loss of fat contour



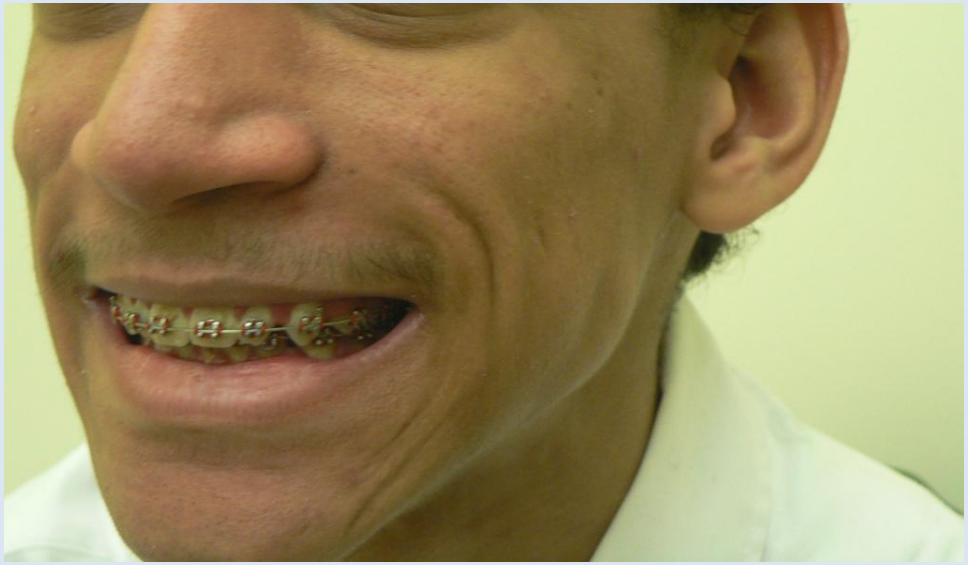


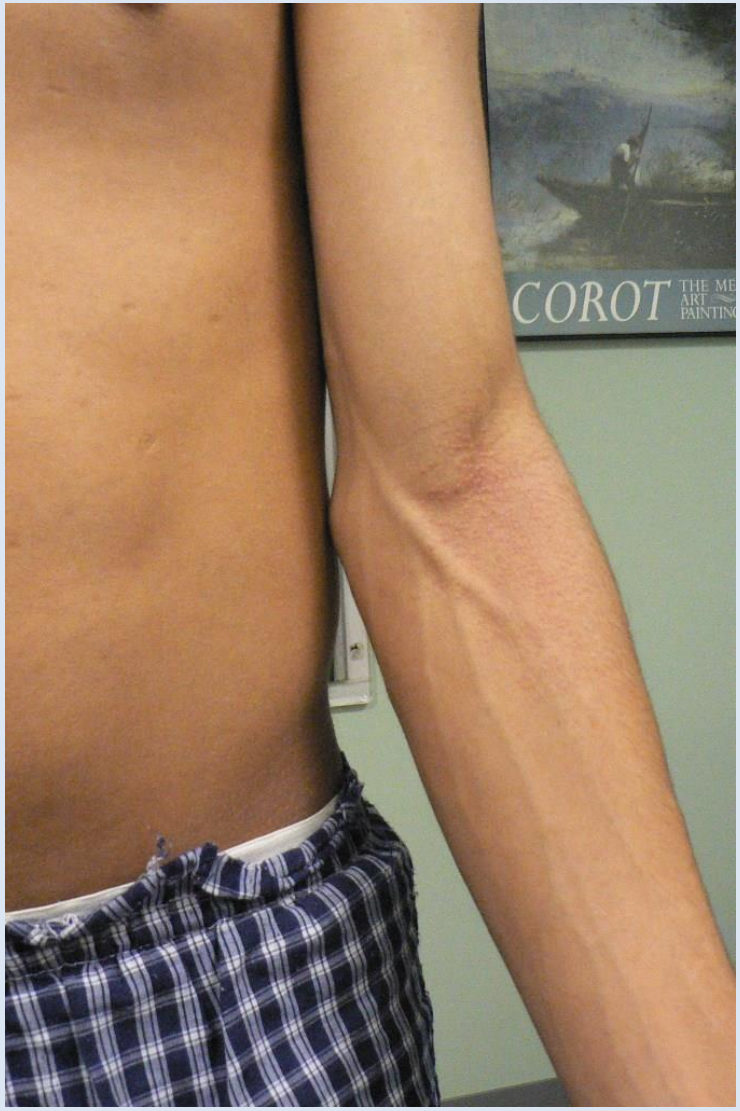




Pictures from South Afr J HIV Med. 2009 December; 10(4): 76–80.

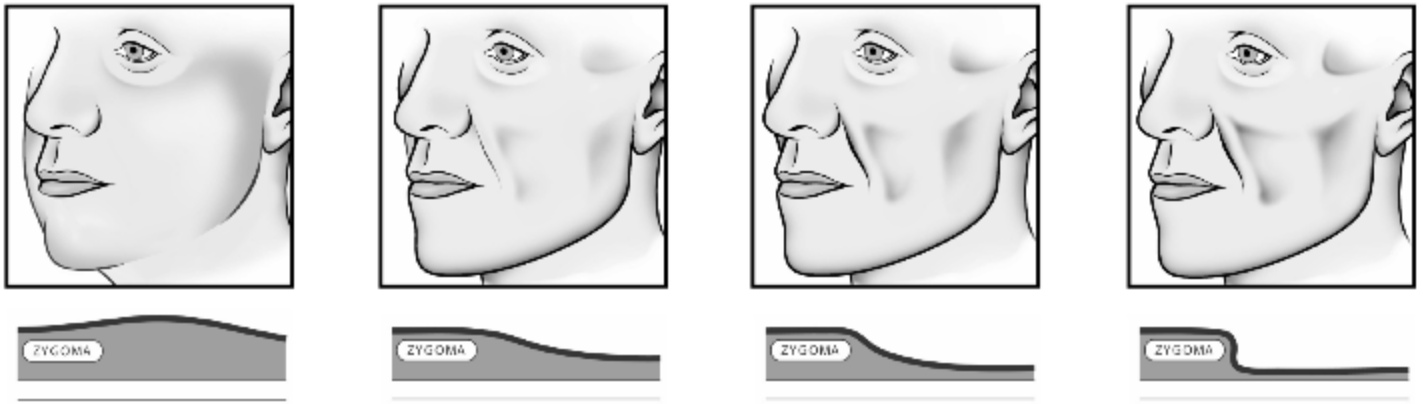
Lipoatrophy in HIV-infected adolescent





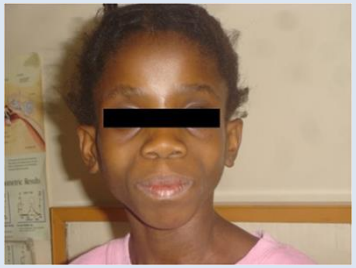
Lipoatrophy-Grades of Severity

Figure 3: Visual scale to grade HIV-related facial lipoatrophy



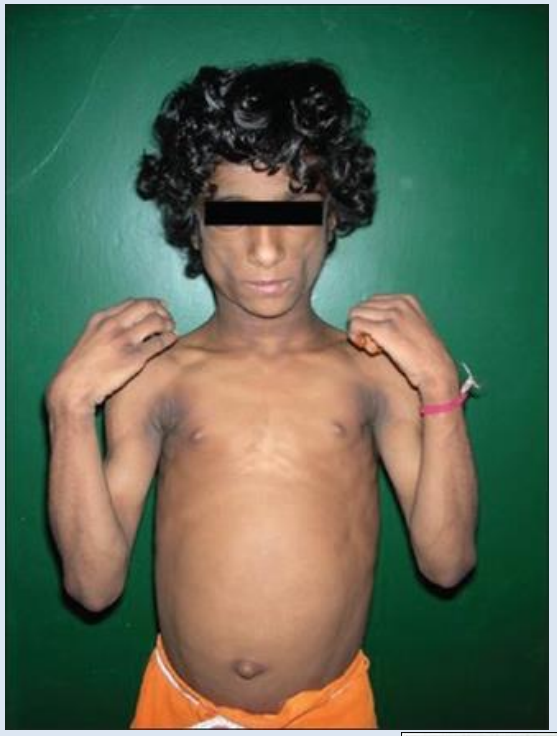
NORMAL	MILD LIPOATROPHY	MODERATE LIPOATROPHY	SEVERE LIPOATROPHY
'Chubby' cheek at or above the level of the zygoma	'Lean' cheek just below the level of the zygoma	'Sunken' cheek noticeably below the level of the zygoma	'Skeleton like' cheek severely below the level of the zygoma

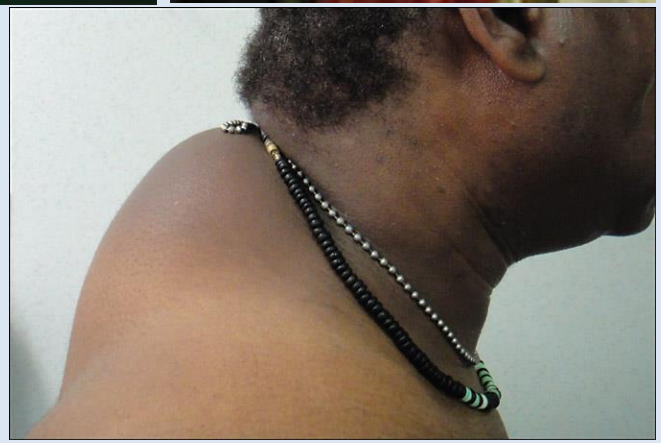
Note: Zygoma = cheekbone. Source: St Stephens AIDS Trust, Chelsea and Westminster Hospital



Lipohypertrophy

- Increased abdominal girth
- Breast hypertrophy
- Dorsocervial fat accumulation





Methods for Monitoring for Lipodystrophy

- There is no practical “gold standard”
- Parent/caregiver questionnaire
- Clinician assessment/checklist
- Anthropometry
  - Waist to hip ratio
  - Skinfold thicknesses and limb circumferences
- Other methods:
  - Bioelectrical Impedance
  - Dual energy x-ray absorptiometry
  - CT and MRI

Parent/caregiver questionnaire

1. Do you consider your child:

   Too thin wt just right Too heavy

2. Compared to last year how do you think your child ‘s appearance has changed?

	Thinner	No change	Larger
My child’s face has become ?			
The back of the neck, around the shoulders have become?			
My child’s legs have become ?			
My child’s belly has become?			
My child’s buttocks has become?			

Management of Lipodystrophy

- Avoid
  - If possible use agents with lower risk profile for fat disorders: ABC, AZT, TDF preferred over D4T
- Monitor
  - Early changes not easily distinguished from normal developmental changes.
  - Early intervention offers best chance for recovery
- **Switch**
  - To less risky medications: ABC, AZT, TDF preferred over D4T
  - Must weigh switching against risk of treatment failure

Management of Lipodystrophy

- Thai study (n=45) 76% recovery from lipoatrophy after substitution of AZT for d4T by 96 weeks (Aurpibul L, PIJD 2013)
- Partial (36%) recovery of limb fat atrophy seen in studies where ABC was substituted for D4T/ZDV (Carr A, JAMA 2002)
- Favorable changes in central fat also noted in substitution of EFV for PI in children. (Vigano A, Antivir Ther 2003)
- Surgery and GH has been used with limited success

WHO Guidelines on d4T Phase Out

- Phase out d4T among children when alternatives are available.
  - applies equally to both adults and children.
- However, considering the limited availability of age-appropriate NRTI formulations, d4T may be used in special circumstances
  - especially in settings where formulations of abacavir for children are not available

d4T Phase Out Implementation Issues

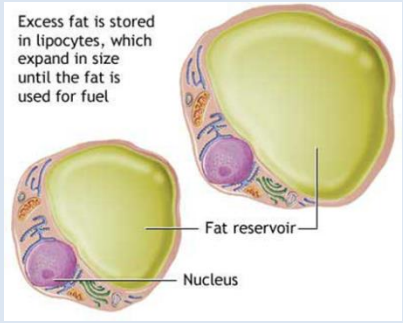
- Patients may safely switch from d4T to AZT without VL testing, preserving ABC for second line treatment
- Switch from d4T to ABC is safer when viral suppression can be assured
- For adolescents can switch to TDF
- Need careful planning to avoid drug stock out
- Clear guidance needed for HCW's
  - When/how existing patients should be switched?
  - What NRTI should they switch to?

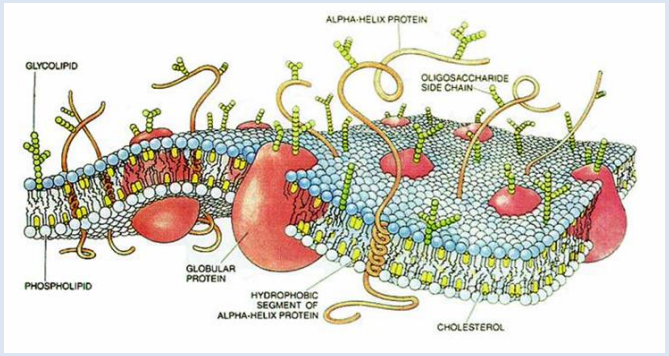
HIV infection and Lipids

- Alterations related to untreated HIV:
  - Decrease in HDL-C and LDL-C
  - Increase in TG (Grunfeld , Am J Med 1989)
  - Inflammation (Miller , HIVMed 2011)
    - MCP-1, fibrinogen, sICAM and sVCAM
    - IL-6 (cholesterol), hsCRP
- These changes are related to disease progression (e.g. RNA and CD4) and inflammation- mediated changes in metabolism.

Dyslipidemia

- Dyslipidemias are a common component of ART-associated LD.
- Function in cell structure (membranes), energy storage and signaling
- Profile is important risk factors for CVD.
  - "HDL-C =good, high TG and LDL-C =bad





Changes with Combination ART (1)

- **Triglycerides**
  - –Original PIs (esp RTV) associated with increased TG.
  - –EFV and D4T also increase TGs
- **LDL-C:** tends to go up modestly with virtually all regimens "normalize"
- **HDL-C:**Increase with NNRTIs

Arapdi S. 2013, Sax P. JAIDS 2004, Gallant JE. J Am Med Ass 2004

Changes with Combination ART: by Drug Class (2)

- **NRTIs:** d4T and AZT associated with adverse effects on lipids relative to TDF (and ABC)

- **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 NNRTIs

- **PIs:** Majority increase TG and LDL-C, but HDL-C typically increases as well

Lipid Abnormalities in HIV-infected Children on ART

- US and European studies-any abnormality: 40%
  - Hypercholesterolemia: 12-38%
    - Increased LDL-C
  - Hypertriglyceridemia :13-50%.
- South Africa
  - Elevated triglyceride: 36%
  - Elevated Cholesterol:16%
- Ugandan study- any abnormality: 34%
    - Hypercholesterolemia: 18%
    - Hypertriglyceridemia: 82%

Strehlau R. JAIDS 2012, Aldrovandi GM. AIDS 2009, Chantry CJ. Peds 2001, European Lipodystrophy Group, 2004

Changes in Insulin/Glucose

- Insulin resistance (common) and hyperglycemia (uncommon) are reported in HIV-infected children and adolescents.
  - inhibition of muscular and adipocyte GLUT4 (insulin-regulated transmembrane glucose transporter), resulting in decrease glucose intake mediated by insulin in these tissues (Tassiopolous ,JAIDS 2008
- Insulin resistance increases during adolescents
- 15% prevalence amongst cohort of ~ 400 US perinatally infected children and adolescents(Geffner ME. *Horm Rsch Ped* 2011)

Factors involved in alterations in lipids and insulin/glucose

- Direct drug effect on metabolic pathways.
- Indirect effects of viral suppression and decreases in immune activation.
- Genetic predisposition.
- Indirect effects mediated through alterations adipocyte function-associated with lipodystrophy.
- Dietary intake of saturated fats especially *trans* fats
- Exercise

Potential Health Consequences

- *Dyslipidemia* and *insulin resistance* are associated with cardiovascular disease in non-HIV conditions
- Higher CV disease (CVD) risk in adults with HIV infection
  - HIV independent risk factor, even with viral suppression (Freiberg *JAMA IM* 2013)
- **Non-HIV context**, CV risk factors in childhood predict CV events in adulthood and cardiovascular disease has clinically silent onset early in life (Berenson Bogalusa NEJM 1998; PDAY JAMA 1990; Franks NEJM 2010)
- Increases in coronary artery disease in HIV infection is increased *independent of ARV treatment*
  - Studies in adolescents reveal altered endothelial function and increased cIMT suggest on-going atherosclerosis

WHO Criteria

	Mild	Moderate	Severe	Life threatening
Cholesterol mg/dL mm/dL	170-<200 4.40-5.15	200-300 5.16-7.77	>300 >7.77	N/A
Triglycerides mg/dL mm/dL	N/A	500-751 5.65-<8.49	751-1200 8.49-13.56	>1200 >13.56
Glucose mg/dL mm/dL (Non fasting)	116-<161 6.44-<8.89	161-<251 8.89-<13.89	251-500 13.89-27.75	>500 >27.75
	Acceptable	Borderline	Elevated	
LDL-C‡	<110	110-129	>130	

‡National Cholesterol Education Program

Monitoring and Managing Lipid and Insulin-Glucose Abnormalities

- Monitor
  - What? : Non-fasting acceptable for TC and HDL; TG and LDL require confirmation by fasting.
  - Who (PI only vs all?)
  - Frequency? (Baseline, every 12 months?)
- Switch: PI to NNRTI
  - Decisions must be weighed against risk of viral relapse and toxicity
- Treat:
  - Who: What thresholds for treating? What ages?
  - What: Diet, exercise, then medications (?)

Medications for Dyslipidemia

- Fish oil (improves TG)
- Fibrates (improves entire profile)
- Statins (improves entire profile)
  - Inhibition/induction of CYP3A4 metabolism by ARVs result in altered statin levels and increased toxicity.
  - Pravastatin (Pravachol) has been evaluated and is preferred.
  - Atorvastatin (Lipitor), an alternative that may be used with caution

Cardiovascular Disease in Pediatric HIV Infection

- HIV-infected adults have increased risk of CVD compared to the general population
  - Due to abnormal lipoproteins, inflammation, endothelial dysfunction and arterial stiffness (Obel A, Clin Infect Dis 2007, Ross AC, Atherosclerosis 2010, Kaplan RC, J Infect Dis 2011)
- Increased carotid intima thickness in children (McComsey GA, AIDS 2007, Vigano A, Cur HIV res 2010)
- Impaired strain and strain rate (ECHO) (Sims J Am Soc Echo 2012)
- Long term effects still unknown
  - But additive risk with increasing obesity, tobacco, sedentary life style

Effects of HIV on Bone

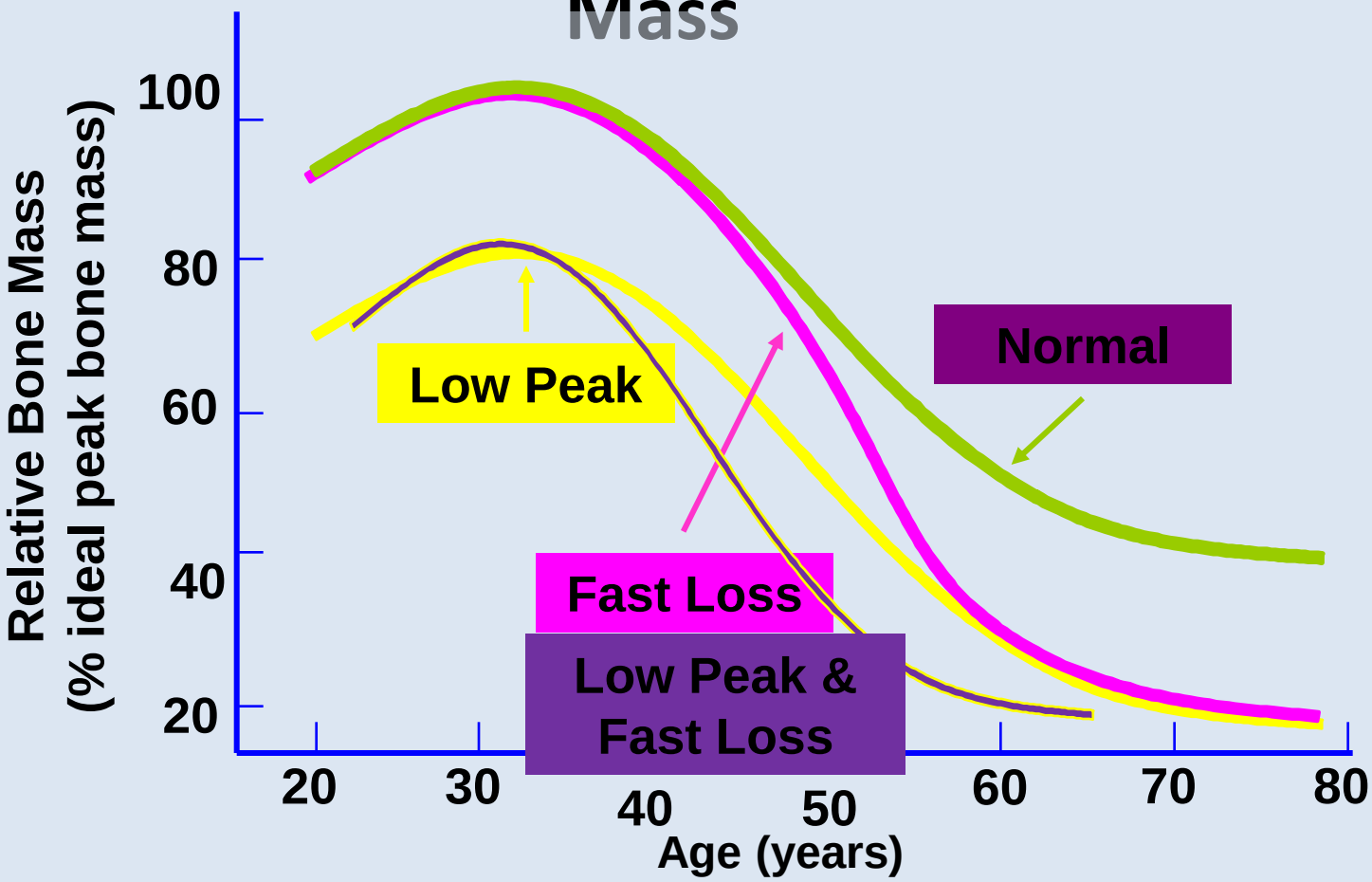
- Adults with HIV infection (Harris , JID 2012)
  - ↑ risk of low bone mineral density (BMD)
  - ↑ risk of fracture
  - Greater risk with effective ART, especially the period after ART initiation and certain drugs (TDF)
- Perinatal HIV infection
  - ↑ risk of low BMD (mean 12 yrs old) (DiMeglio , AIDS 2013)
  - Risk of sub-optimal peak BMD in adulthood?
  - No clear↑ risk of fracture…. yet (Siberry , ARHR 2012)

Bone Abnormalities in Perinatally Infected Children and Adolescents

- Multicenter cross sectional analysis perinatally infected children versus HEU
- 87% on HAART, Mean age 12.6years
- 23% had Total body BMD z-score < 1.0
- 21% had Lumbar spine BMD z-score < 1.0
- Total BMD z-score < -2 .0 was 7% compared to 2% in control
- Most children had not yet entered adolescent growth spurt
- Prepubertal factors associated with BMD, magnified or carried forward, may result in sub-optimal peak BMD in adulthood.

(DiMeglio, *AIDS* 2013)

Osteoporosis: The Importance of Peak Bone Mass



Bone Outcomes after Perinatal HIV Infection

- Long duration of exposure to HIV infection & treatment
- Unique developmental periods: Fetal, Infancy and Puberty
- Low BMD in adolescents-> suboptimal Peak Bone Mass) DiMeglio *AIDS* 2013

Vitamin D Deficiency

- Prevalence is very high in the HIV-infected population, including in HIV-infected adolescents (Eckard AR. PIDJ 2013 ,Rutstein R. Clin Nut 2011, Stephensen CB. Am J Clin Nut 2006)
- Risk factors include longer duration of HIV disease and cumulative use of ART, NNRTIs, and NRTIs.
- Efavirenz and some PIs have been associated with vitamin D deficiency but their role in vivo is still unclear (Brown TT. Antir Ther 2010, Cozzolino M. AIDS 2003)
- More trials are needed to define the role that vitamin D plays on immune reconstitution and metabolic and cardiovascular co-morbidities

Conclusion

- The benefits of long-term ART are recognized all over the world with infected children maturing into adults and HIV infection becoming a chronic illness.
- Improved survival is associated with serious metabolic complications, including lipodystrophy (LD), dyslipidemia, insulin resistance, and bone loss which programs need to monitor and address

THANK YOU