HIV Associated Metabolic Complications

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Myanmar Medical Association

64th Myanmar Medical Conference

Beyond ART

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MMA
YGN

HIV Associated Metabolic Complications

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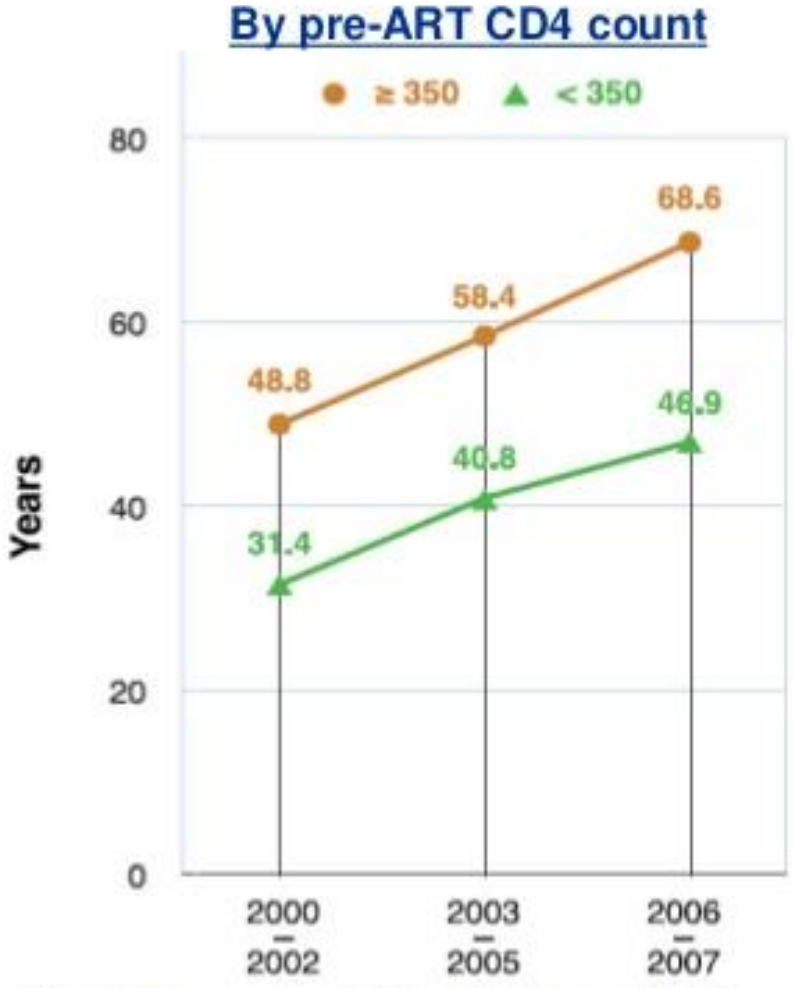
COMPLICATION

- The main complication of HIV is **weakened immune system:**
  - Disease of the respiratory system
  - Disease of the cardiovascular system
  - Disease of the oropharynx and gastrointestinal system
  - Hepatobiliary disease
  - Disease of the kidney and genitourinary tract
  - Disease of the endocrine system and metabolic disorders
  - Immunologic and rheumatologic disease
  - Immune reconstitution inflammatory syndrome
  - Disease of the hematopoietic system
  - Dermatologic disease
  - Neurologic disease
  - Ophthalmologic disease
  - Disseminated infections and wasting syndrome
  - Neoplastic disease

Life Expectancy* May Start to Approach General Population with Early ART



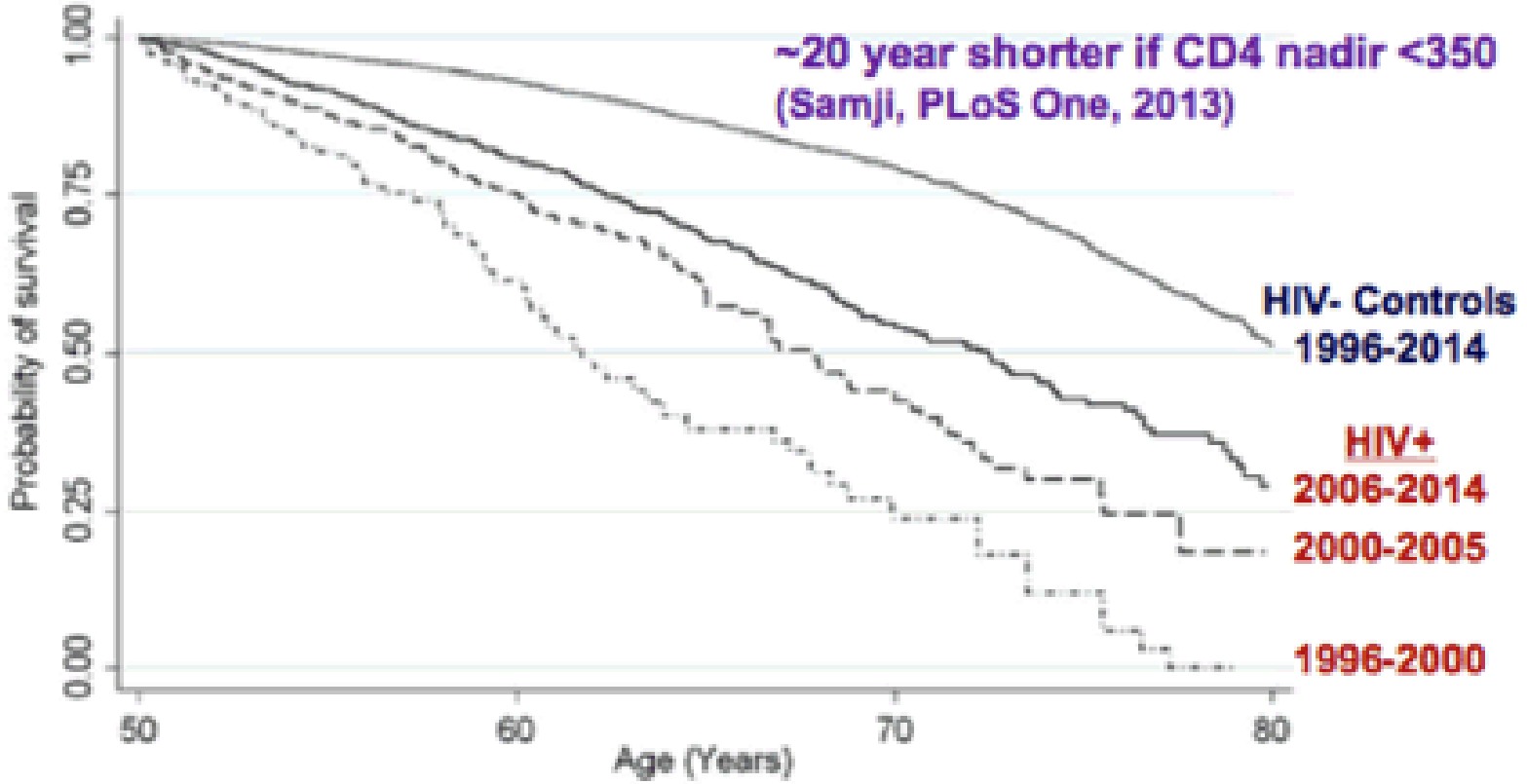
*For 20-year old initiating ART

- Life expectancy of patients on or starting ART in North America
- ~23,000 person-years FU
- 1,622 deaths
- May overestimate life expectancy
  - Excludes those out of care
  - "Survivorship bias" for older patients who survived 80s and 90s.
- Majority of HIV+ around the world still starting ART <350.

Samji for NA-ACCORD, PLoS One, 2013

10y Decreased Life Expectancy in Older HIV+ Adults in Modern ART Era

Danish Cohort



Legarth/Obel, JAIDS, 2016

- Non- AIDS diseases Now Account for Majority of Deaths in HIV (1996-2006)

1,876 deaths among 39,727 patients

Non-AIDS related deaths accounted for 50.5%

CVD 15.7%

Liver 14.1%

Renal 3.0%

Non-AIDS infection 16.3%

Non-AIDS malignancy 23.5%

Clin Infect Ds 2010.50:1387-1396

Many age-associated morbidities also increased in treated HIV

- CVD
- Cancer
- Bone Fractures/osteoporosis
- Liver disease Kidney Disease
- Cognitive decline
- Frailty

Freiberg et al, 2011

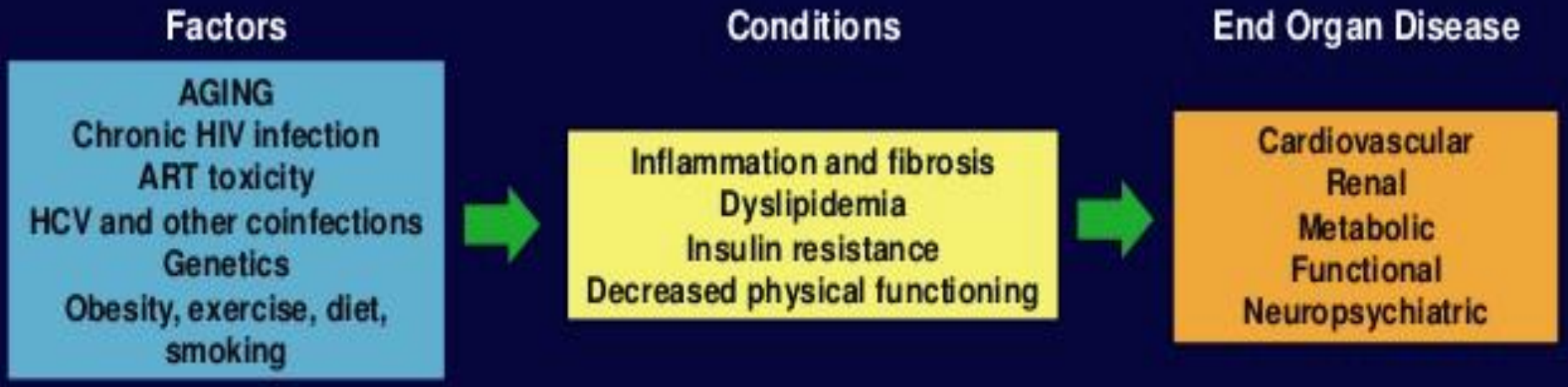
In Myanmar

Estimated 220,000 PLHIV

130,000 receiving ART

Annual Death rate - 17,000 in 2009 to 7800 in 2016

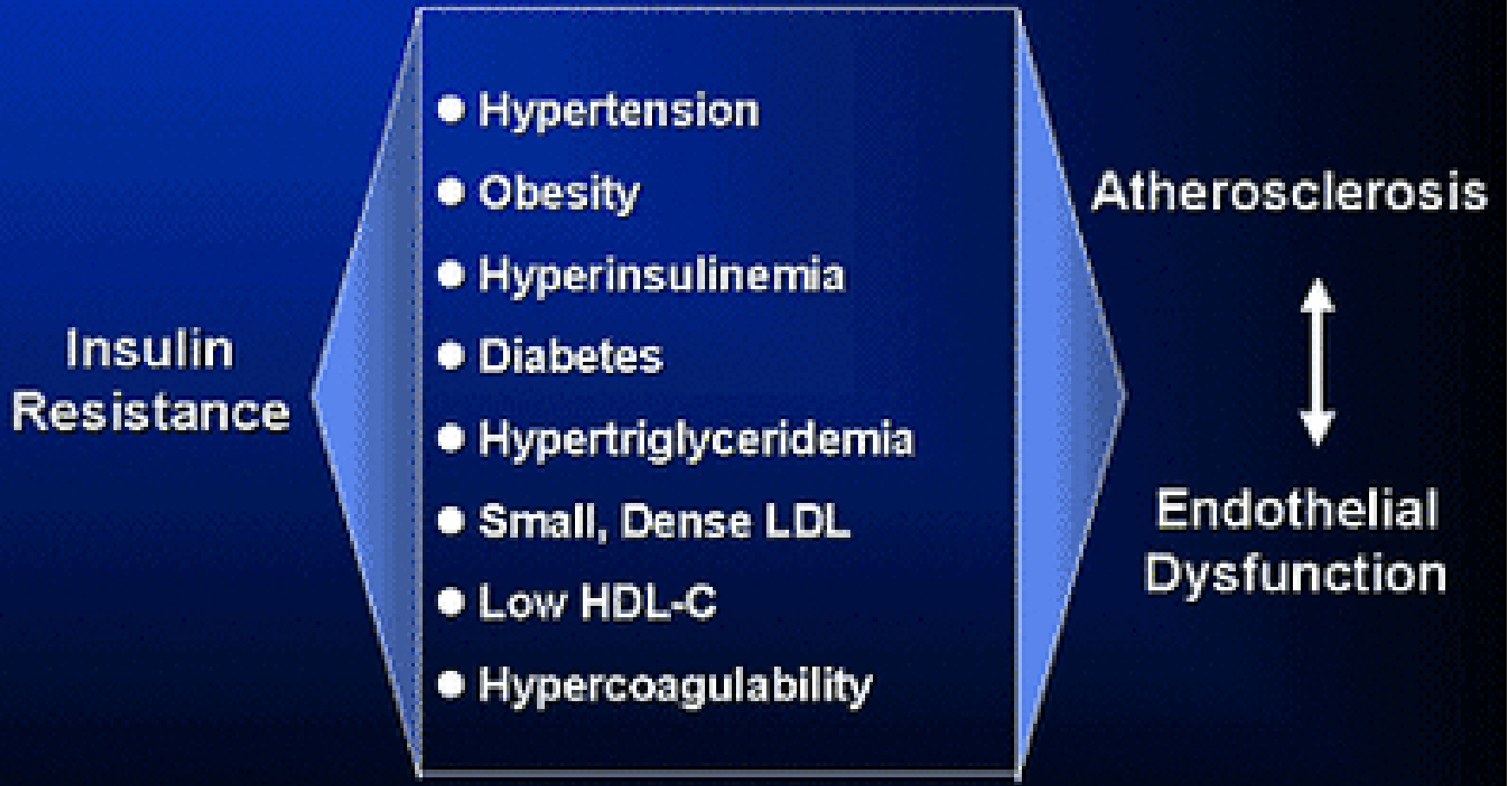
Factors Related to Non-AIDS Comorbidities in HIV-Infected Pts



Warriner AH, et al. Infect Dis Clin North Am. 2014;28:457-476.

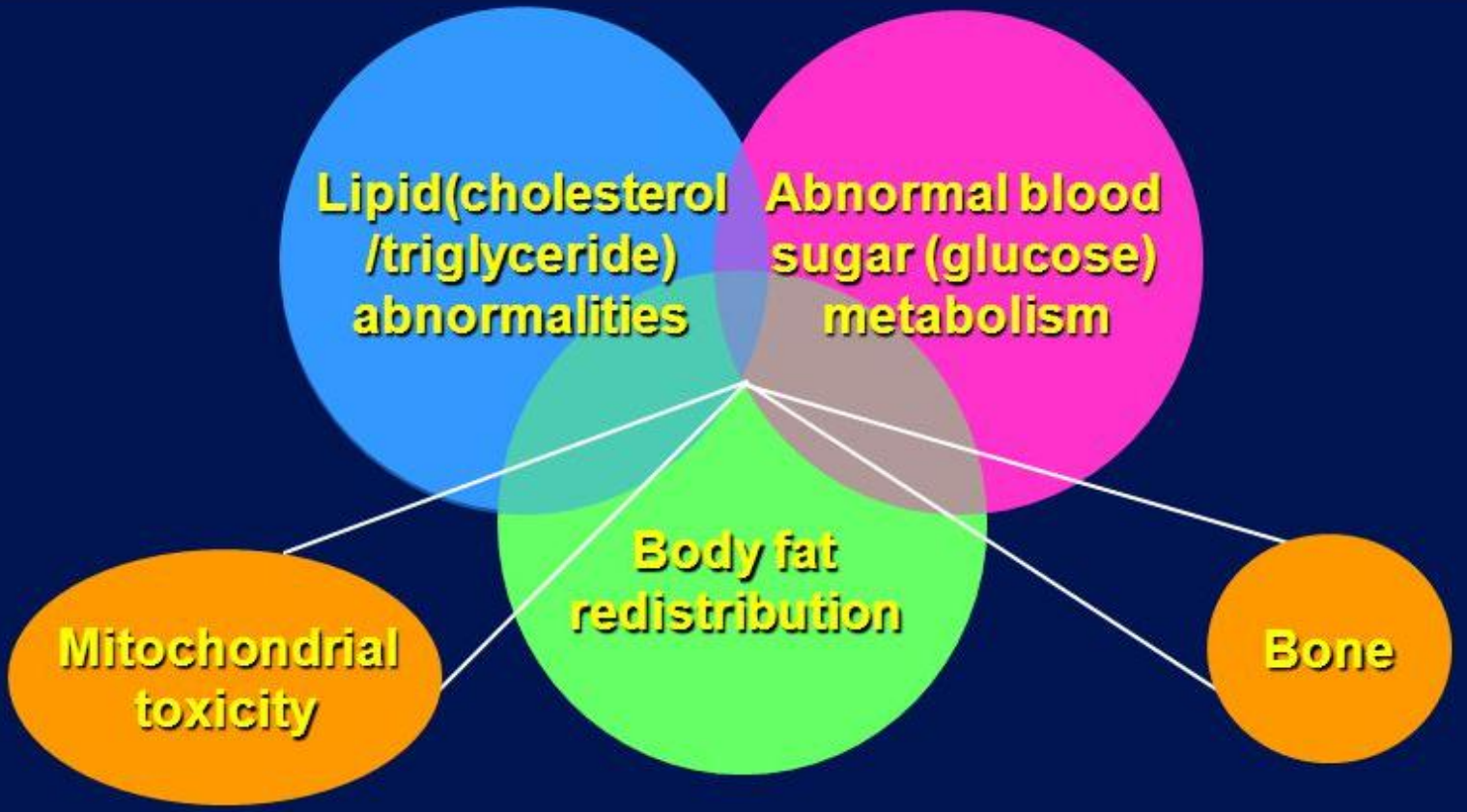
Slide credit: clinicaloptions.com

Metabolic Syndrome Associated With CV Risk Factor Cluster



Deedwania PC. *Am J Med* 1998;105(1A):1S-3S

HIV-Related Metabolic Complications



- One syndrome or several?
- One etiology or multifactorial?

HIV and metabolic complications: CVD

- Increased risk secondary to[1]:
  - direct effects from HIV
  - traditional risk factors
  - effects and toxicities from ARVs
    - older ARVs and early PIs[2]
      - mitochondrial toxicity and associated metabolic effects[3]
        - » insulin resistance, lipoatrophy, lipohypertrophy, dyslipidemia

1. Kaplan-Lewis E. et al. Aging with HIV in the ART era. Semin in Diag Path, 2017, 6 April 2017. http://dx.doi.org/10.1053/j.semdp.2017.04.002.
2. P. Domingo *et al.* Effects of switching from stavudine to raltegravir on subcutaneous adipose tissue in HIV-infected patients with HIV/HAART-associated lipodystrophy syndrome (HALS). A clinical and molecular study. PLoS One, 9 (2) (2014), p. e89088.
3. E. Hammond et al. Human immunodeficiency virus treatment-induced adipose tissue pathology and lipoatrophy: prevalence and metabolic consequences Clin Infect Dis Publ Infect Dis Soc Am, 51 (5) (2010), pp. 591–599.

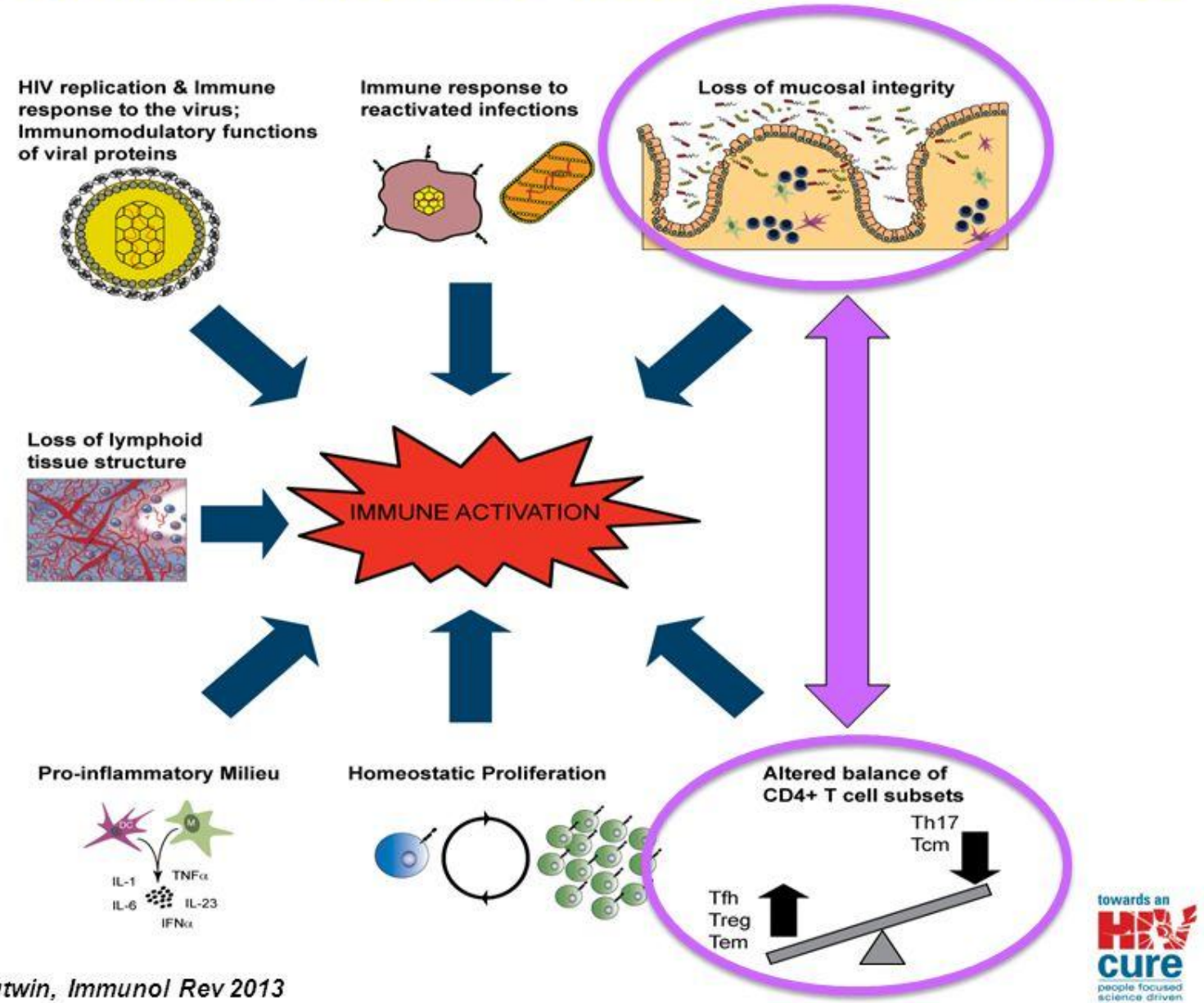
Metabolic Complications of HIV Infection and Its Therapy

- HIV/HAART-associated lipodystrophy syndrome
- Insulin resistance and glucose homeostasis abnormalities
- Dyslipidemia
- Metabolic syndrome

Pathogenesis of Metabolic Complications in HIV-infected Patients

- HIV infection increase inflammatory cytokines
  - TNFα inhibits the uptake of FFA by adipocyte, increase lipogenesis
  - IL-6 and adipocytokines cause dyslipidemia and lipodystrophy
  - May directly induce insulin resistance
- Protease inhibitor
  - Effect several steps causing dyslipidemia, IR, and lipodystrophy
- NRTI
  - Cause mitochondrial dysfunction$\rightarrow$lactic acidosis $\rightarrow$adipocyte death

Contributors to chronic immune activation



Paiardini & Muller-Trutwin, Immunol Rev 2013

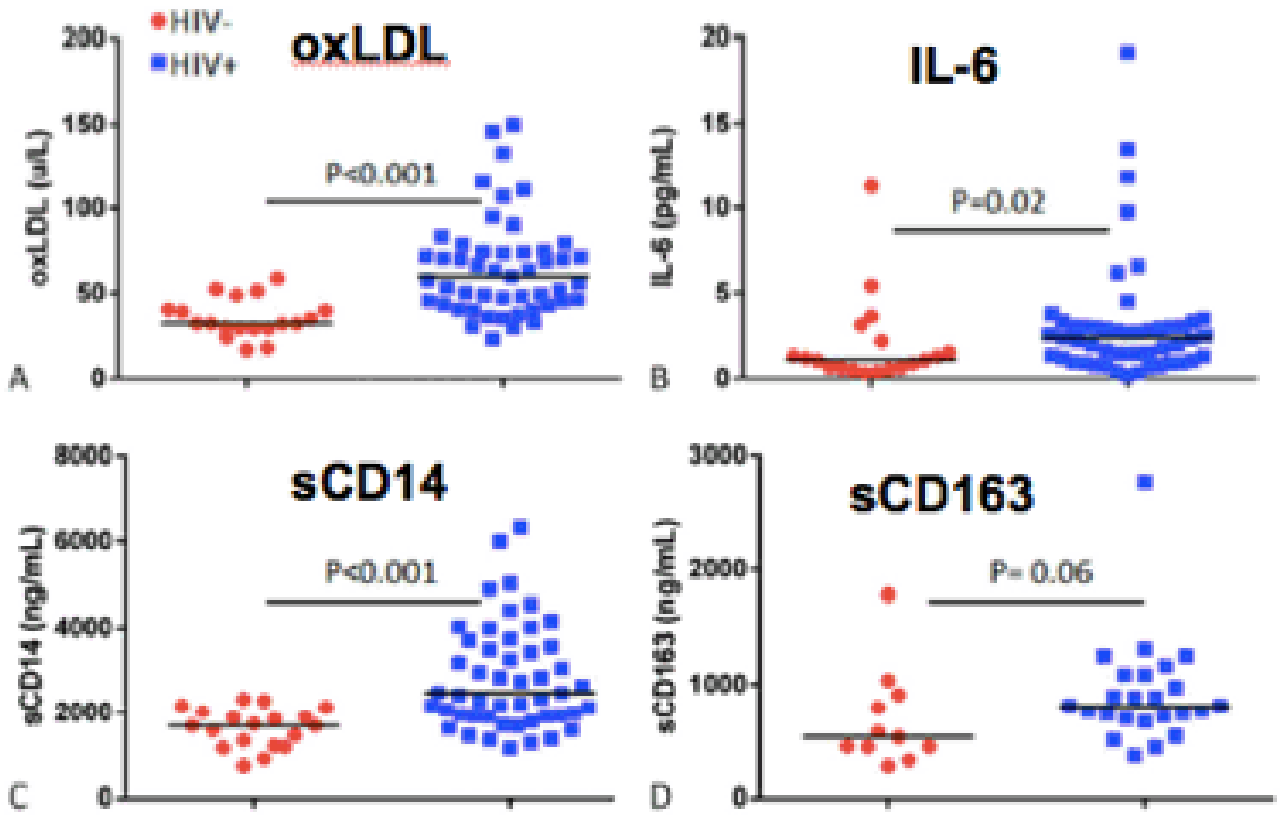
towards an HIV cure
people focused science driven

Oxidative stress is linked with immune activation and inflammation

Oxidative stress is important in the pathogenesis of metabolic complications in HIV

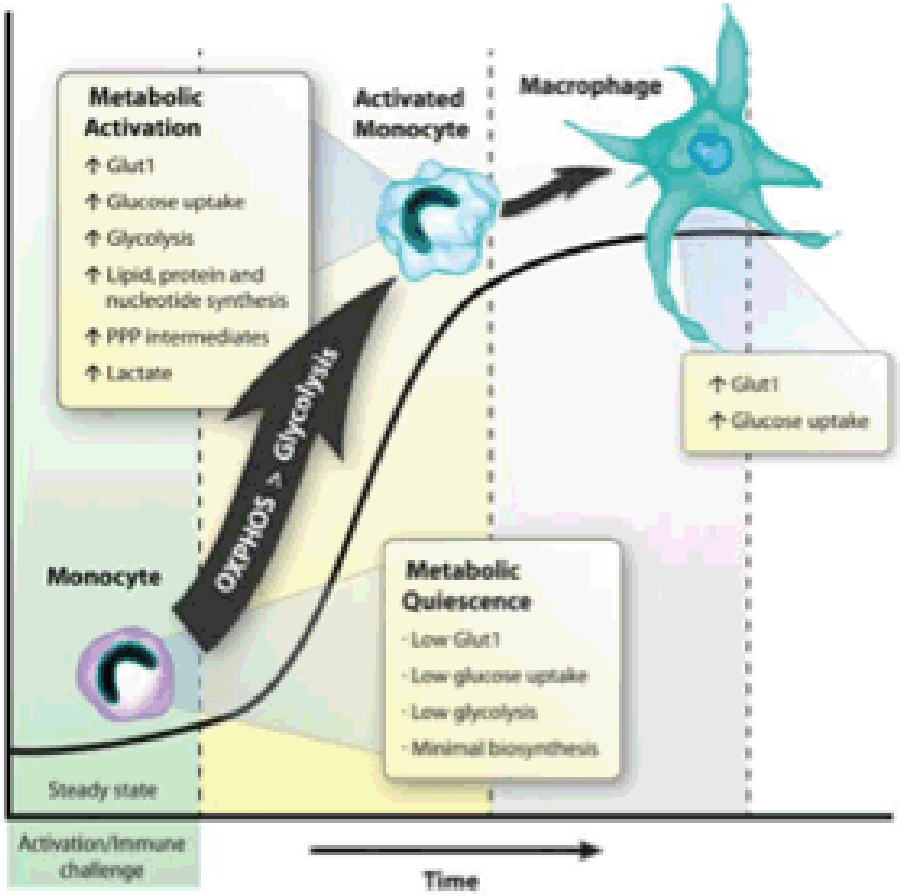
- **Oxidative stress**
  - Important component of metabolic dysregulation
  - Imbalance between oxidants (ROS) and antioxidants
- **Reactive oxygen species (ROS):** eg peroxides, OH radical
  - ROS levels cause tissue damage
- **Oxidative Stress contributes to inflammatory and metabolic complications of HIV**
  - Cardio-metabolic disease, NASH, visceral adiposity, osteoporosis
  - OxLDL: marker of oxidative stress of lipoproteins
  - Mitochondrial dysfunction: oxidative stress damages mitoDNA

Increased plasma oxLDL in HIV+ with VL<20 correlates with innate immune activation



Zidar DA (Funderburg) et al JAIDS 2015 69:154

Glucose metabolism in monocytes is needed for energy



Glucose is needed for energy

Glut1 is major glucose transporter

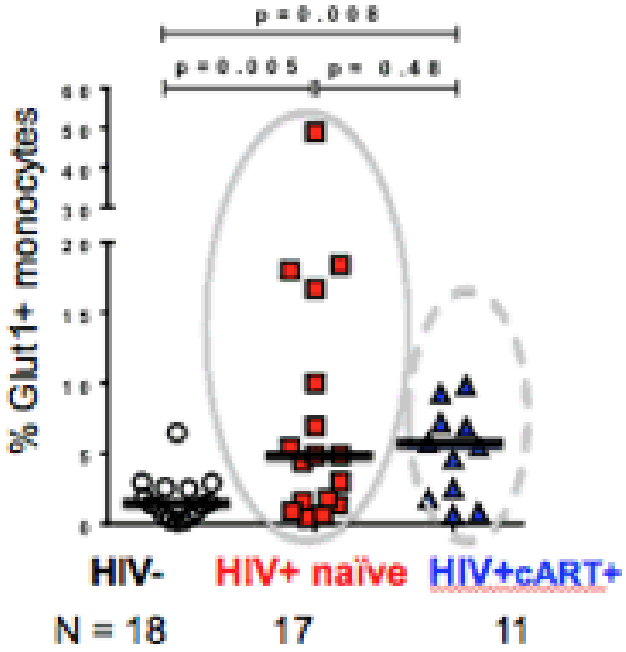
Activated monocytes dramatically increase Glut1 expression & glucose uptake

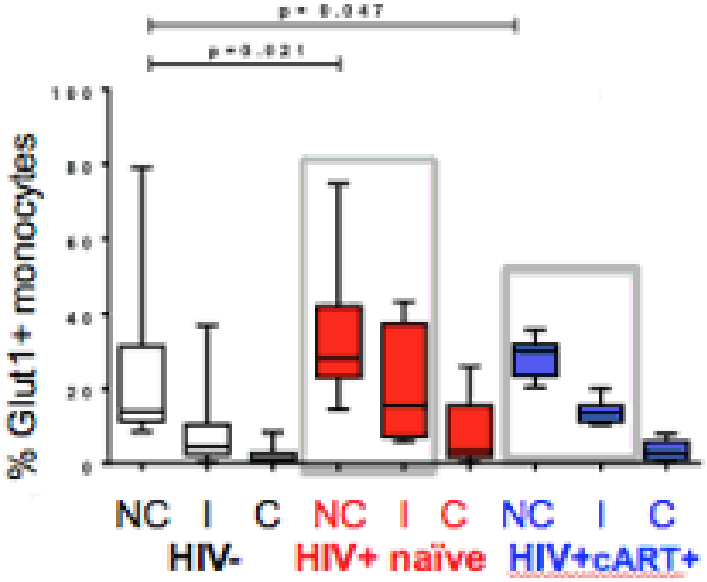
Switch from oxidative phosphorylation to glycolytic metabolism

Palmer CS, Crowe SM et al EBioMedicine (2016 in press)

HIV increases glucose metabolic activity in CD16+ monocytes and is correlated with D-dimer levels

- Increase in proportion of Glut1+ monocytes in HIV+
  - Not restored by ART





- Glut1 expression is ↑ on CD16+ intermediate (I) & non-classical (NC) monocytes in HIV+
  - Not restored by ART
  - Correlates with D-dimer levels

Palmer C et al J Immunol 2014 (Dec 1) 193:5595

LIPODYSTROPHY AND INSULIN RESISTANCE IN HIV-INFECTED PATIENTS TREATED WITH ANTI-RETROVIRAL THERAPY

Dr Kyaw Swar Lin

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1. The prevalence of metabolic syndrome was 27.7% and the prevalence was not different between the two groups

2. Metabolic derangements were significantly worse in patients with lipodystrophy than those not having it (FI, IR, TG and HDL). But after exclusion of MS, this difference disappeared, except TG.

Risks for CVD in HIV

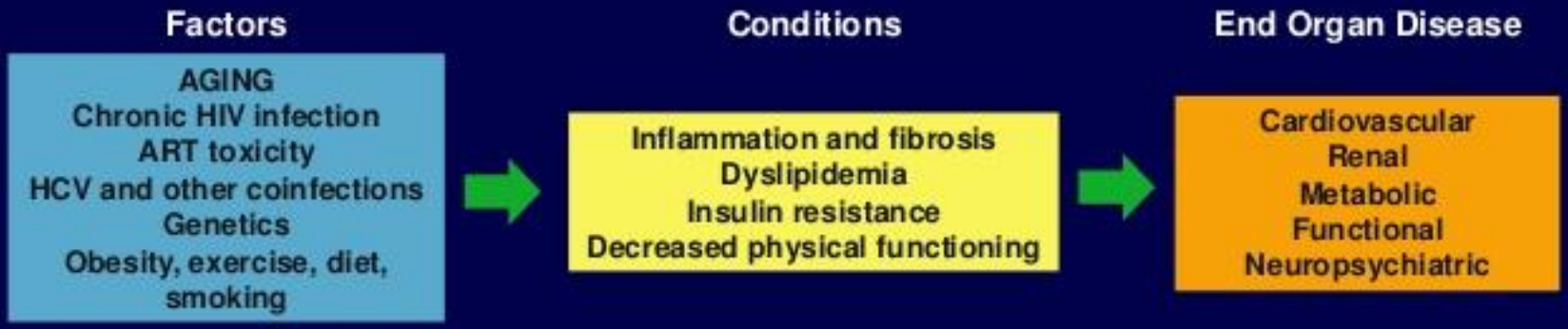
- Host
  - Genetics
  - Modifiable risk factors (smoking, diet, exercise)
  - Age
- HIV
  - Increased CRP (?)
  - Low HDL and high TG in untreated HIV
- Treatment
  - Selected PIs lead to atherogenic lipid profiles
  - Select ARVs lead to insulin resistance
  - Increased risk with overall PI therapy (?)
  - Treatment associated body shape abnormalities

- Seen in situations of insulin resistance
- Besides in DM, also seen in the following:
  - Carcinomas, especially of the stomach
  - Secondary to drugs (nicotinic acid, estrogen, or corticosteroids)
  - Pineal tumors
  - Other endocrine syndromes (PCOS, acromegaly, Cushing's disease, hypothyroidism)
  - Obesity
- Pathogenesis
  - it may be related to insulin binding insulin-like growth factor receptors on keratinocytes and dermal fibroblasts

Facial and peripheral lipoatrophy + in > 6 months d4T Rx , 38%, (International J of AIDS STD 2012)

23% improve after mean 45 months , if before adolescense

Factors Related to Non-AIDS Comorbidities in HIV-Infected Pts



Warriner AH, et al. Infect Dis Clin North Am. 2014;28:457-476.

Slide credit: clinicaloptions.com

Why is early ART important?

One of the most effective ways to contain the HIV reservoir, preserve immunity and reduce immune activation

May optimize responses to immune-based interventions aimed at achieving HIV remission

Is essential to prevent sexual transmission of HIV during acute infection

May be a critical step in clinical research towards HIV cure

Prevention of Metabolic Complications in HIV-Infected Children & Adolescents

- Healthy life style
  - weight control
  - regular exercise
  - low saturated fat diet, eat fish and veggies
  - No smoking
- Avoid PI *(25% of Asian children are receiving PI)*
  - Serious with adherence to first line NNRTI regimens, NVP has the least long-term problem
- Screening and early intervention in borderline dyslipidemia

THANK YOU for YOUR

KIND ATTENTION