Antiretroviral Toxicities and their Management

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Outline

- Toxicities of recommended and alternative antiretrovirals (ARVs)
- Management of some key acute and chronic toxicities
- General principles of antiretroviral toxicity management

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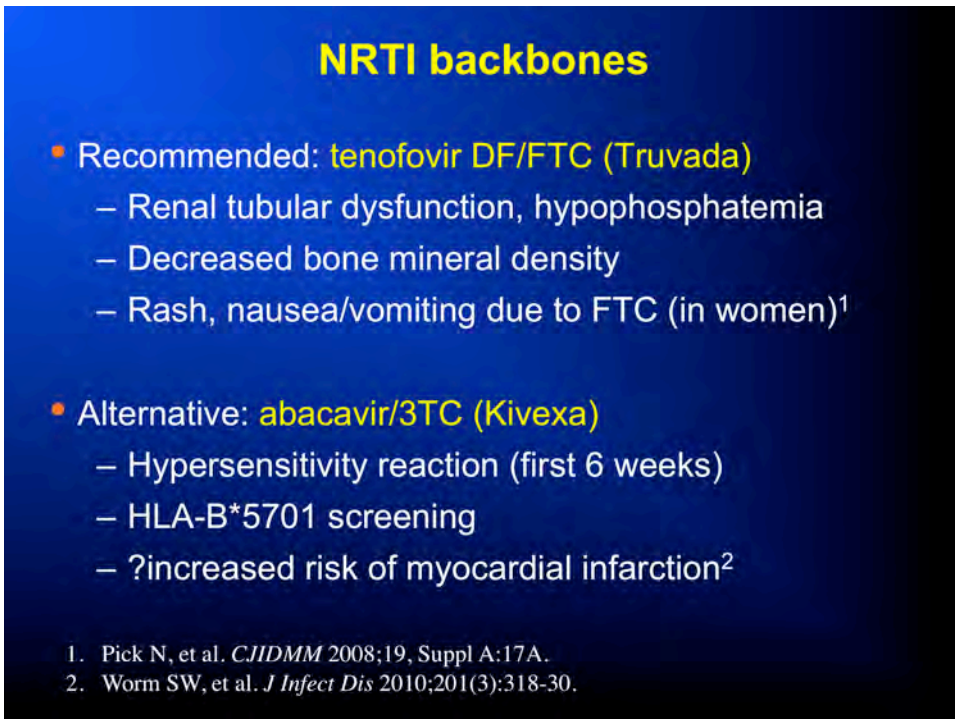


• The fixed-dose combinations Truvada and Kivexa are the recommended NRTI backbones agents in first-line antiretroviral (ARV) therapy.

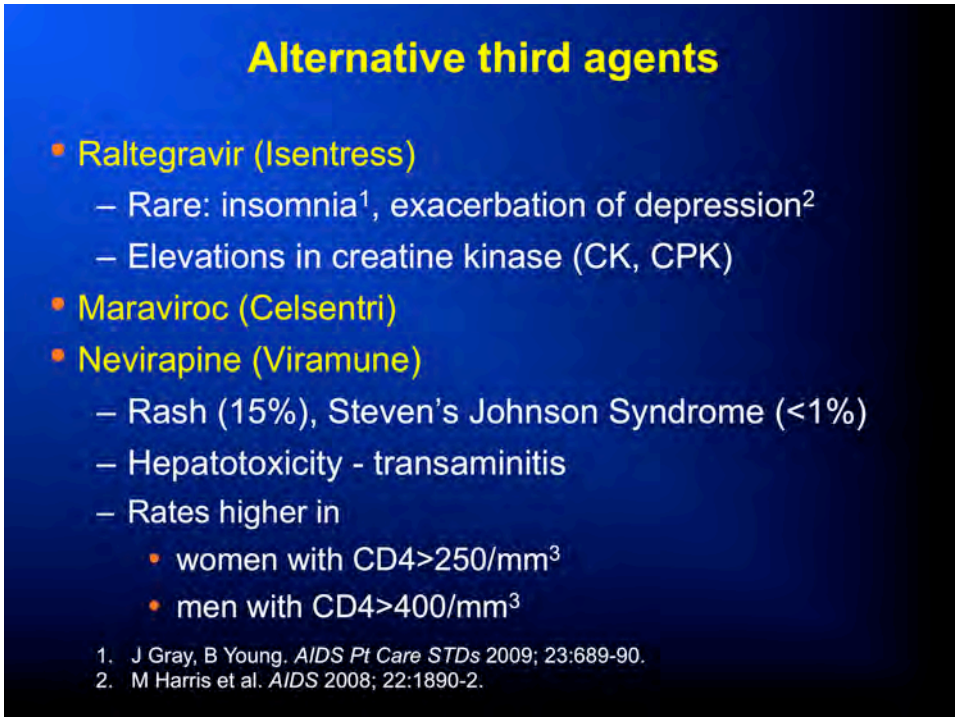
•Up to 30% of women may develop rash and/or GI upset due to the FTC component in Truvada.

• The abacavir component in Kivexa is associated with a hypersensitivity reaction in people who are positive for the HLA-B*5701 allele. Therefore, screening for HLA-B*5701 is required prior to initiating abacavir.

• There is currently some controversy related to increased MI risk in patients on abacavir. In those HIV + patients who are known to be at high risk of cardiovascular disease , it is generally recommended to avoid this drug.

• Due to the potential for fetal neural tube defects, it is important not to prescribe efavirenz (either as Sustiva or as the fixed-dose combination Atripla) in women who are trying to become pregnant or who are already pregnant, particularly in the first trimester.

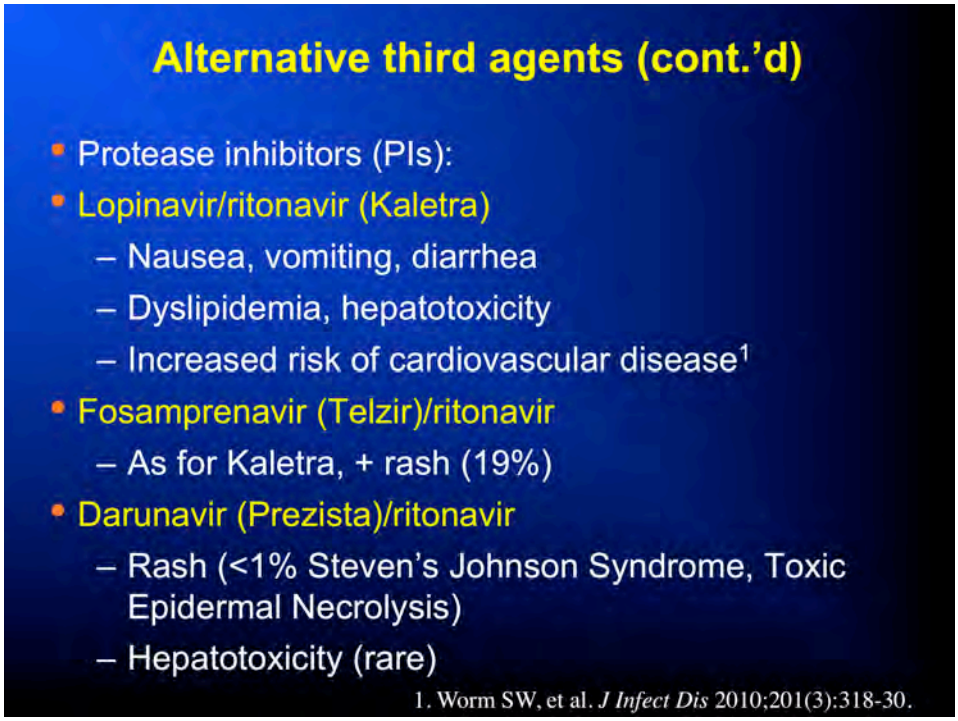
• Atazanavir is associated with benign hyperbilirubinemia which can manifest as jaundice and/or scleral icterus; however, it is usually not associated with elevated liver enzymes.



• Raltegravir is generally well-tolerated; clinically significant side effects and toxicities are rare.

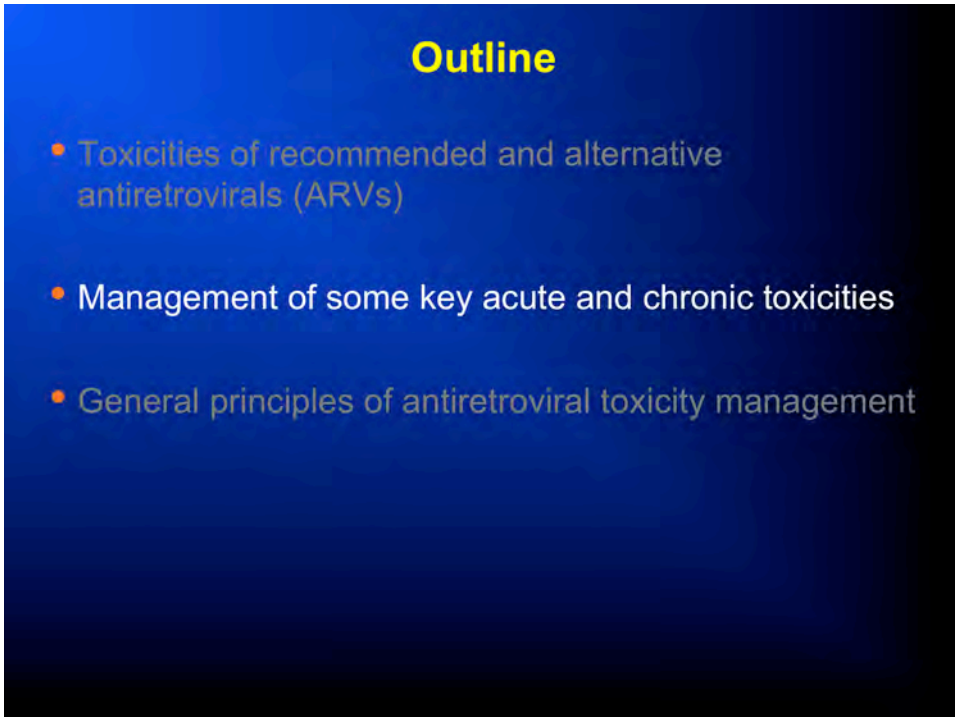
•Tropism testing is required to determine which patients may respond to maraviroc. It is also well-tolerated with a low incidence of significant side effects and toxicities.

• Nevirapine should not be initiated in treatment naïve patients with CD4 cell counts above the indicated thresholds, due to a higher incidence of rash and/or hepatotoxicity, which may be severe.



• Some large cohort studies indicate an increased risk of cardiovascular disease, which increases cumulatively over time, with exposure to lopinavir/ritonavir or fosamprenavir/ritonavir.

• In clinical use darunavir/ritonavir is associated with a low incidence of significant toxicity. To date, cohort studies have not included sufficient patients taking this agent to permit analysis of its association with cardiovascular disease.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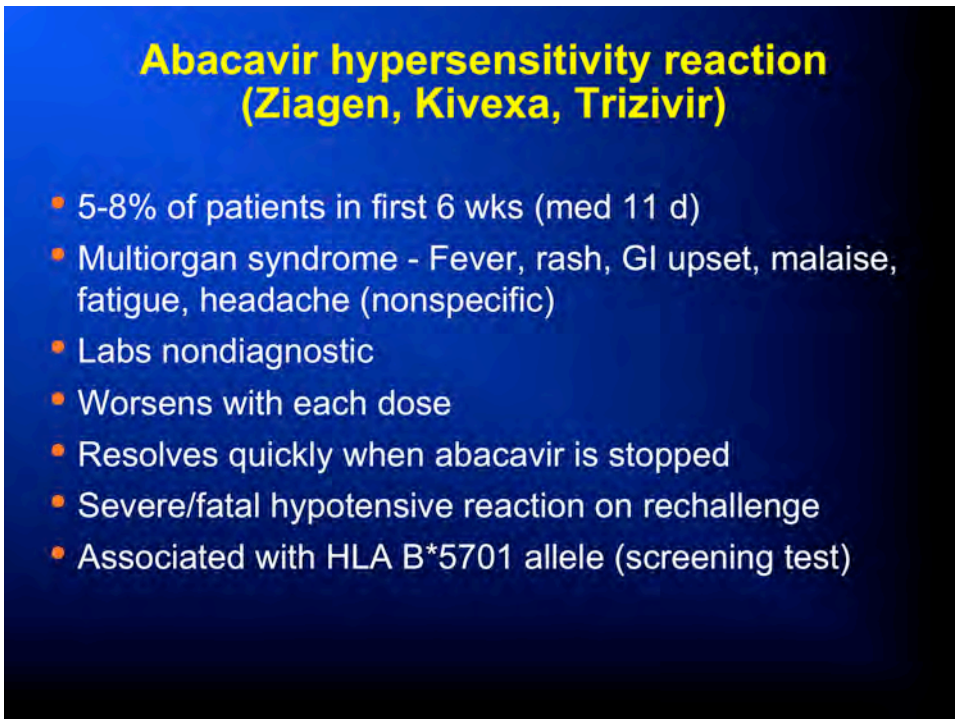
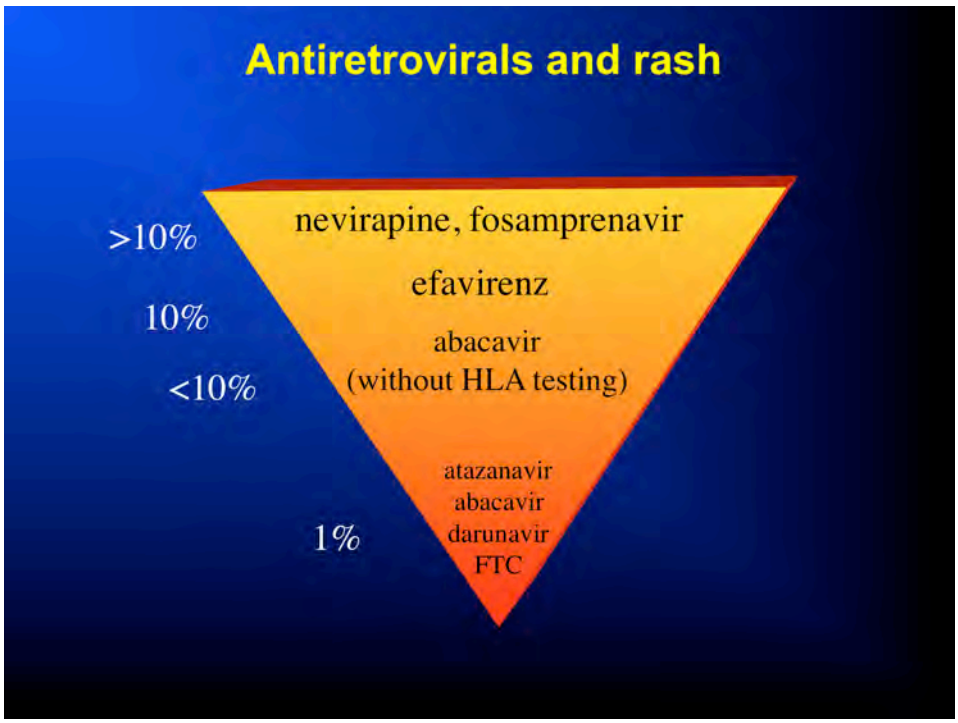


• Abacavir hypersensitivity reaction presents with non-specific, flu-like symptoms – making it difficult to diagnose.

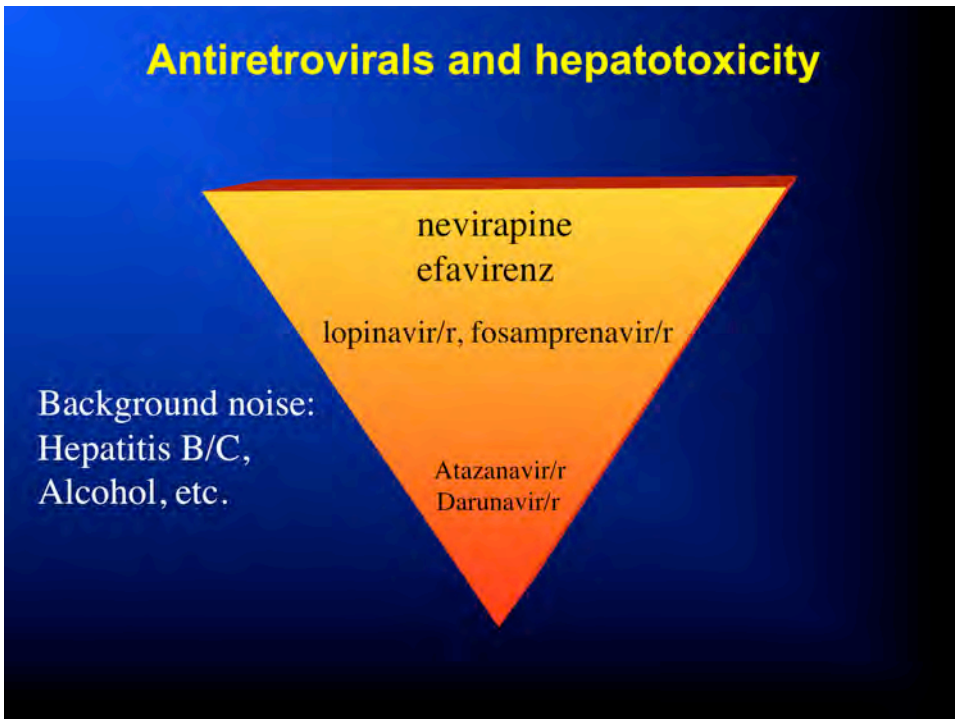
•There is no specific diagnostic test.

• HLA-B*5701 screening is required for all patients before they start abacavir.

•Abacavir should not be used in patients who test positive for the HLA-B*5701 allele.



• Nevirapine and fosamprenavir are the ARVs most commonly associated with rash.



• The NNRTIs (nevirapine and efavirenz) are the ARVs most likely to cause hepatotoxicity.

•Risk of ARV hepatotoxicity is increased in the setting of comorbid conditions such as hepatitis B/C and substance abuse.

Presentation of tenofovir nephrotoxicity

- Renal tubular dysfunction
- Fanconi syndrome - Hypophosphatemia, acidosis, glycosuria, aminoaciduria, hypokalemia
- Chronic
  - phosphate wasting, hypophosphatemia
  - increase in creatinine, decrease in GFR
- Refer to nephrology if[1]
  - progressive decline in eGFR
  - Creatinine 1.5x baseline

1. Canadian Society of Nephrology, www.csnscn.ca

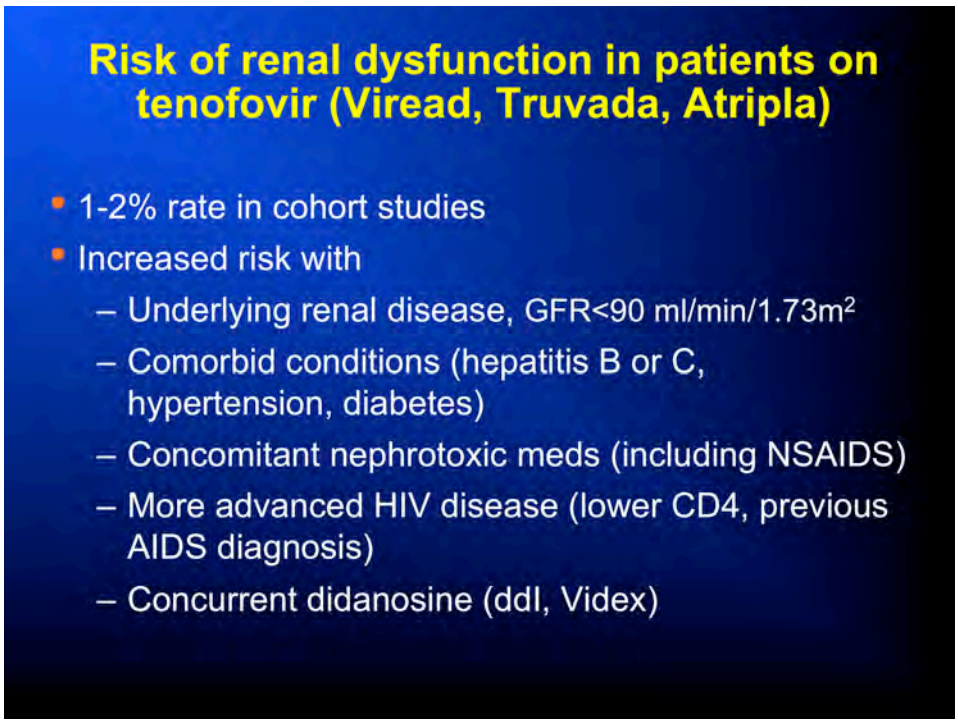
• Classic Fanconi syndrome is a rare consequence of tenofovir therapy.

•Chronic renal dysfunction may occur in patients receiving tenofovir over the long term, particularly in those with other risk factors for renal disease.

•Due to the multifactorial etiology of renal disease in HIV patients, referral to a nephrologist is often required.

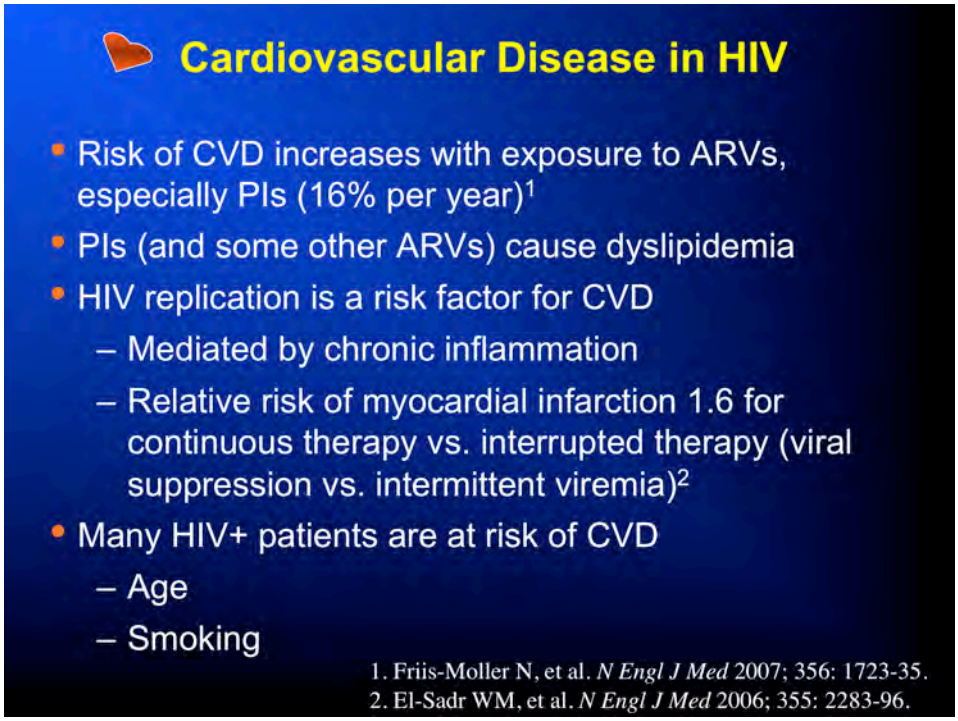
•Do not assume that renal disease is caused by tenofovir until the etiology has been investigated (may require renal biopsy).

•On the other hand, tenofovir is a known nephrotoxin, so should be discontinued and replaced by another agent in the setting of progressive renal disease, if other effective options are available.



• Risk of renal dysfunction in patients on tenofovir is low at approximately 1-2% in large cohort studies.

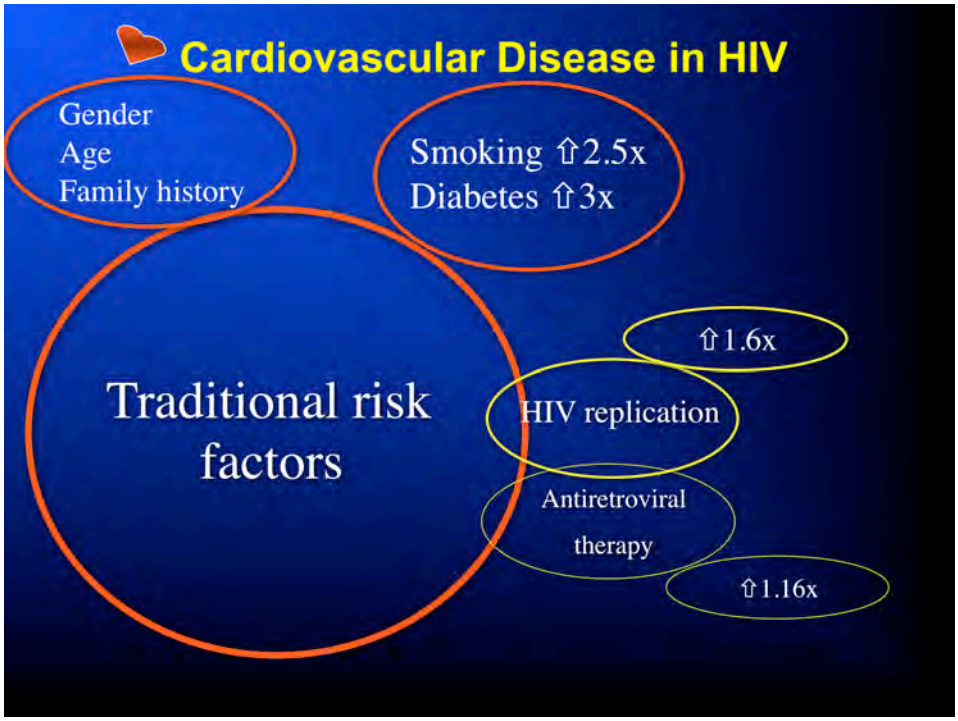
•The risk is increased in the presence of a number of factors, many of which are seen quite commonly in HIV clinic populations, e.g. hepatitis coinfection.



• The increased risk of cardiovascular disease associated with ARV therapy is partly, but not entirely, due to their dyslipidemic effects; however, ARVs are associated with an increased risk of cardiovascular disease beyond that explained by dyslipidemia.

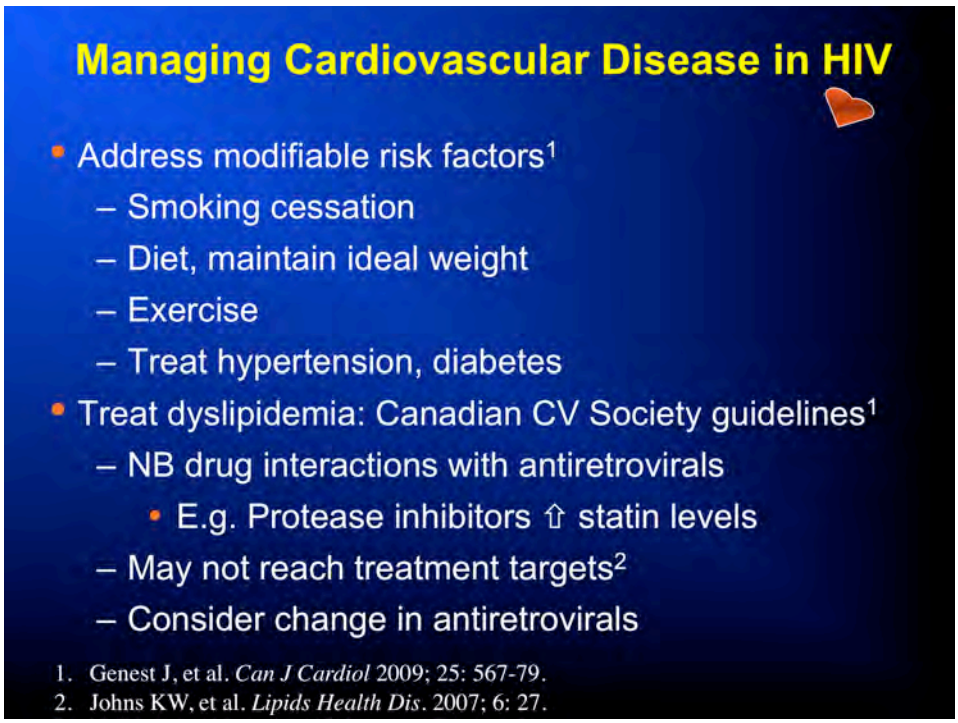
• HIV infection itself is a risk factor for cardiovascular disease, as a result of chronic inflammation.

•In the SMART Study, the relative risk of myocardial infarction was 1.6 for intermittent, CD4-guided ARV therapy vs. continuous, virally suppressive ARV therapy.



• While ARV therapy and HIV infection are independently associated with cardiovascular disease, the relative risk incurred by traditional cardiovascular risk factors is much greater.

• Traditional cardiovascular disease risk factors (e.g. age, gender, smoking) are the most important contributors to cardiovascular disease in the HIV+ population.



• Prevention of cardiovascular disease is critical in the HIV+ population, particularly as they age.

• As with HIV negative individuals, priority should be given to addressing modifiable risk factors, particularly smoking.

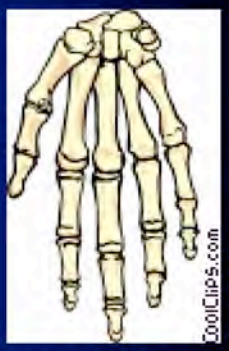
Bone disease and HIV

- Continuous antiretroviral therapy is associated with[1]
  - Gradual ↓ in bone mineral density (> aging)
  - ↑ fracture rate (5x vs. intermittent therapy)
- No specific agent consistently implicated (tenofovir?)
- HIV itself is associated with
  - Accelerated osteoporosis, including young men[2]
  - Fracture rates > general population[3]

1. Grund B, et al. *AIDS* 2009; 23: 1519-1529.
2. Brown T, Qaqish R. *AIDS* 2006; 20:2165-2174.
3. Triant VA,et al. *J Clin Endocrinol Metab*. 2008; 93:3499-3504.

Preventing bone loss

- Weight-bearing exercise
- Maintain ideal weight
- Quit smoking, moderate alcohol intake
- Calcium – diet and supplements
  - Optimal dose ?1200-1500 mg/day
- Vitamin D – diet and supplements
  - low vitamin D levels common in HIV+ (as in the general population)
  - Should probably receive vitamin D – optimal dose unknown but probably 1000-2000 IU/day



www.osteoporosis.ca

• Primary care providers should begin thinking of strategies to prevent bone loss in their HIV+ patients, including men, at an early age.

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General principles
Before starting antiretroviral therapy
– Assess for co-morbid conditions and risk of organ disease (cardiovascular, renal, hepatic, etc.)
– Manage modifiable risk factors
During antiretroviral therapy
– Monitor and refer as appropriate
– Rule out other causes of abnormalities – do not assume due to HIV and/or antiretrovirals
– Remember toxicities due to drug interactions1
– Role of prevention of long-term conditions
1. www.hiv-druginteractions.org

General principles

- If significant acute or refractory drug-related chronic toxicity is identified:
- DO NOT stop one drug at a time
- Avoid sequential mono- or dual therapy
- Either stop all antiretrovirals, OR
- Replace causative agent with another agent (without overlapping toxicity)
- Need to maintain fully suppressive therapy with at least 3 agents to prevent emergence of drug-resistant virus

Summary

- Acute toxicities less common with newer agents
- Long-term toxicities (CV, renal, bone) becoming more important as HIV+ patient population lives longer
- Age-related conditions may interact with complications of antiretroviral treatment
- Frequency of monitoring during antiretroviral therapy may be adjusted according to underlying risk
- Appropriate work-up to rule out diagnoses unrelated to HIV or antiretroviral meds
- Risk of uncontrolled HIV >> risk of antiretrovirals