The Association between Antiretroviral Medication Adherence and Class-Specific Antiretroviral Resistance

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Outline

- Background
- Potency (Adherence-Response Relationships)
- Antiretroviral Medication Resistance Barrier
- Replication Capacity and Fitness
- Potential for Differential Drug Exposure
  - Differential Adherence
  - Pharmacokinetics
- Class-Specific Adherence-Resistance Relationships
- Conclusions

Background

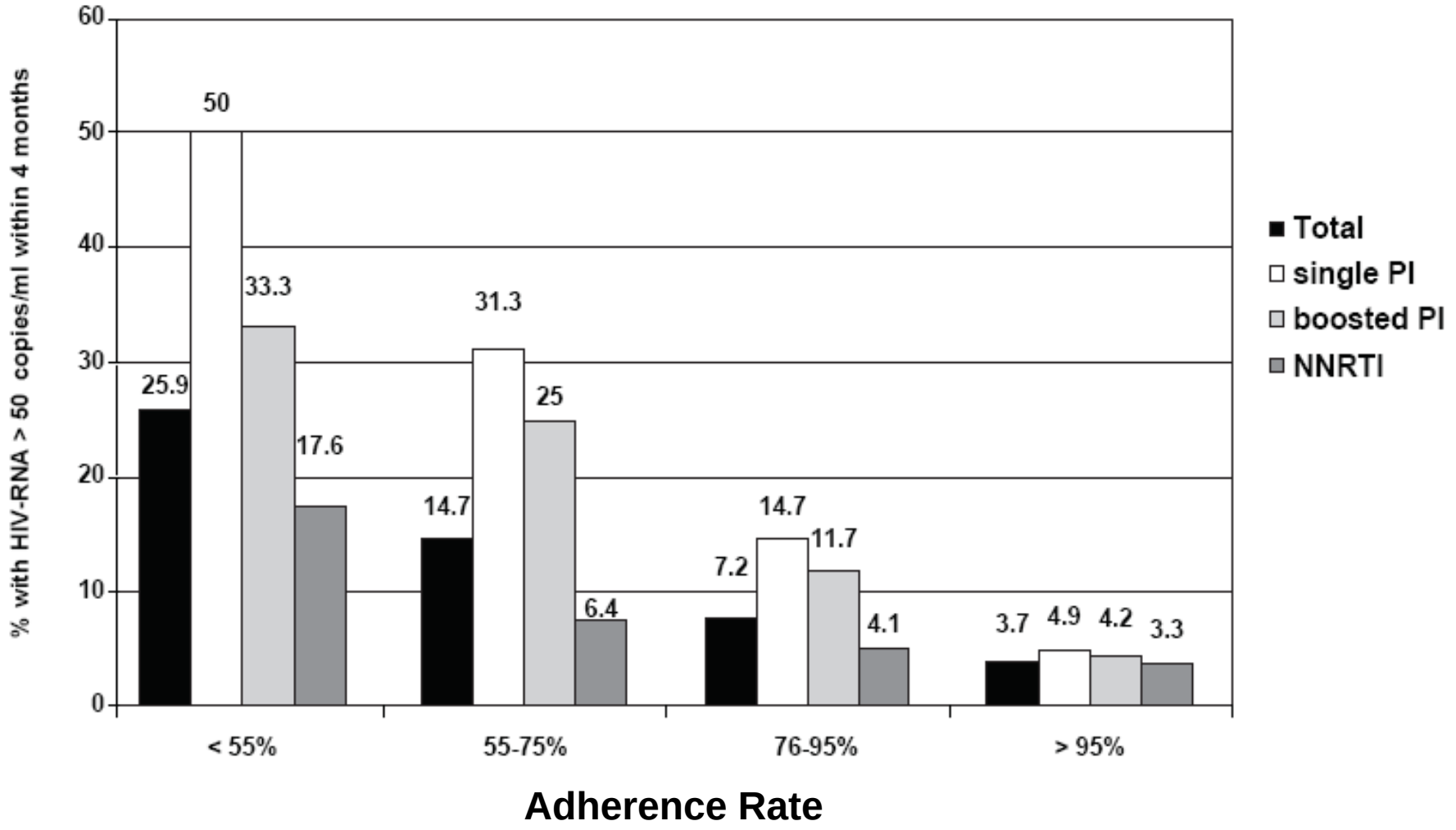
- It is thought that every point mutation occurs 1,000 – 10,000 times each day in HIV-infected individuals not on therapy*
- Clinical relevance occurs when increased numbers of resistant viruses are present:
  - Non-suppressive antiretroviral therapy
  - Transmission of resistant virus
- Antiretroviral resistance limits future treatment options because of cross-resistance
- Emergence of antiretroviral resistance during therapy is associated with increased mortality**

*Coffin J. Science 1995;267:483-9, **Hogg et al. PLOS Med 2007;3:1570-77

Adherence-Response Relationships

- Suppression of viral replication is the goal of antiretroviral therapy
- At the lower limits of measurable viral replication evolution of drug resistance mutations is zero (or pretty close)
- The more potent a drug (or regimen) is:
  - The more likely it is for one to have an undetectable viral load
  - Therefore, the less likely that they will develop resistance (particularly at high adherence levels)

Adherence-Response Relationships



Maggiolo et al. HIV Clin Trials 2007;8(5):282–292

Genetic Barrier to Antiretroviral Resistance

- Definition: the number of viral mutations required to overcome drug-selective pressure*
- Low-barrier antiretroviral medications
  - A single mutation leads to high-level resistance
    - NNRTI – efavirenz and nevirapine
    - NRTI – lamivudine and emtricitabine
    - Enfuvirtide
- Moderate-barrier medications
  - Requires several mutations to impact potency
    - NNRTI – etravirine
    - NRTI – thymidine analogs, didanosine, abacavir, tenofovir
    - Non-boosted PIs and some boosted PIs
- High-barrier medications
  - Require several to many mutations to effect potency
    - Some boosted PIs

*van de Vijver et al. JAIDS 2006;41:352-60

Replication Capacity and Fitness

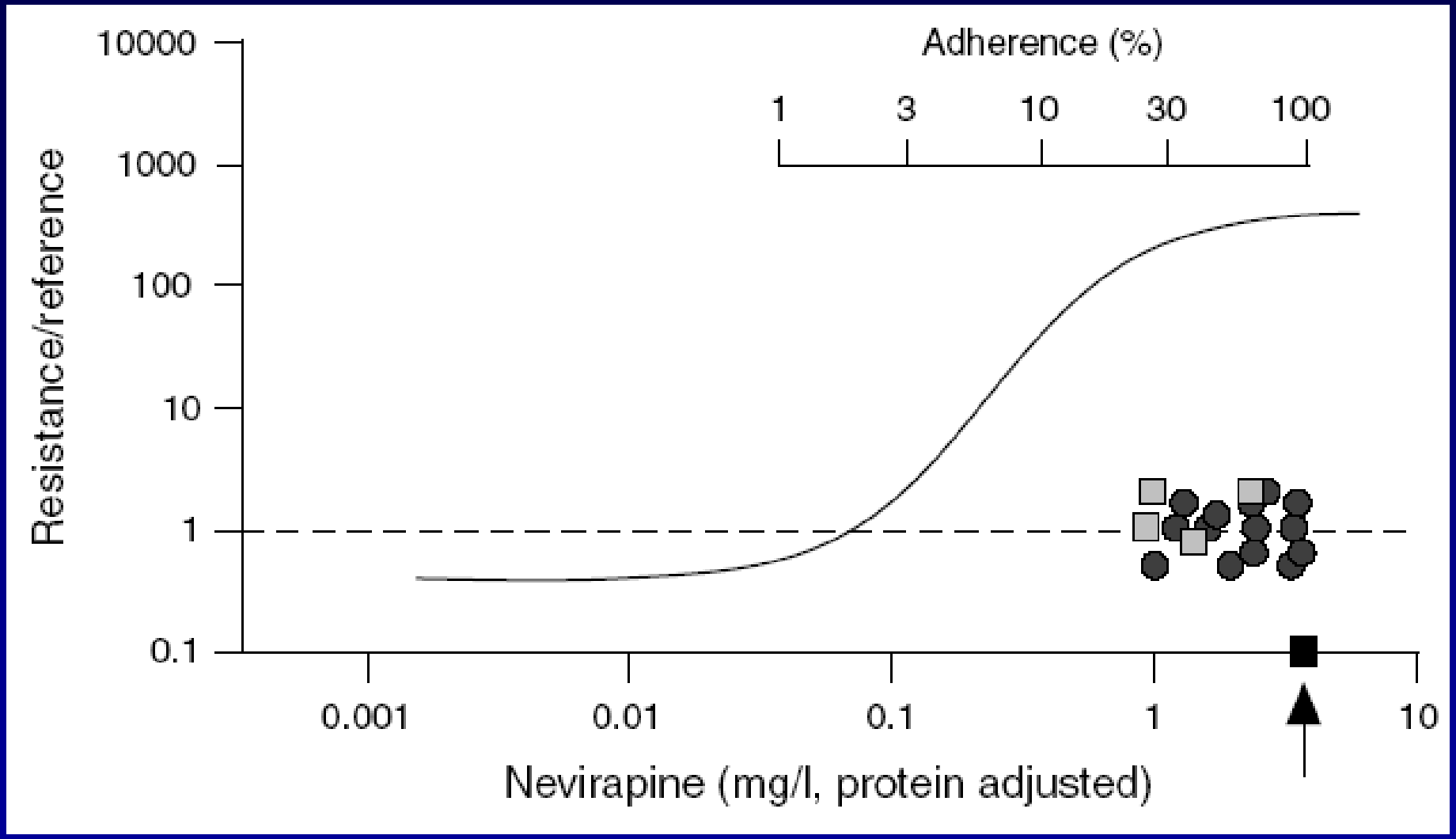
- Most resistance mutations act by decreasing drug-target binding
- Resistance mutations at the enzymatic active site are likely to impair that enzyme's normal activity
- Replication capacity refers to the ability of HIV to replicate in the absence of drug pressure
- Fitness refers to the ability of HIV to replicate compared to wild-type HIV in a defined environment
  - e.g., in the presence of antiretroviral medications

Bangsberg et al. Curr HIV/AIDS Rep 2007;4:65-72

Fitness and Resistance

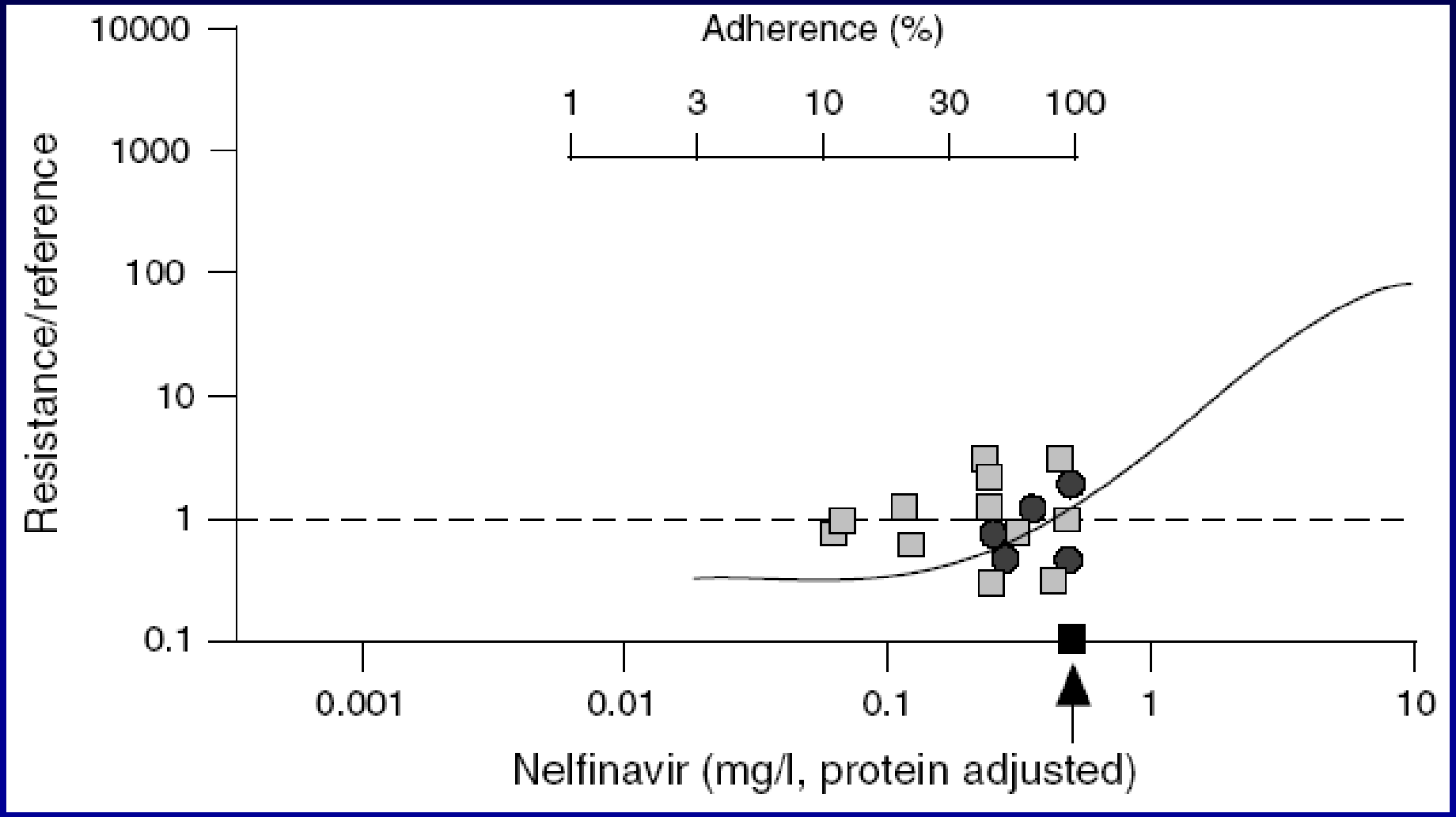
- Replication of wild-type virus is impaired in the presence of antiretroviral medication
- Replication of resistant (mutated) virus is impaired because of decreased replication capacity (usually)
- Circulating viral populations are determined by the interplay of three major factors:
  - Drug exposure (partially determined by adherence)
  - The ability of wild-type virus to replicate in the presence of drug
  - The ability of resistant virus to replicate in the presence of drug

Nevirapine Example



Bangsberg et al. AIDS 2006;20:223-31

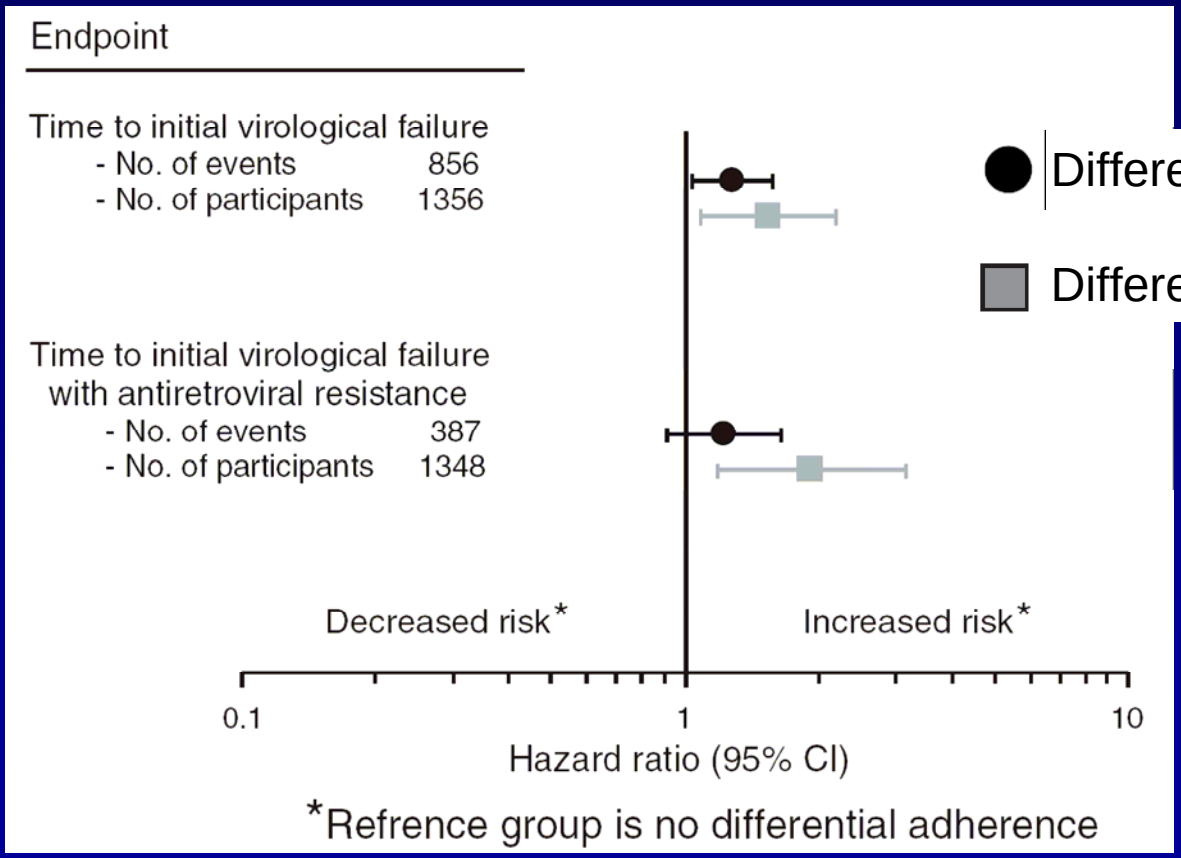
Nelfinavir Example



Bangsberg et al. AIDS 2006;20:223-31

Differential Drug Exposure

- Differential adherence occurs when adherence to individual components of a multi-drug regimen is different
  - Increases the risk of virologic failure
  - Increases the risk of virologic failure with resistance



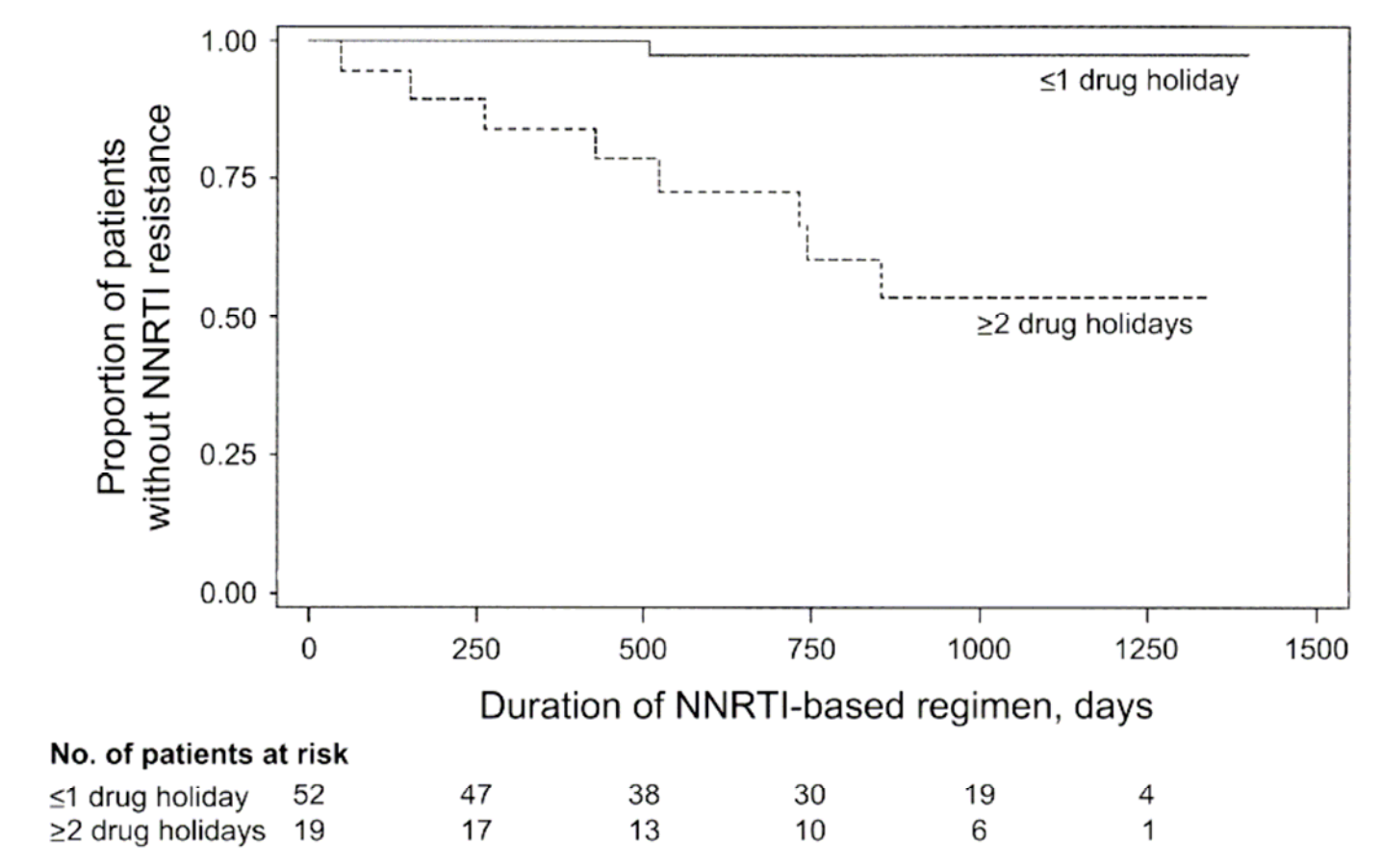
Differential adherence once

Differential adherence more than once

Gardner et al. AIDS 2008;22:75-82

Differential Drug Exposure

- Differential exposure occurs during treatment interruptions when drugs with different half-lives are used together
  - 'Drug holidays' (48 hour gaps in therapy) are significantly associated with NNRTI resistance



Parienti et al. Clin Infect Dis 2004;38:1311-16

Differential Drug Exposure

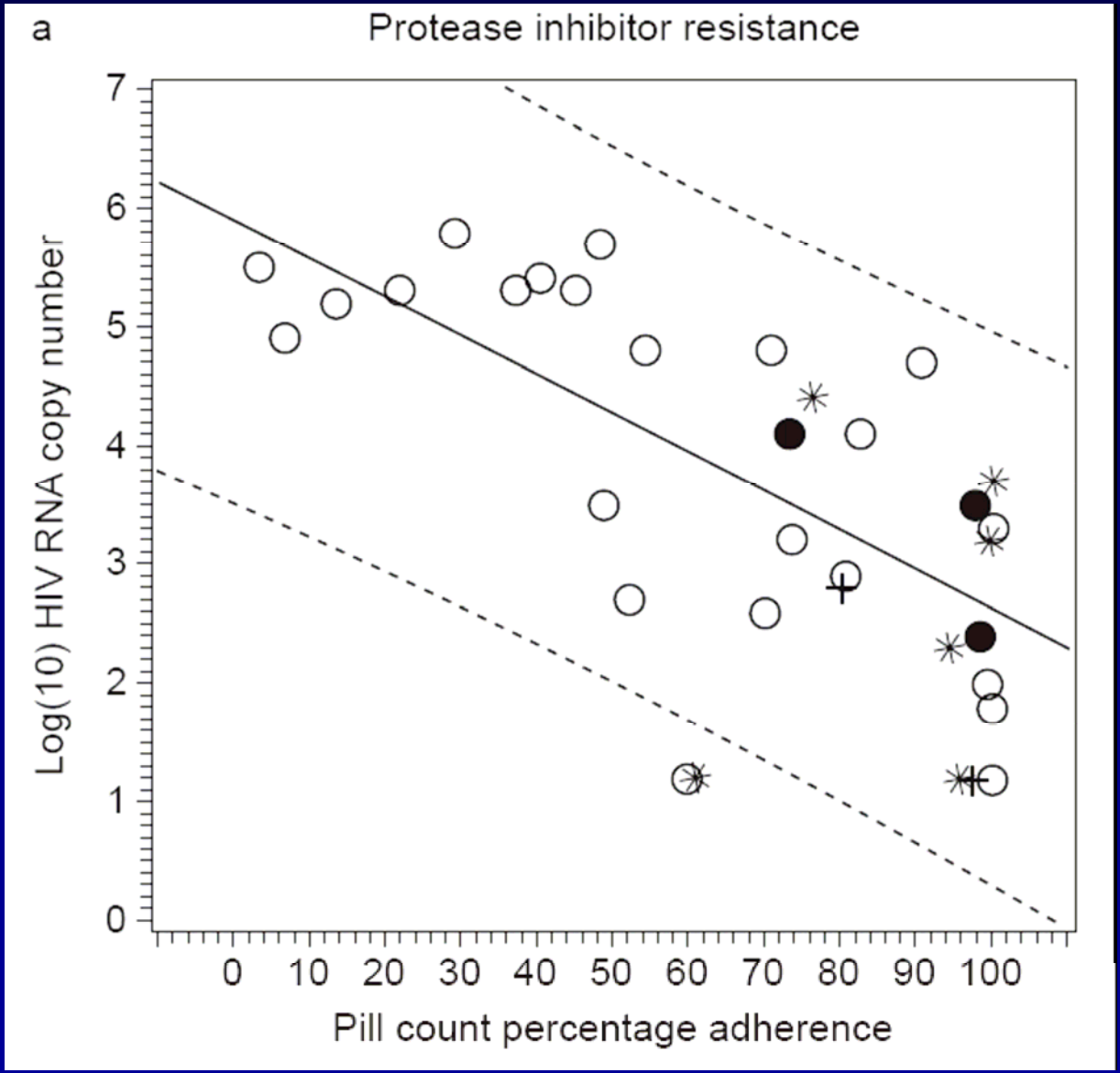
- Other pharmacokinetic/pharmacogenomic factors can lead to differential drug exposure
  - Absorption
  - Distribution
  - Metabolism
  - Drug Efflux pumps
  - Other

Adherence and Resistance

- Class-Specific Adherence-Resistance Relationships are Defined by the Following:
  - Potency
  - Genetic Barrier to Resistance
  - Replicative Capacity and Fitness
  - Potential for Differential Drug Exposure
  - (other)

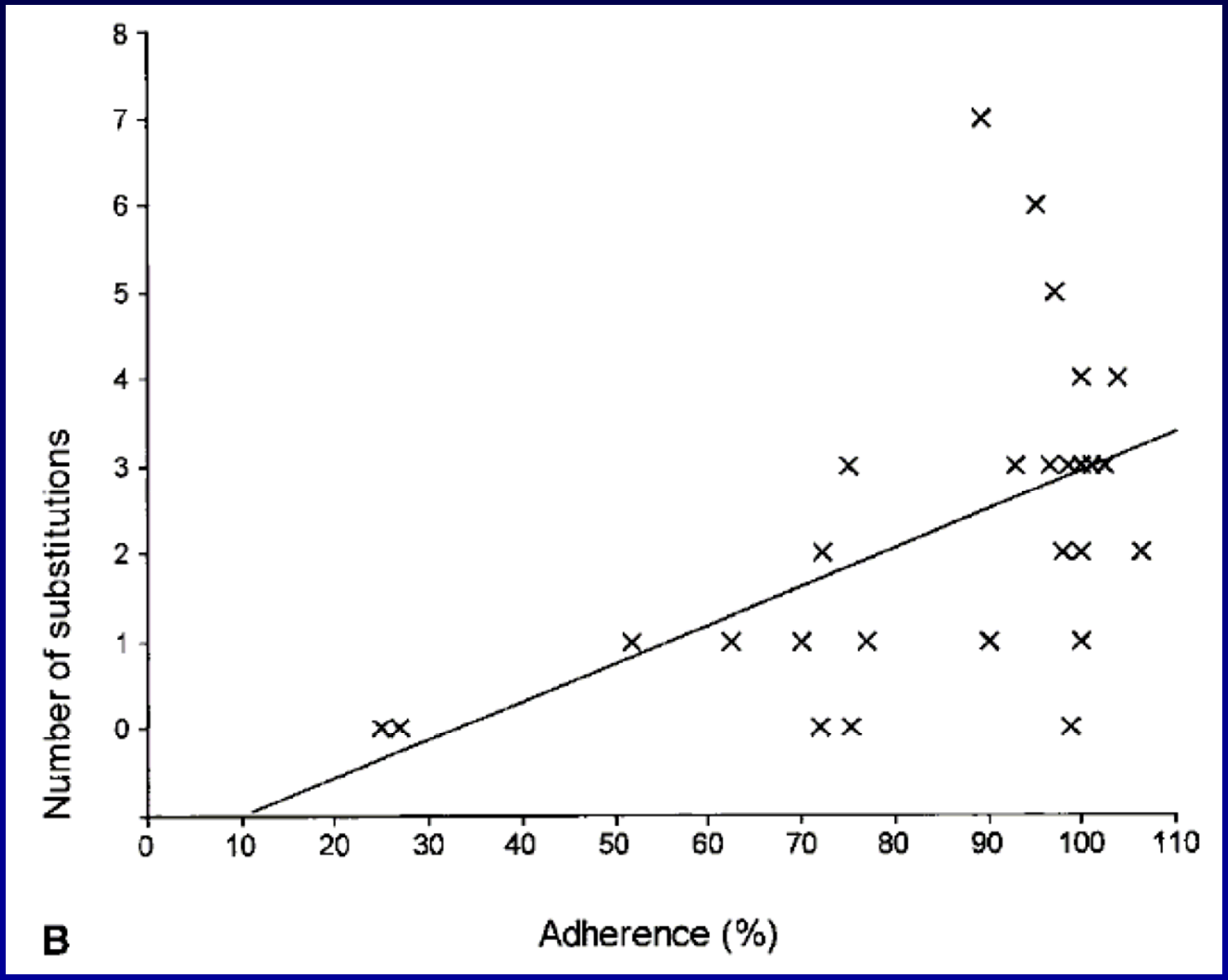
Let’s look at the data…

Non-Boosted Protease Inhibitors



Bangsberg et al. AIDS 2000;14:357-66

Non-Boosted Protease Inhibitors



Walsh et al. JAIDS 2002;30:278-87

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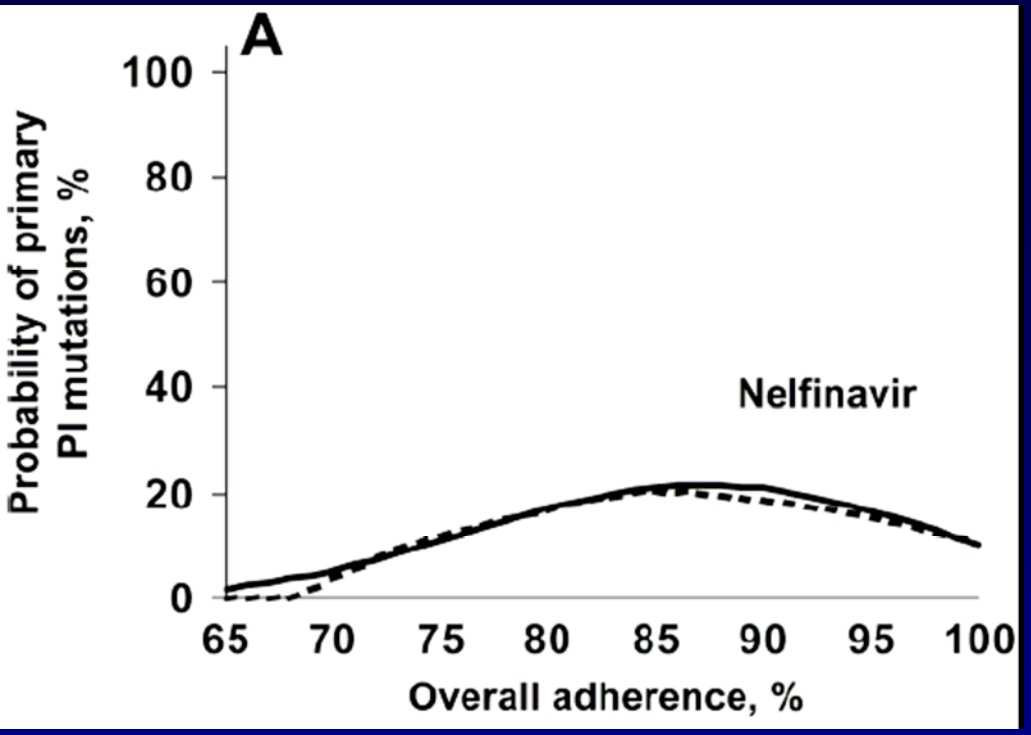

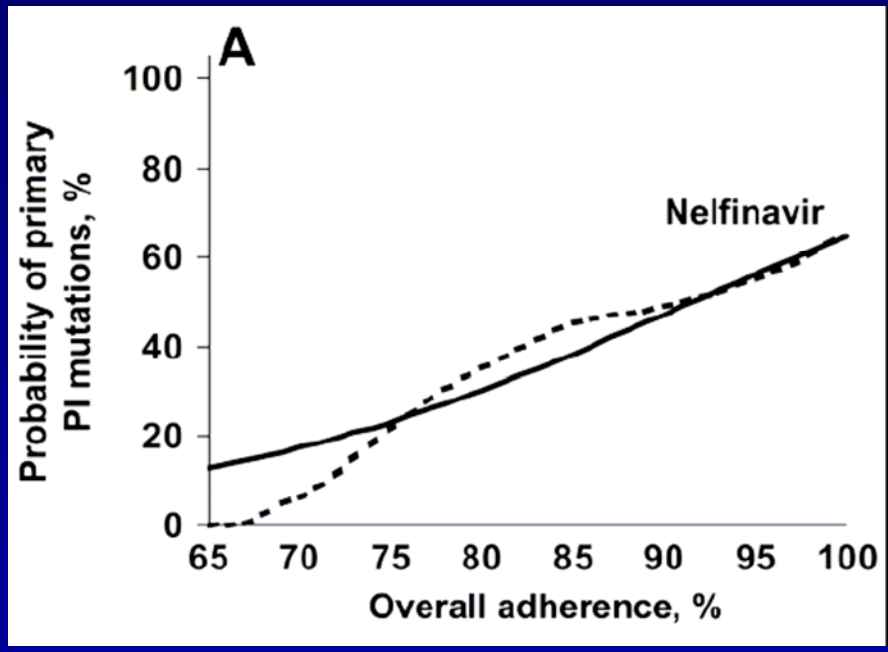

King et al. J Infect Dis 2005;191:2046-52

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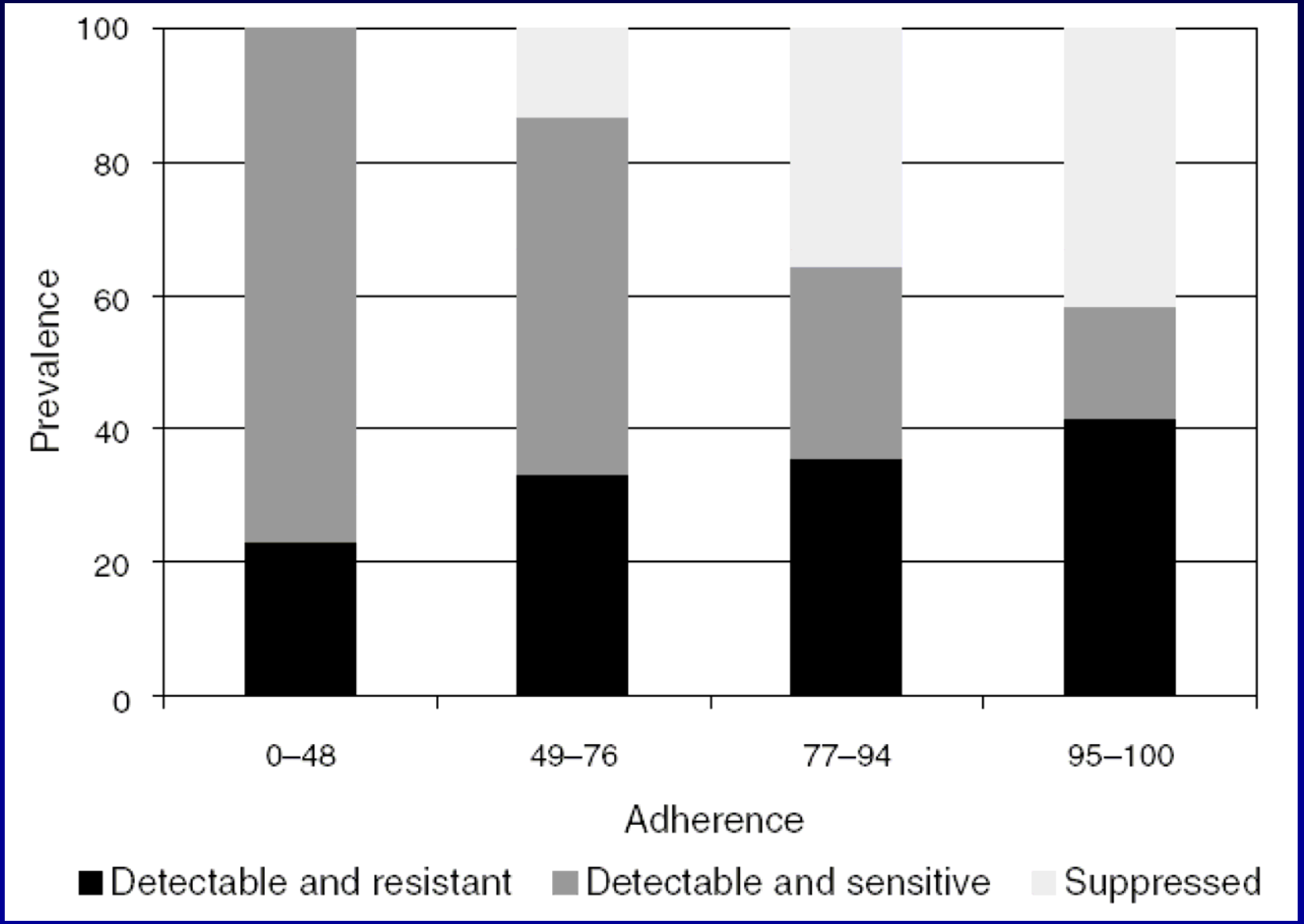

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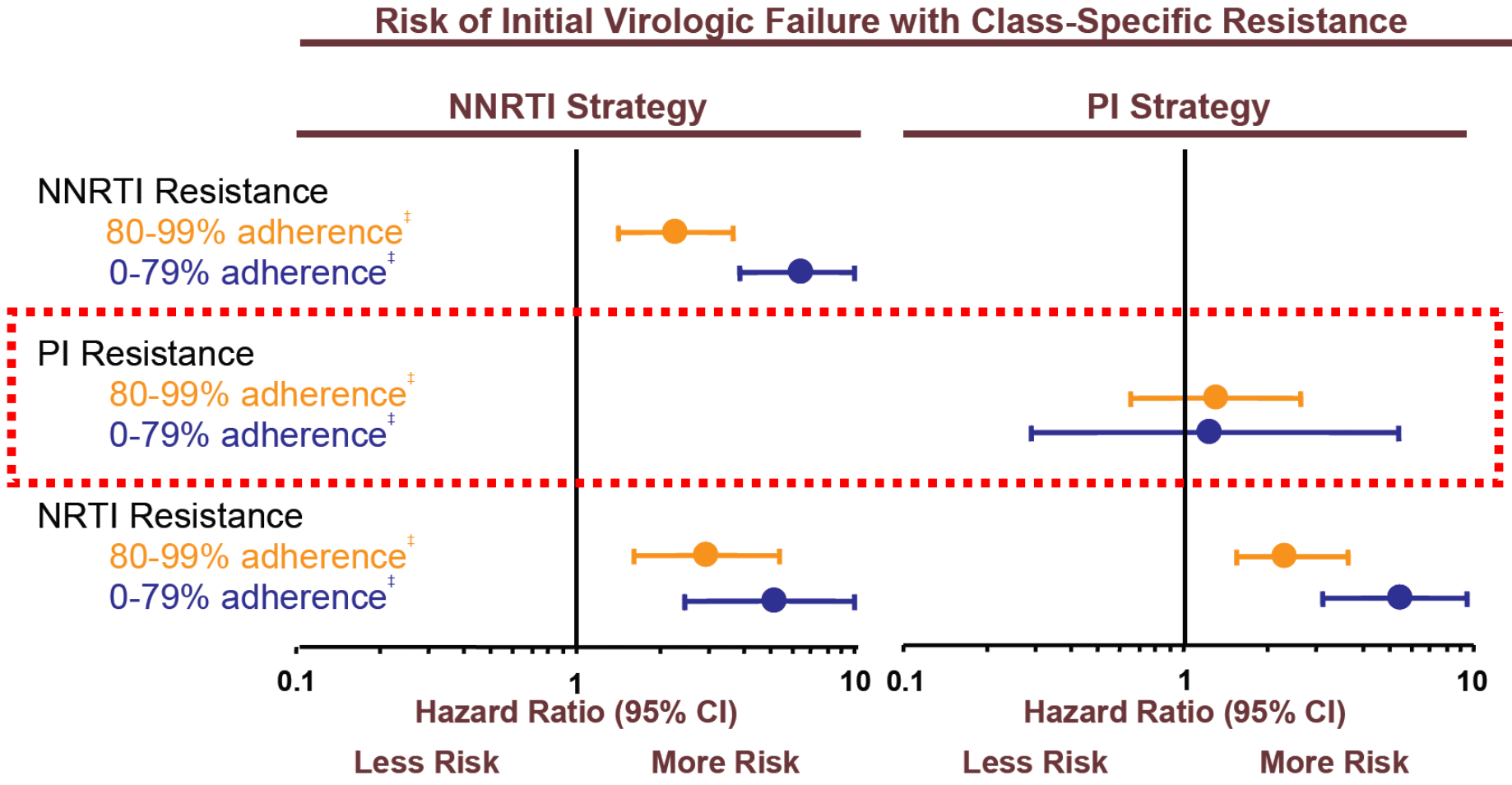
Figure 2: Risk of initial virologic failure with resistance by adherence categories: Hazard ratio† (95% confidence interval)*



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† Adjusting variables include age, gender, race, prior clinical AIDS, baseline CD4 cell count and HIV-RNA level and time updated ART status

‡ Time updated cumulative mean adherence categories; compared to 100% cumulative mean adherence

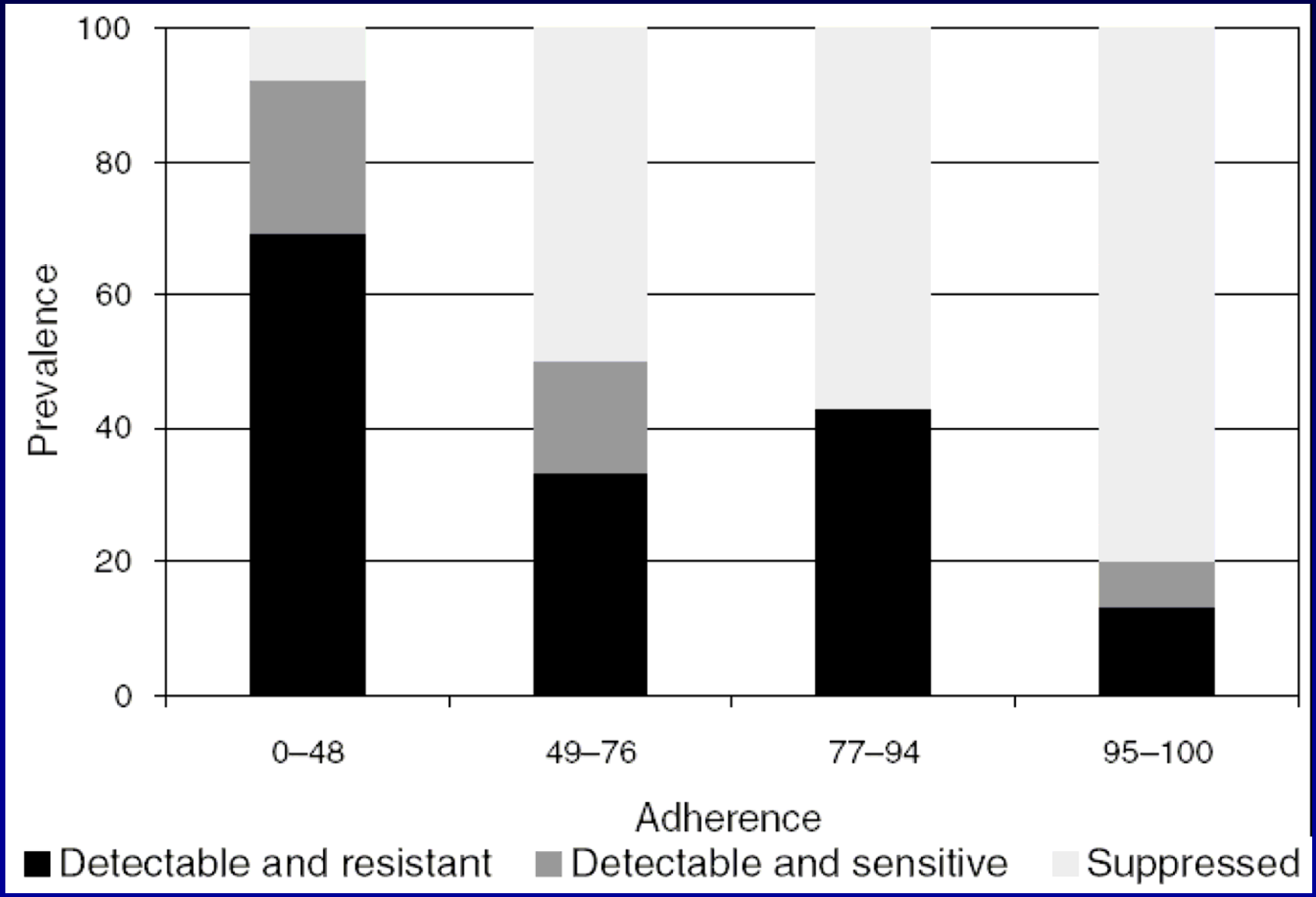
Gardner et al. CROI Abstract # 777, February, 2008

Non-Boosted Protease Inhibitors

- Potency: Moderate
- Resistance Barrier: Moderate
- RC with Resistance: Impaired
- Differential Potential: Moderate

- Resistance to non-boosted PIs occurs at moderate to high levels of adherence
  - In viremic patients the higher the adherence, the more likely resistance will develop

Non-Nucleoside Reverse Transcriptase Inhibitors



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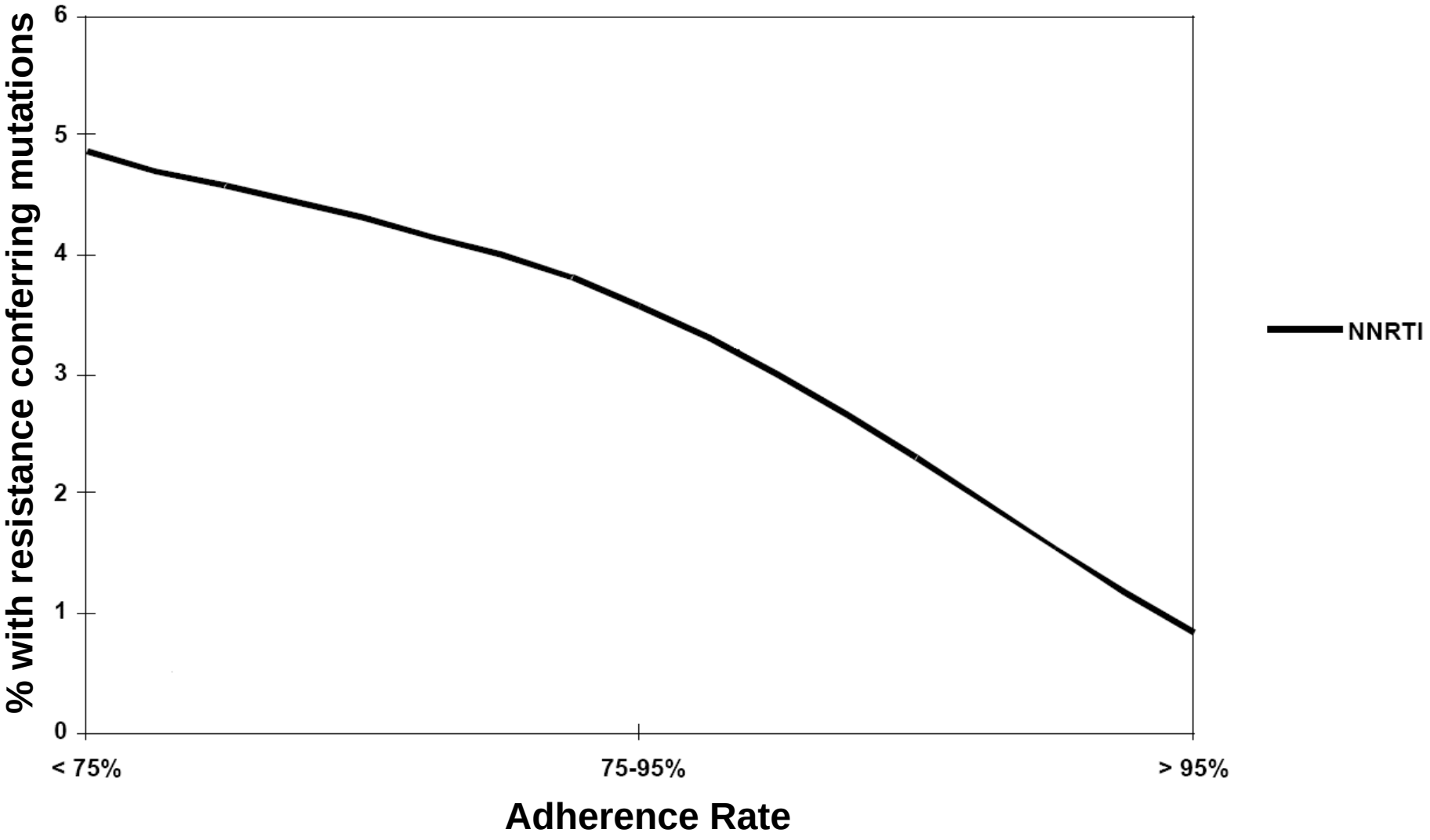

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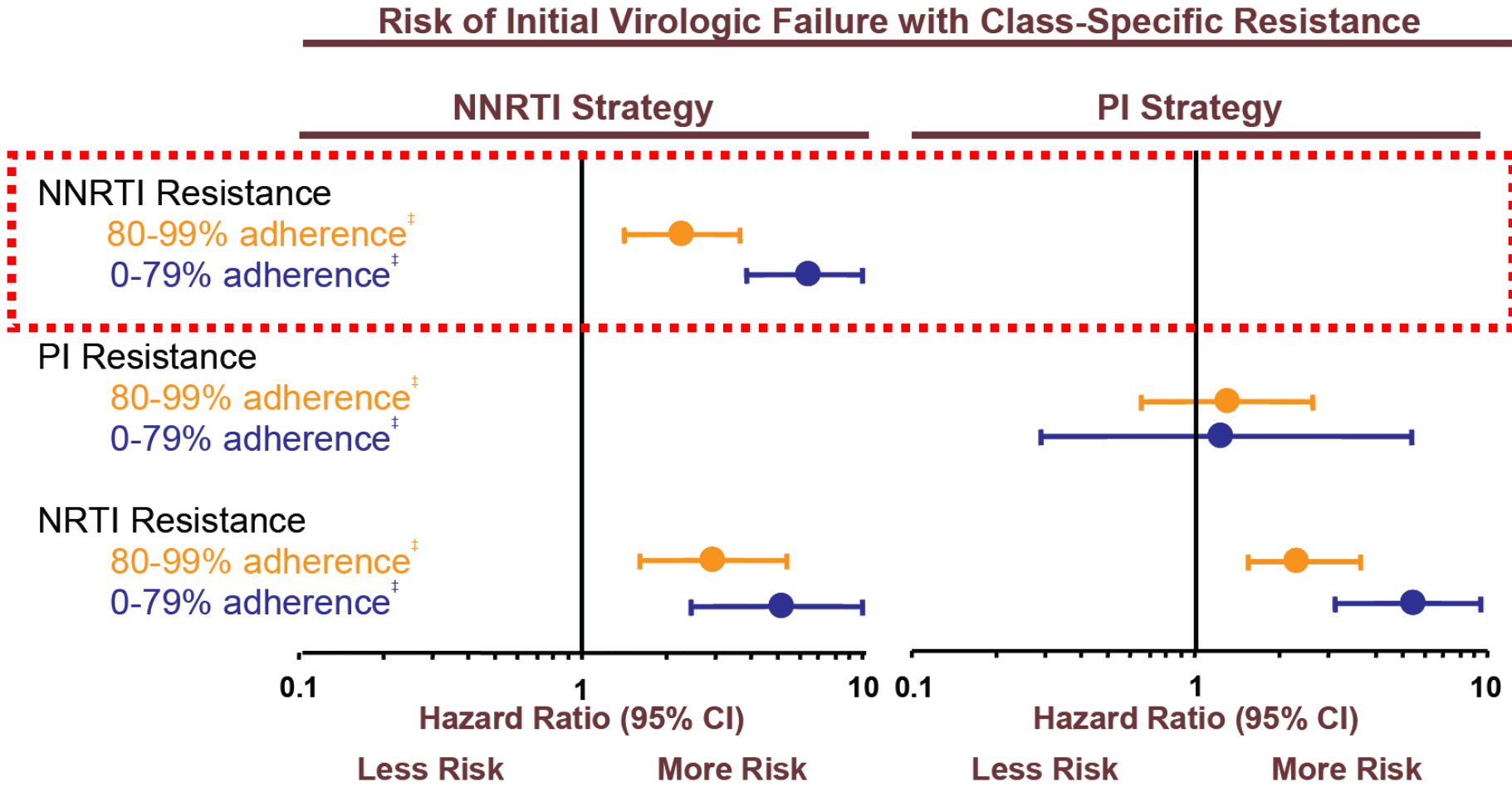

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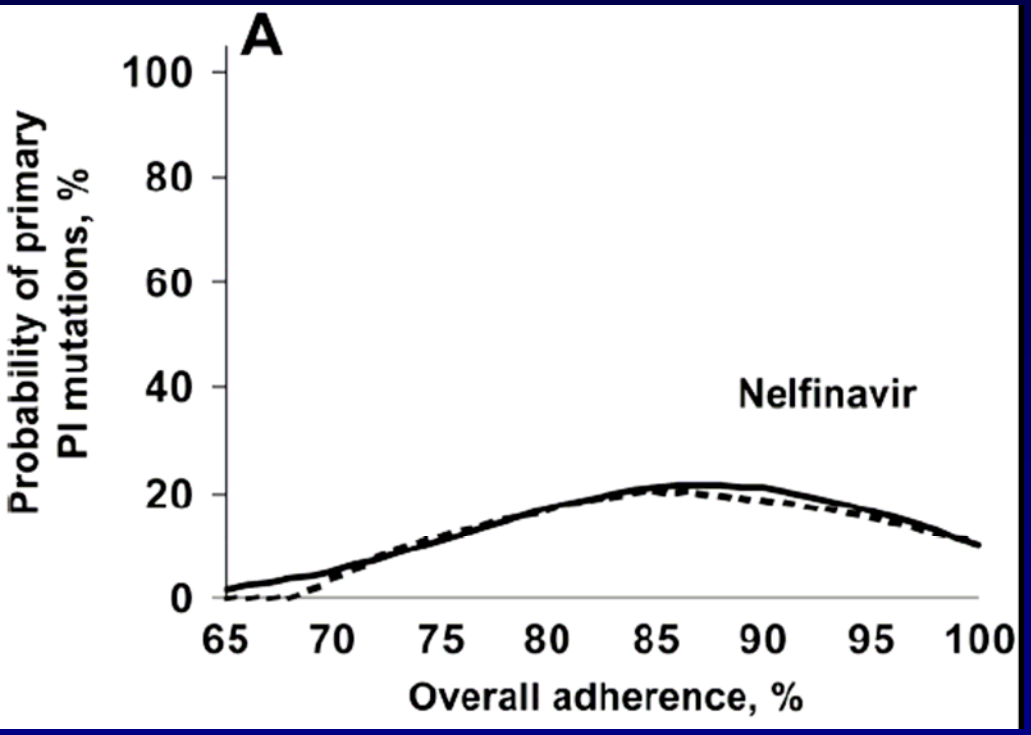
Gardner et al. CROI Abstract # 777, February, 2008

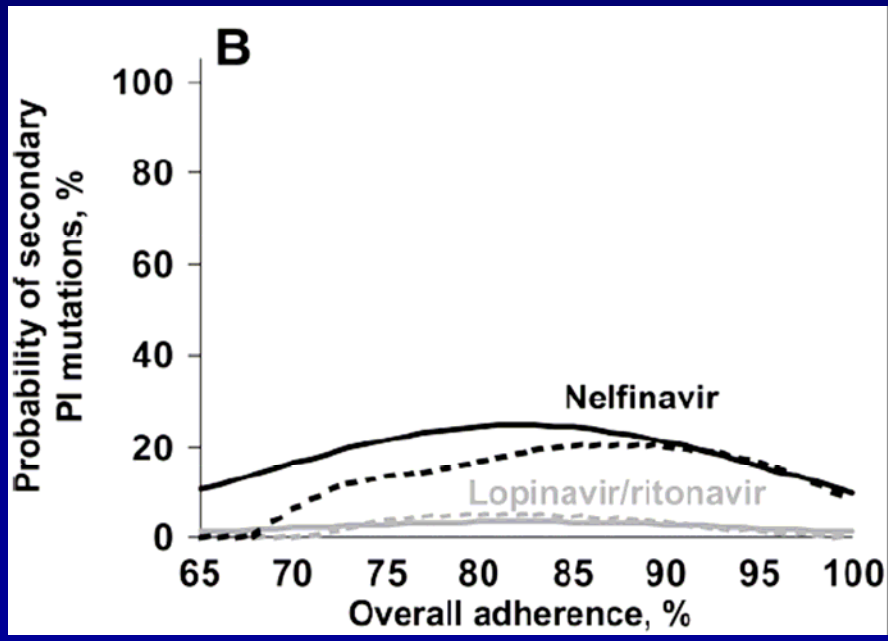
Non-Nucleoside Reverse Transcriptase Inhibitors

- Potency: High
- Resistance Barrier: Low
- RC with Resistance: Not Impaired
- Differential Potential: High

- Resistance is common in NNRTI treated patients with virologic failure
  - The adherence-resistance relationship is thus directly related to the adherence-response relationship

Boosted Protease Inhibitors





King et al. J Infect Dis 2005;191:2046-52

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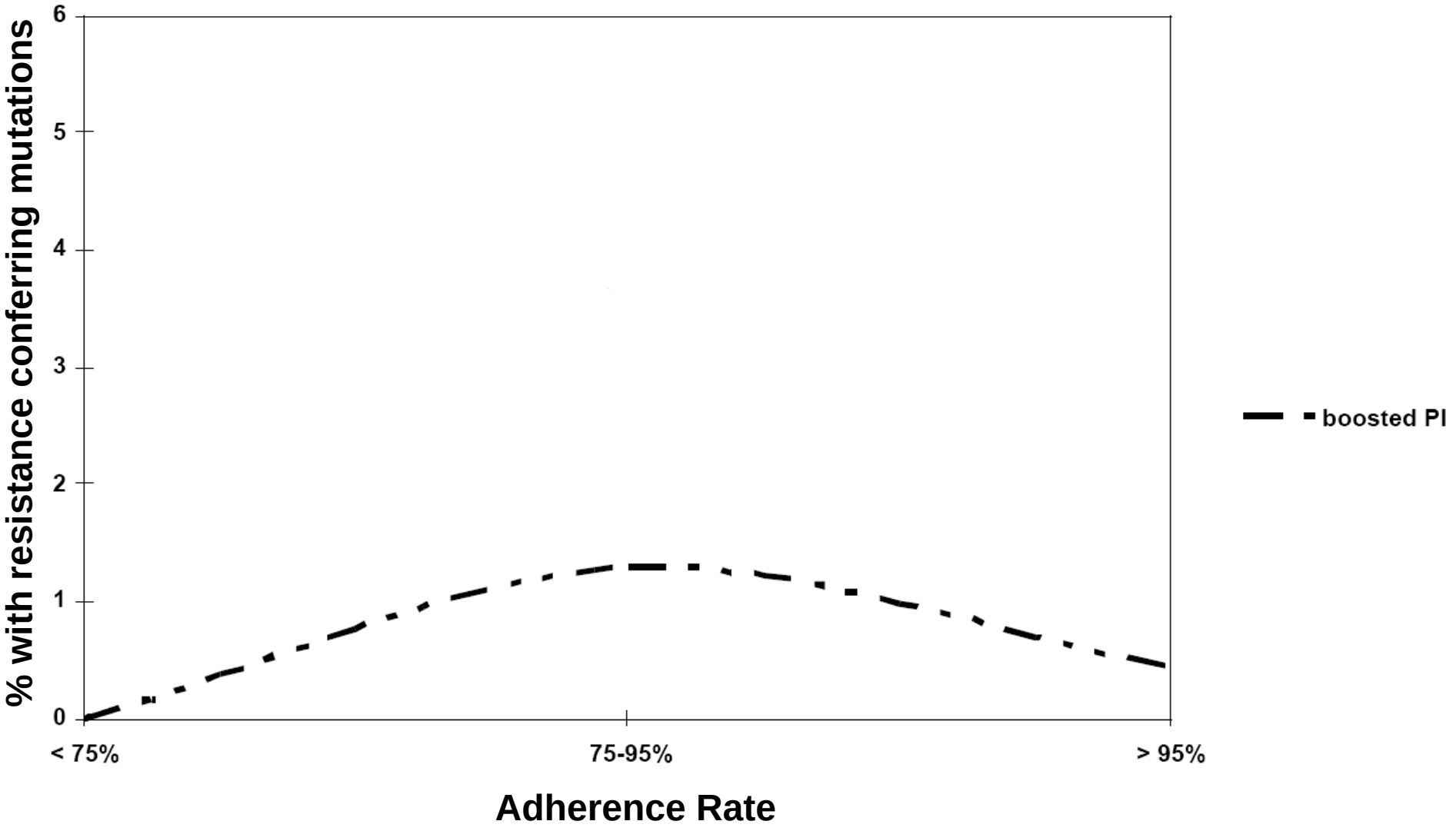

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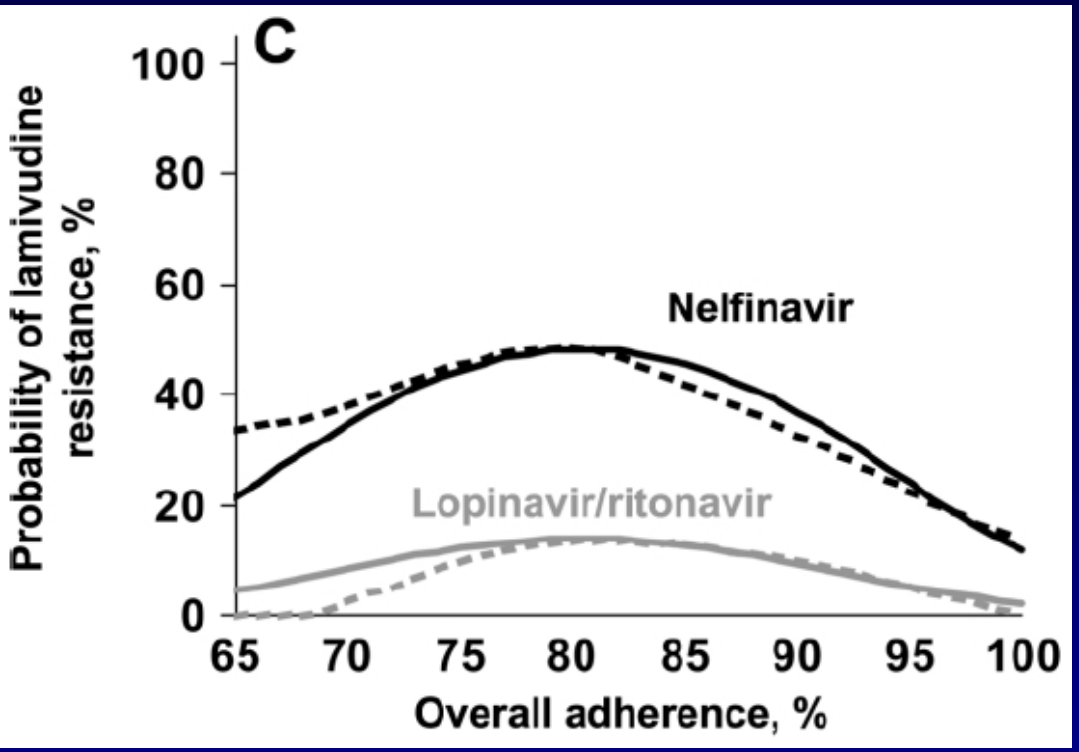
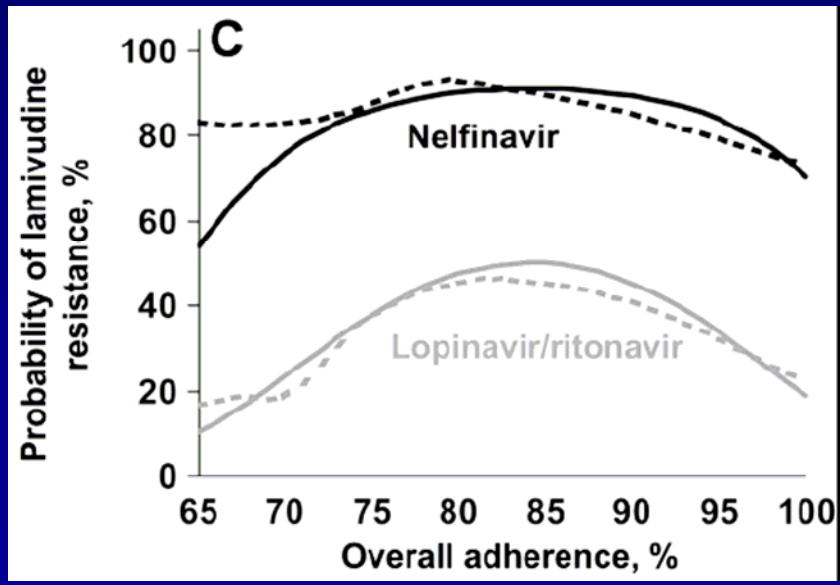
Boosted Protease Inhibitors

- Potency: High
- Resistance Barrier: Moderate - High
- RC with Resistance: Impaired
- Differential Potential: Moderate

- Resistance to boosted PIs is uncommon at any adherence level

Lamivudine





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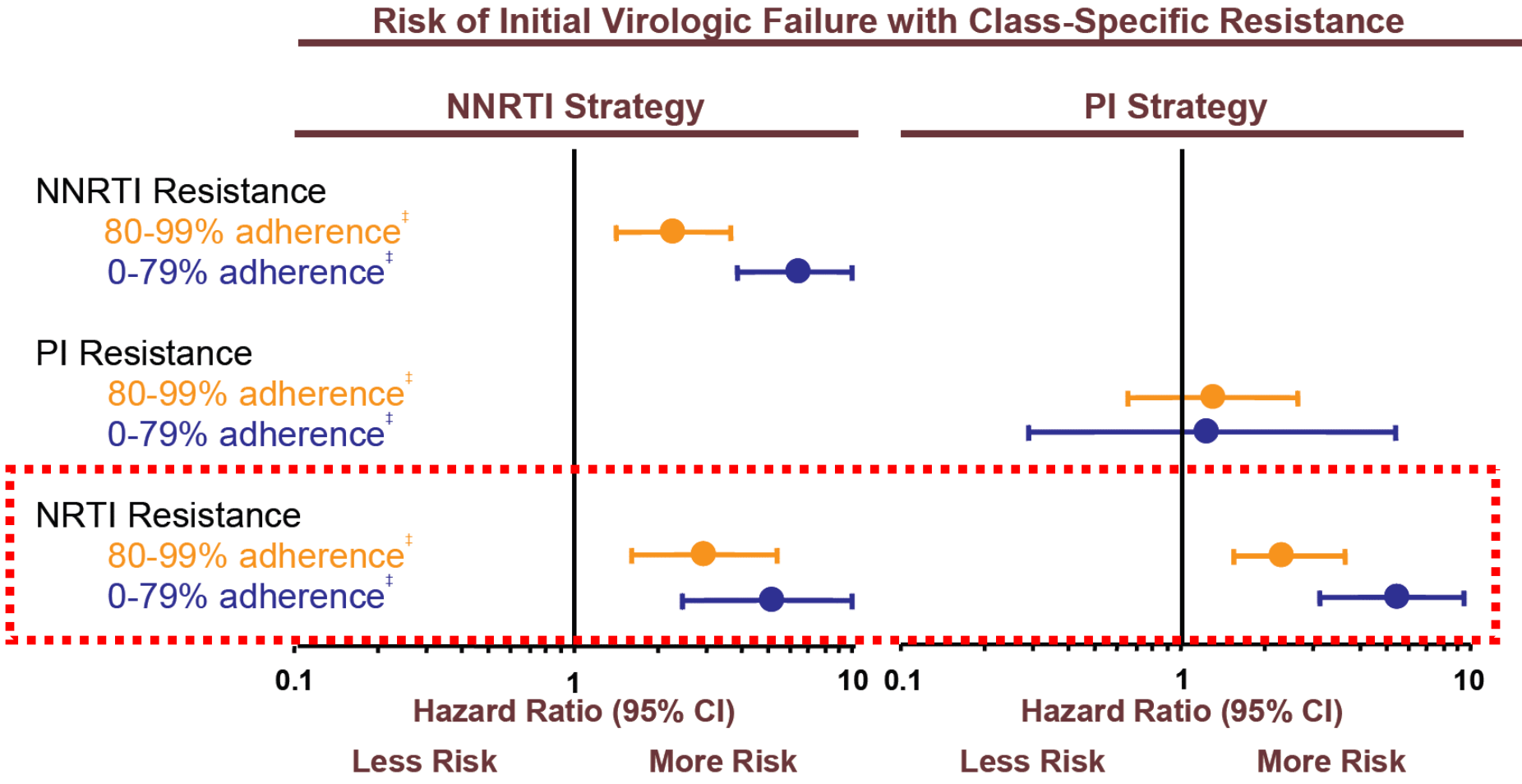

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Gardner et al. CROI Abstract # 777, February, 2008

Lamivudine and Emtricitabine

- Potency: High
- Resistance Barrier: Low
- Fitness with Resistance: Impaired
- Differential Potential: Low

- Resistance to 3TC and FTC occurs at low to moderate levels of adherence

Other NRTIs

- Potency: Moderate
- Resistance Barrier: Moderate
- RC with Resistance: Impaired
- Differential Potential: Low

- Resistance to NRTIs probably occurs at higher levels of adherence
  - Pattern similar to non-boosted PI
- As with lamivudine and emtricitabine, the other regimen components strongly influence this association

Enfuvirtide

- Potency: High
- Resistance Barrier: Low
- RC with Resistance: Impaired
- Differential Potential: Very High

- Resistance to enfuvirtide probably occurs at low to moderate levels of adherence
  - Pattern similar to lamivudine

CCR5 Receptor Antagonists

- Potency: High
- Resistance Barrier: Moderate
- RC with Resistance: Complicated
- Differential Potential: Low

- The association between adherence and resistance to CCR5 receptor antagonists is unclear at this time

Integrase Inhibitors

- Potency: High
- Resistance Barrier: Low
- Integrase Activity with Resistance: Impaired
- Differential Potential: Low

- Resistance to integrase inhibitors probably will occur at low to moderate levels of adherence
  - Pattern similar to lamivudine

Etravirine

- Potency: High
- Resistance Barrier: Moderate
- RC with Resistance: Not Impaired
- Differential Potential: Low

- Resistance to etravirine may be similar to NNRTIs but is likely to take longer to develop and/or occur at lower frequency

Clinical Implications

- Cessation of viral replication remains the goal of antiretroviral therapy
- What if a patient is failing a regimen (or failed one in the past) and viral load and/or resistance testing are not available?
- Does this information help us sequence regimens better?
- Does this information help us choose better drug combinations?

Conclusions

- Complete viral suppression is the goal of antiretroviral therapy
- Viral replication in the presence of drug creates selective pressure for drug resistance mutations
- Class-specific adherence-resistance relationships are defined by the following:
  - Potency
  - Genetic Barrier to Resistance
  - Fitness and Replicative Capacity
  - Potential for Differential Drug Exposure

Conclusions

- Non-boosted PI - resistance occurs with high levels of adherence
- NNRTI - resistance is likely in patients on NNRTI based therapy who have viremia
- Boosted PI – resistance is very uncommon
- Lamivudine – resistance is more likely at low to moderate levels of adherence
- Adherence-response relationships for other drugs and drugs classes are unknown
  - Relationships are best approximated by their similarities to PIs, NNRTIs, or Lamivudine

Thank You