

# ART Adherence and Class-Specific Resistance: Implications for Substance Users

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NIDA Technology, Adherence, and Substance Abuse Treatment

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# Goals of This Presentation

1. To demonstrate antiretroviral adherence-resistance relationships
2. To describe how these relationships may or may not apply to substance abusing populations

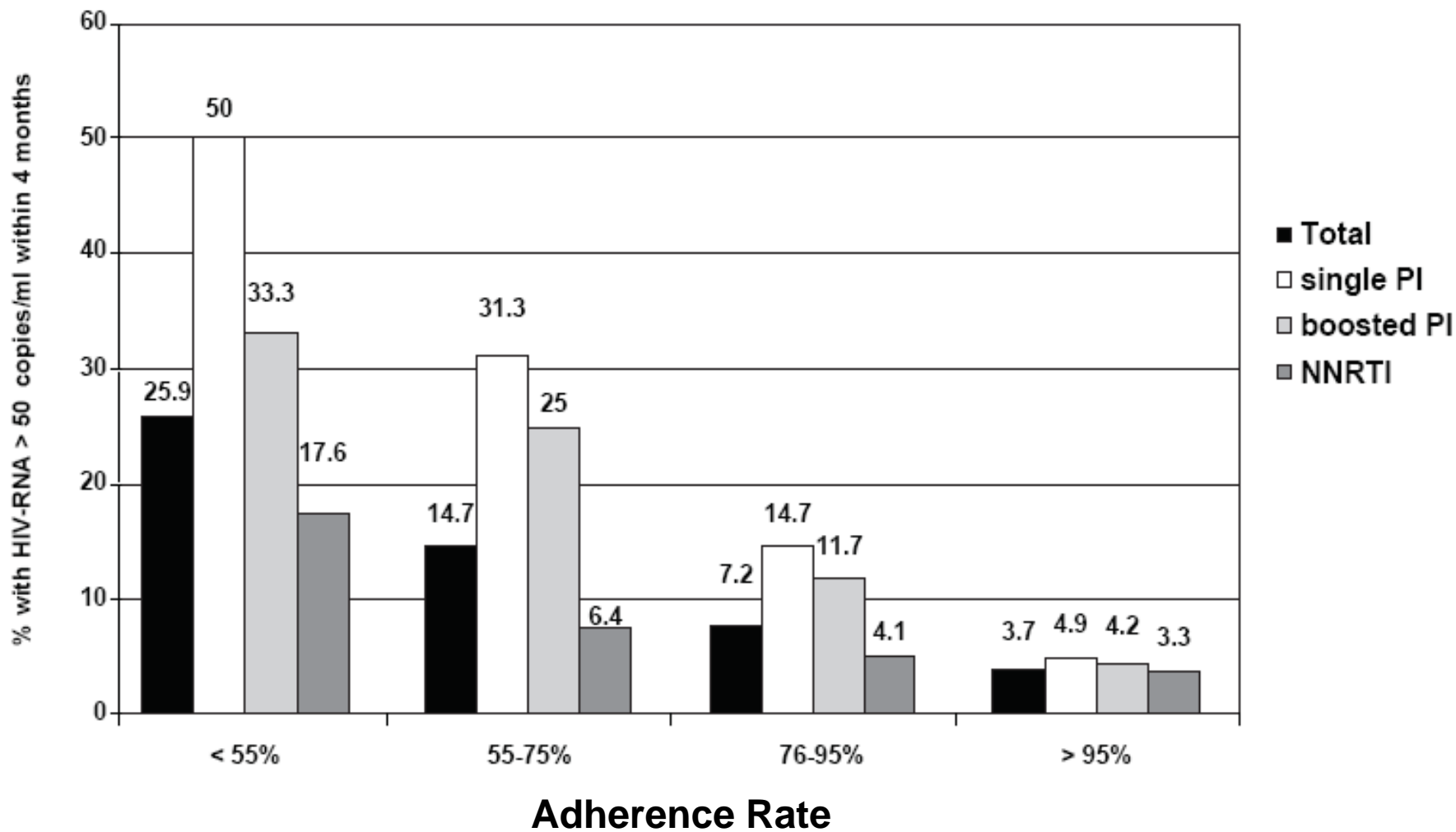
# Resistance - General

- HIV-1 reverse transcriptase fidelity is low:
  - Every point mutation occurs 1,000 – 10,000 times daily in HIV-infected individuals not on therapy

# Five Factors Influence Adherence-Resistance Relationships

- Potency (adherence-response relationship)
- Replication capacity and fitness
- Genetic barrier to resistance for antiretroviral agents
  
- Differential medication exposure
- Other regimen components

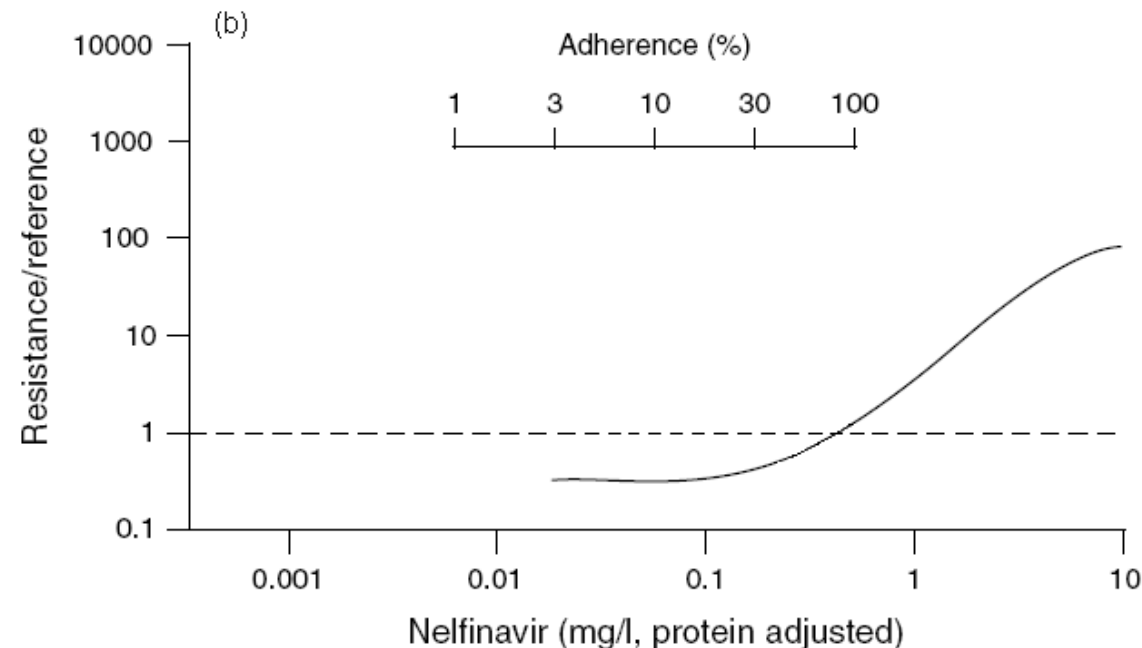
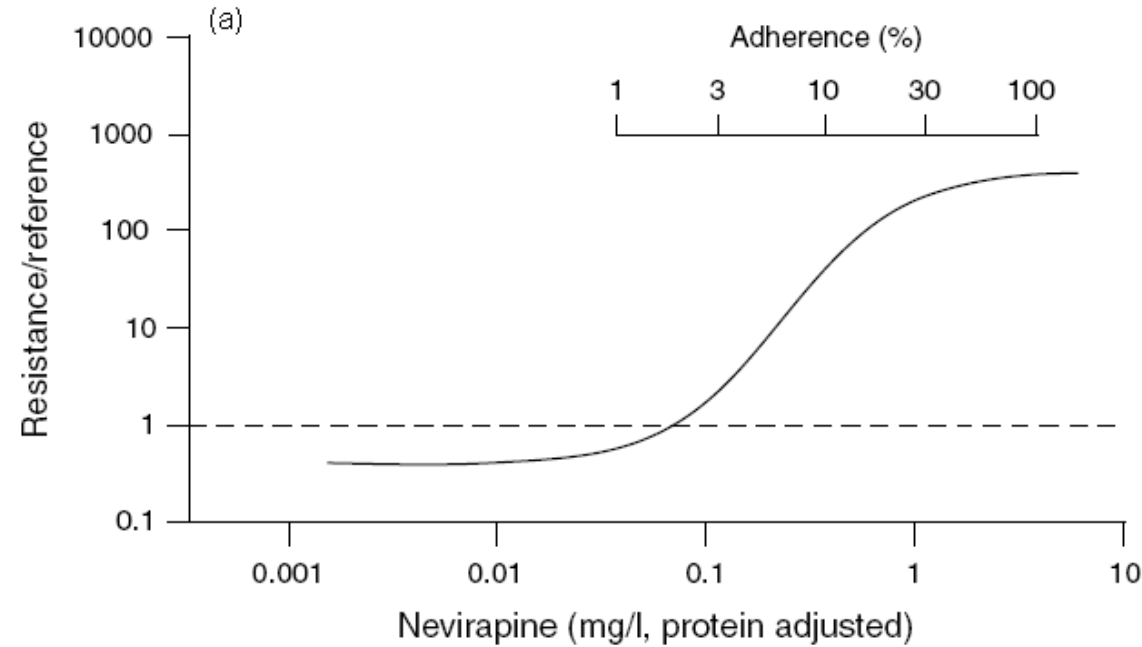
# Regimen Potency: (Adherence-Response Relationships)



## Replication Capacity and Fitness

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

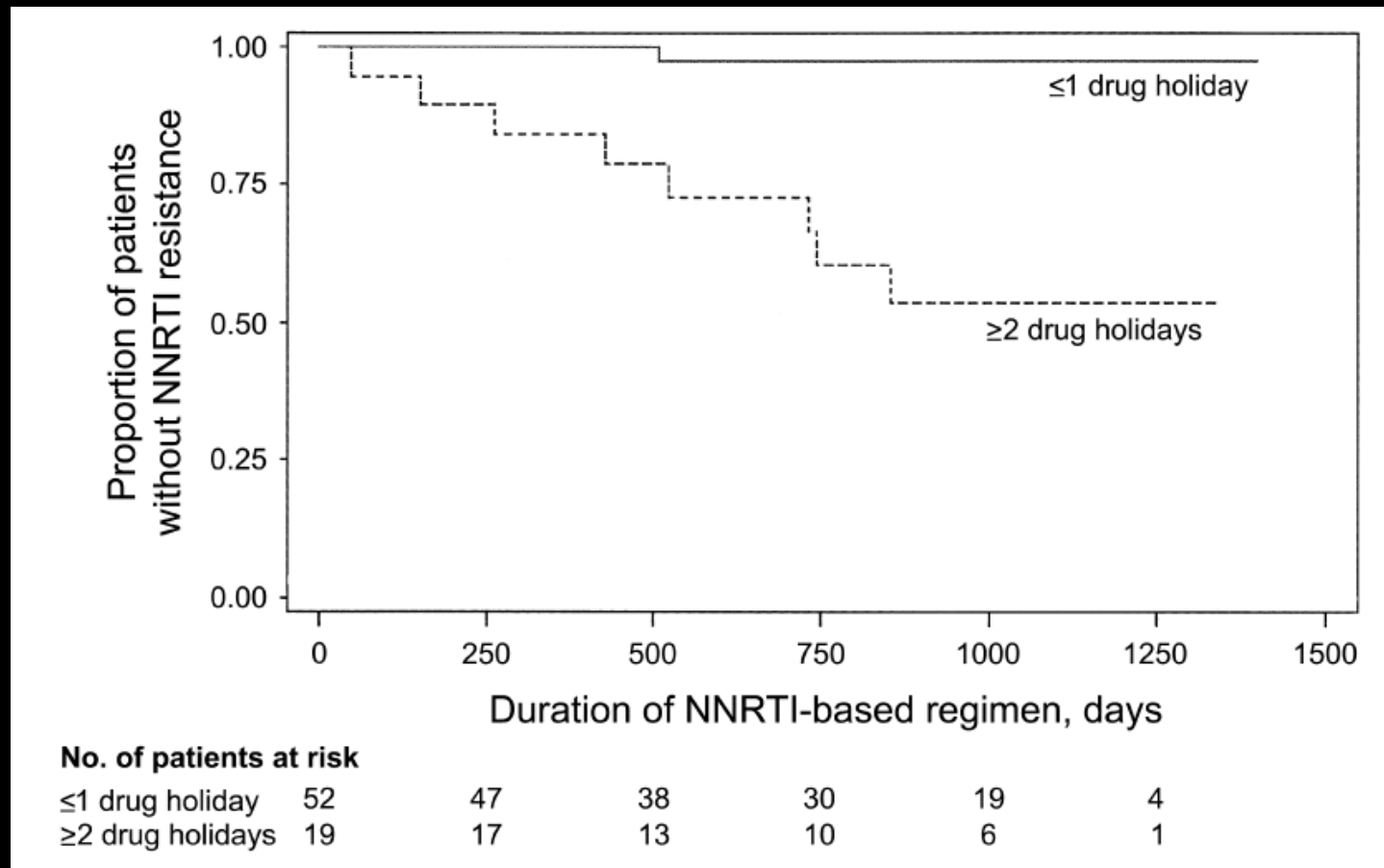


# Genetic Barrier to Antiretroviral Resistance

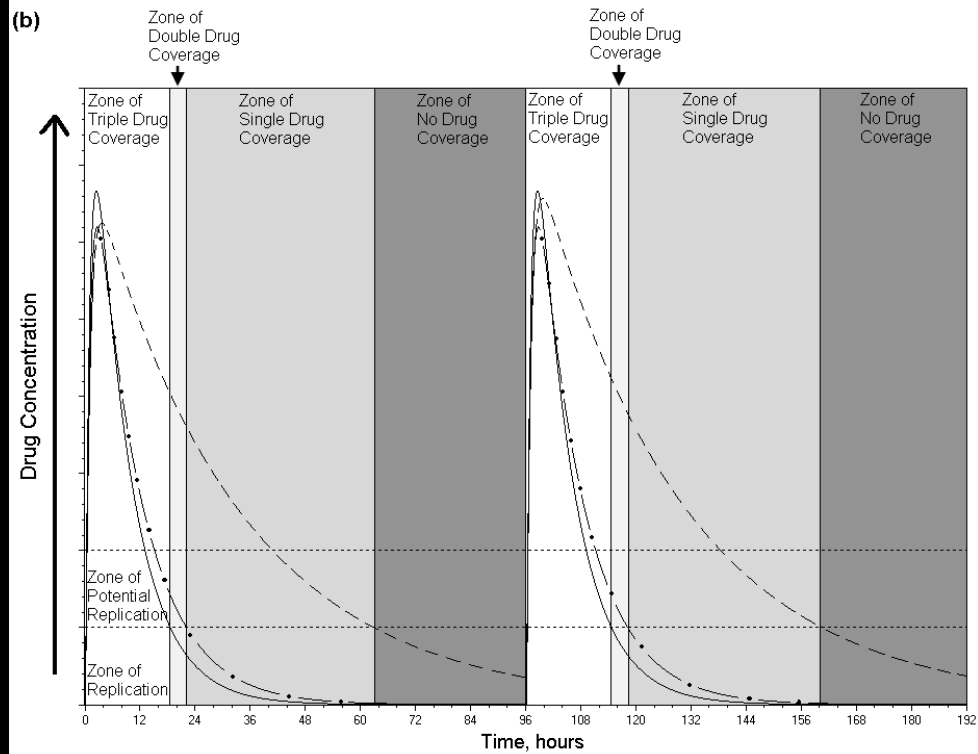
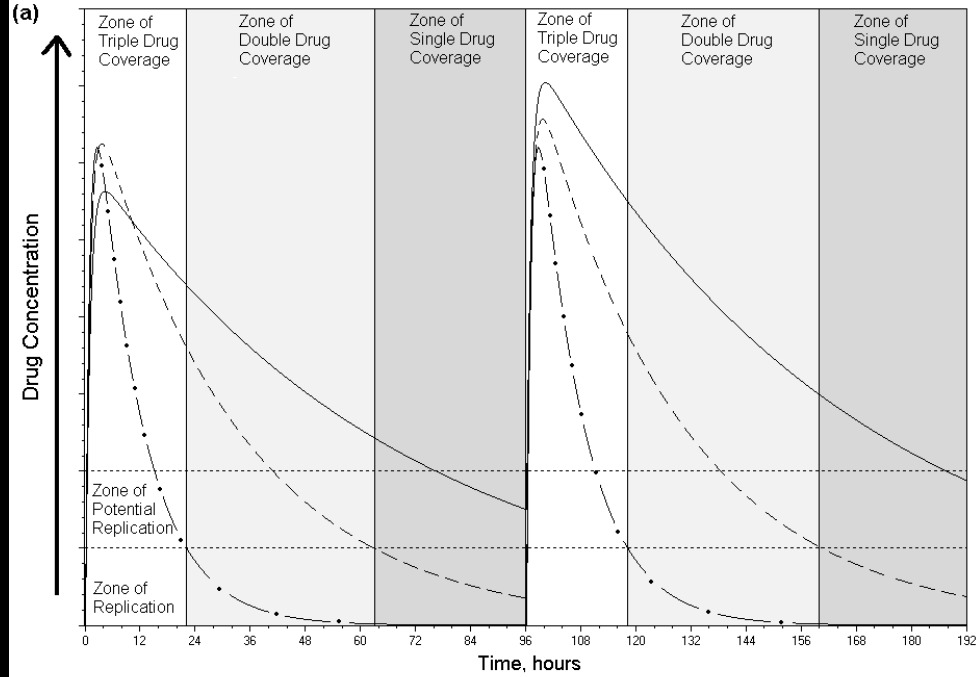
- Definition: the number of viral mutations required to overcome drug-selective pressure\*
- The lower the genetic barrier to resistance the greater the likelihood (rate) of developing resistance during viremia
- Low-barrier antiretroviral medications
  - A single mutation leads to high-level resistance
    - NNRTIs (efavirenz and nevirapine), NRTIs (lamivudine and emtricitabine), enfuvirtide, and raltegravir
- Moderate-barrier medications
  - Requires several mutations to impact potency
    - Etravirine, non-cytidine analog NRTIs, Non-boosted PIs, and some boosted PIs
- High-barrier medications
  - Require several to many mutations to effect potency
    - Some boosted PIs (darunavir, tipranavir)

# 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

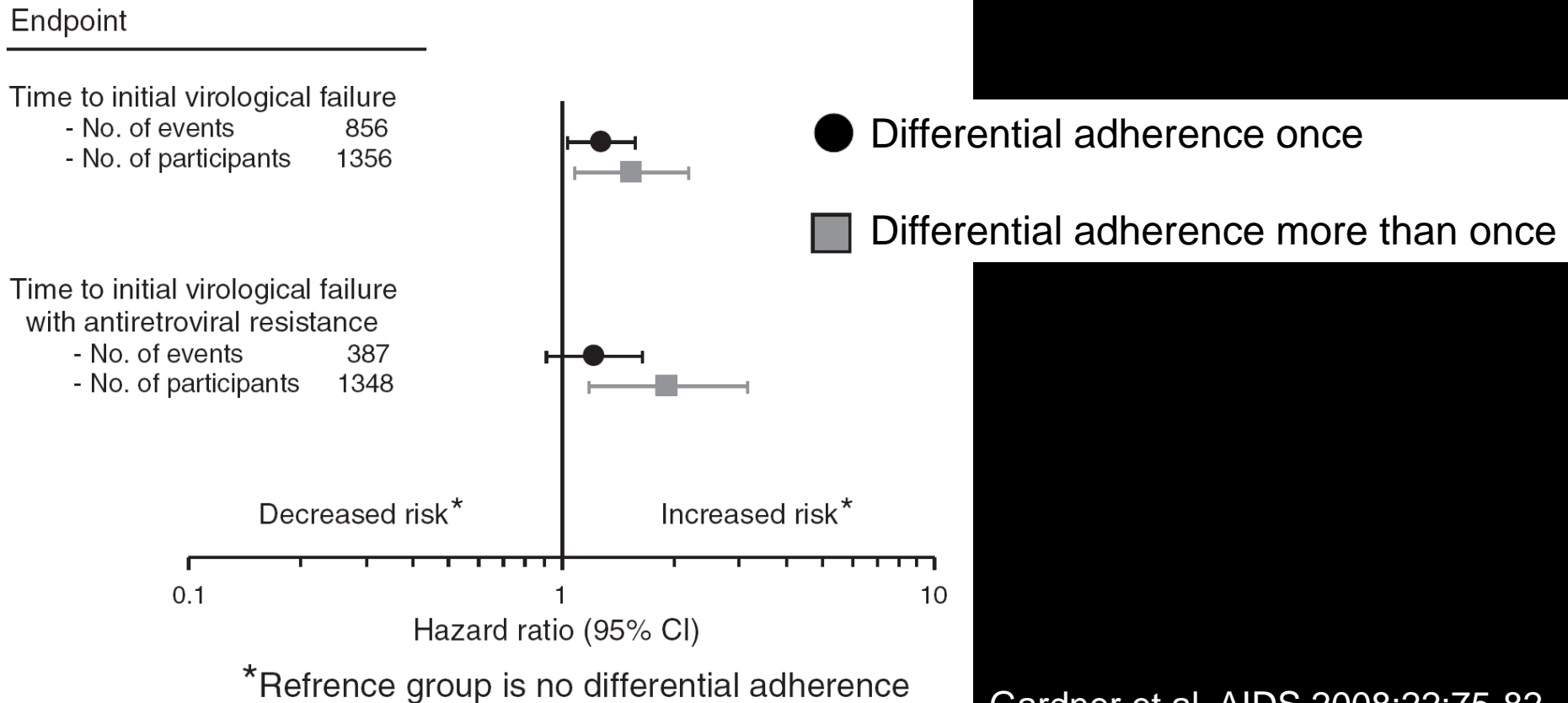




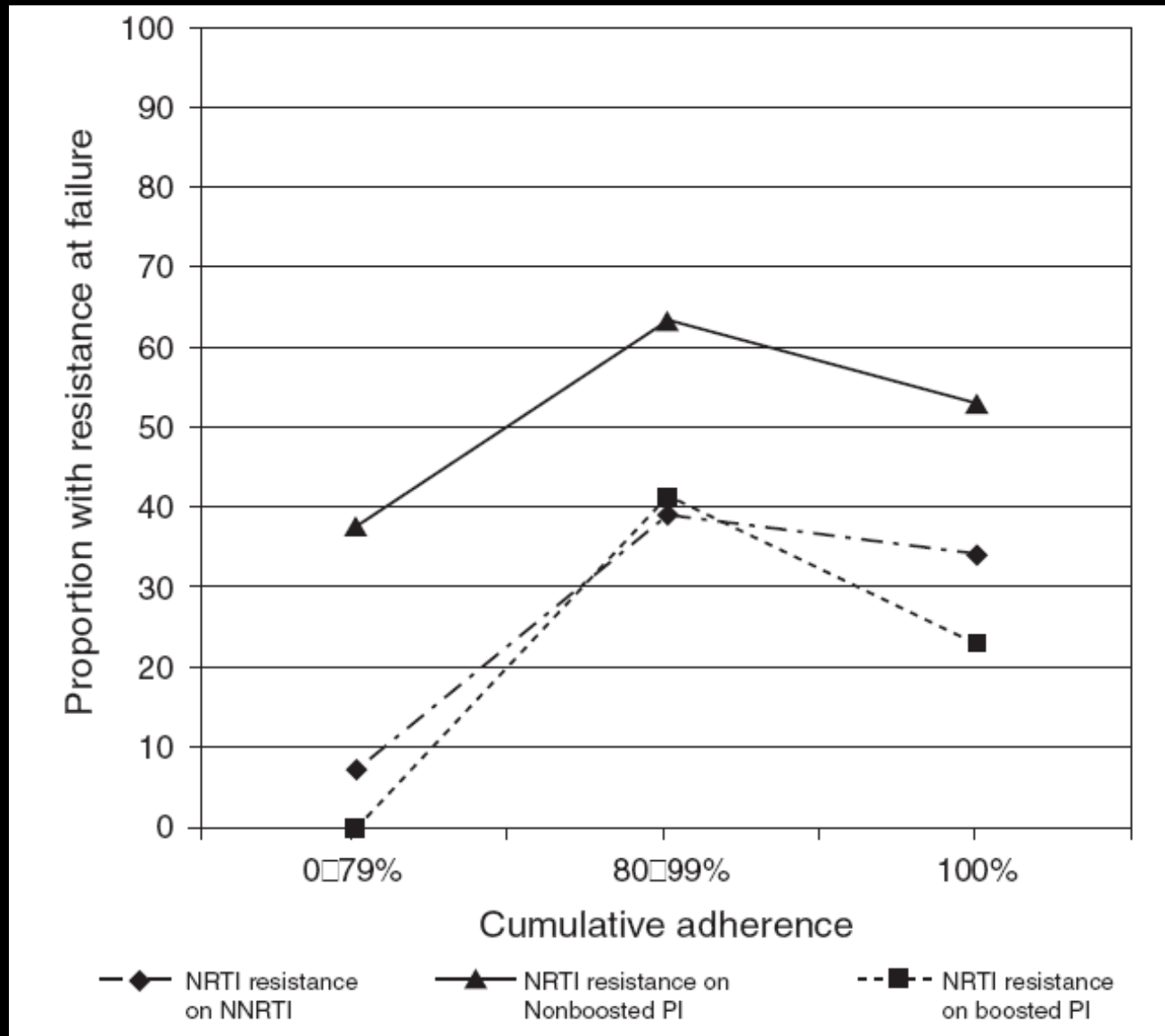


# Differential Adherence

- 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



# Protection by Third Regimen Component



# Implications For Substance Users

# Non-Individual (non-host) Factors

- Potency, replicative capacity, and resistance barrier are drug and virus specific factors
  - Not host specific
  - The same is true for ‘other regimen components’
- These factors are important in substance users because of
  - Access to care and therapy
  - Receipt of (and quality of) therapy
  - Adherence to therapy

# IDU are Less Likely to Receive HAART

- In Brazil a nationwide study of access to therapy in AIDS patients was performed over 7 years (2000 – 2006):
  - 12,231 IDU were compared to 16,195 MSM
  - 24% of IDU vs. 31% of MSM ever received HAART
  - Adjusted mortality was 77% higher for IDU
  - Within IDU, nonwhite ethnicity was associated with a 32% increased risk of mortality

# Resistance comes from Poor Adherence

- Substance Abuse and Resistance
  - In British Columbia, the hazard of failing with any key drug resistance mutation was higher in IDUs
    - Multivariate HR = 1.22 (1.04 – 1.71), p =0.23
      - No longer associated when adjusted for adherence
        - » Harrigan JID 2005;191:339-47.

# Poor Adherence is More Common in IDU

- Adherence is lower in injection drug users
  - 220 (54%) of 407 IDU in a British Columbia cohort had <95% adherence
    - » Fielden JIAPAC 2008;7:238-44.
- Adherence is lower in alcohol users
  - OR for good adherence in alcohol users estimated at 0.55 to 0.65 (35 – 45% reduction in odds of good adherence) compared to non-users
    - » Hendershot JAIDS 2009;52:180-202.

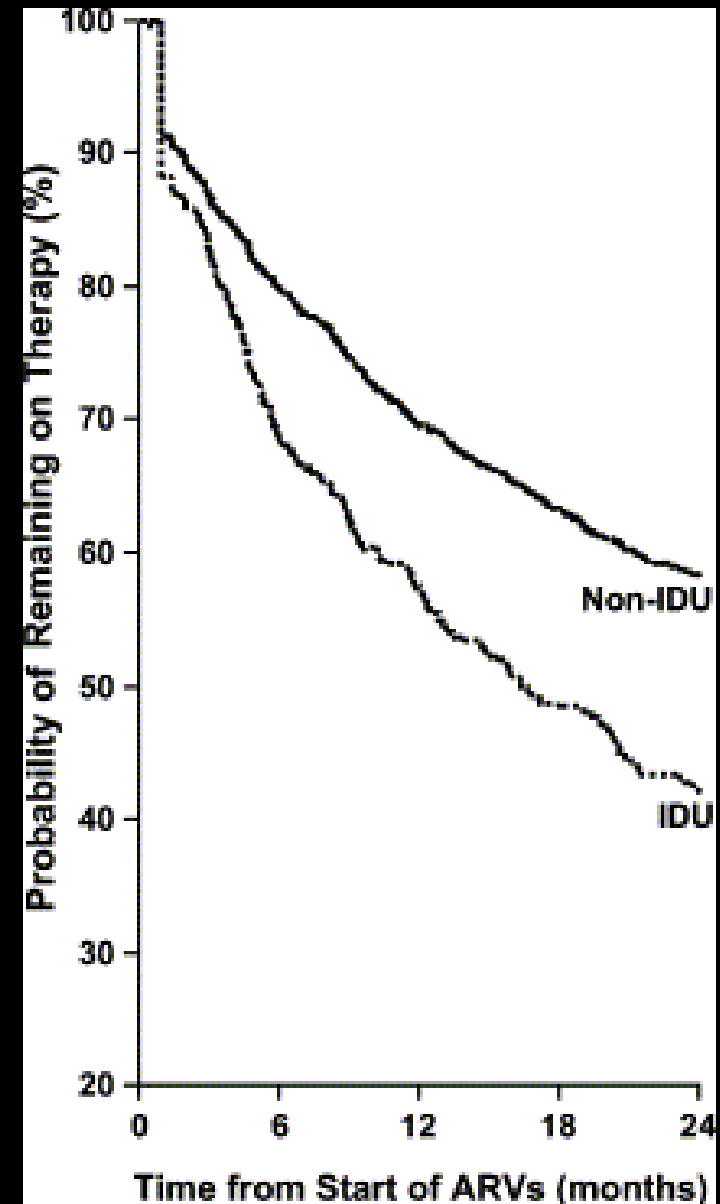


# Differential Drug Exposure

- Patterns of Antiretroviral Adherence
  - Differential Adherence
    - No association between substance use and differential adherence in a clinic cohort
      - » Gardner JAIDS 2005;40:295-300.
    - No association between IDU as HIV-risk factor and differential adherence in a clinical trial
      - » Gardner AIDS 2008;22:75-82.
  - But studies thus far are limited

# Persistence with Therapy is Lower in IDU

- Gaps in therapy (persistence)
  - In British Columbia over 1 year:
    - 43% of 359 IDU had a treatment gap  $\geq 3$  months
      - Compared to 30% of 1063 non-IDU ( $p < 0.001$ )
    - aHR = 1.4 (1.2 - 1.7)



# Pharmacokinetic Interactions

- Methadone had PK interactions with multiple antiretroviral Medications
  - Methadone levels are decreased substantially by NNRTIs
    - Could lead to gaps in ART or differential adherence
  - However, there is generally no effect on the ART components

# Conclusions

- Access to and receipt of ART is of critical importance in substance abusing populations
- Antiretroviral resistance develops mostly as a result of poor adherence
- Factors specific to resistance include:
  - Patterns of Adherence
    - Gaps in therapy
    - Differential Adherence
  - Persistence with therapy
  - Drug-Drug interactions
- Adherence interventions should integrate these concepts into their design when possible

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Thank You