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

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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

Gardner EM. AIDS 2009;23:1035-46
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

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

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

![Graph showing the proportion of patients without NNRTI resistance over the duration of NNRTI-based regimen, with a comparison between ≤1 drug holiday and ≥2 drug holidays.](image)

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

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

Endpoint

Time to initial virological failure
- No. of events 856
- No. of participants 1356

Time to initial virological failure with antiretroviral resistance
- No. of events 387
- No. of participants 1348

*Reference group is no differential adherence
Protection by Third Regimen Component

![Graph showing the proportion of resistance at failure with varying cumulative adherence.](image)

- NRTI resistance on NNRTI
- NRTI resistance on Nonboosted PI
- NRTI resistance on boosted PI

Gardner AIDS 2010, 24:395–403
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

Malta JAIDS 2009;52:629-35.
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
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
Differential Drug Exposure

• Patterns of Antiretroviral Adherence
  – Differential Adherence
    • No association between substance use and differential adherence in a clinic cohort
    • No association between IDU as HIV-risk factor and differential adherence in a clinical trial

• 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 ≥ 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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