Paradoxes HIV Antiretroviral Adherence and Resistance

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Background

• The prevalence of ARV drug resistance is rising
• Nonadherence is widely viewed as a risk factor for drug resistance
• The relationship between adherence and drug resistance is not well characterized
Outline

• The bell shaped adherence-resistance curve
• Reshaping the adherence-resistance curve
• Matching regimens, resistance and population-specific adherence
• Clinical implications of a reshaped curve
• Global priorities to prevent drug resistance
Bell-shaped Adherence and Resistance Curve

- Increasing probability of selecting mutation
- Inadequate Drug Pressure To Select Resistant Virus
- Complete Viral Suppression
- Drug Pressure Selects Resistant Virus
- Increasing Adherence
Vanhove, Schapiro, Winters, Merigan, Blaschke

- Randomized controlled trial of
  - AZT/NVP vs. AZT/DDI vs AZT/NVP/DDI
- Virus isolated at 6 months in 5/24 patients on AZT/NVP/DDI
- 5/5 had NVP phenotypic resistance
  - 4/5 were nonadherent defined by:
    ≥1 reported missed dose over 6 months
TB Threat: Not Taking The Medicine
Partly Cured Patients Are Deadliest Carriers

By LISA BELKIN

The fight against the ominous increase in tuberculosis cases in the metropolitan region comes down to one seemingly simple problem: how to get people to take their medicine.

Elsewhere in the United States doctors have experimented with bribery. In Denver, for example, they have offered free cans of beer to patients who keep their clinic appointments. Denver and other cities have also resorted to sending a social worker to every patient’s house every day to watch them swallow their pills.

But those cities do not have a problem the size of New York’s. There were 3,520 new cases of tuberculosis diagnosed here last year, a 38 percent increase over the 2,545 cases in 1989 and a rate for the city’s
Sontag and Richardson
Doctors withhold HIV pill regimen from some

New York Times
March 2, 1997:A1
Leading Views on Adherence and Resistance in Resource-Poor Settings

Will “widespread, unregulated access to antiretroviral drugs in sub-Saharan Africa, lead to the rapid emergence of drug resistant viral strains, spelling doom for the individual, curtailing future treatment options, and [leading] to transmission of resistant virus?”

“It is entirely unclear what effect [expanding antiretroviral therapy] will have on the many millions of people in developing countries already infected with HIV. Making anti-AIDS drug more widely available is not likely to be sufficient to improve the situation drastically. If treatments are not adhered to consistently and correctly, there could be disastrous consequences both for individuals on antiretroviral therapy and for the HIV epidemic as a whole.”

“Preventing antiretroviral anarchy in sub-Saharan Africa”

“First, Do No Harm”
Popp and Fischer AIDS 2002:16:666
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• Global priorities to prevent drug resistance
Cross-sectional Adherence and Resistance
Bangsberg DR, et al. AIDS. 2000:14:357

*Primary Drug Resistant Mutation  IAS-USA
Cross-sectional Adherence and Resistance
Bangsberg DR, et al. AIDS. 2000:14:357

*Primary Drug Resistant Mutation  IAS-USA
Cross-sectional Adherence and Resistance
JC Walsh, K Hertogs, BG Gazzard JAIDS 2002

Correlation = 0.59
p = 0.001
Genotypic Resistance is Less Frequent in Subjects with Poor Adherence

AA Howard, JH Arnsten, MN Gourevitch, P McKenna, K Hertogs, EE Schoenbaum
IDSA #460 2002
Self Reported Adherence and Resistance
Gallego et al AIDS 2001:15:1701

- 87 Patients first virologic rebound on IDV
- >90% self reported adherence
  - 51% reverse transcriptase mutation
  - 27% protease mutation
- <90% self reported adherence
  - 0% reverse transcriptase mutation
  - 0% protease mutation
Adherence and Prospective Accumulation of Drug Resistance Mutations in The REACH Cohort

>7 mo HAART w/o change in regimen

>1mo HAART

Genotype #1
VL >50 copies

6 mo HAART

≥3 mo pill count

Genotype #2
VL >50 copies

Outcome:

# IAS-USA primary or secondary drug resistant mutations at Genotype #2 not present at Genotype #1

Bangsberg et al AIDS 2003:17:1325
Proportion VL>50 copies/ml by Adherence Quintile
REACH Cohort n=148

p=<0.0001

Bangsberg et al AIDS 2003:17:1325
New Drug Resistance Mutations Over 6 Months in by Adherence Quintile in Viremic Patients
REACH Cohort n=57

p=0.0002

Bangsberg et al AIDS 2003:17:1325
Resistant Virus Requires Drug Pressure Because It Is Less Fit

SG Deeks et al NEJM 344:472-480
Constructing The Adherence-Resistance Curve
DRM Over 12 Months

Bangsberg et al JID in press
Constructing The Adherence-Resistance Curve
DRM Over 12 Months and VL<50

Bangsberg et al JID in press
Constructing The Adherence-Resistance Curve
DRM Over 12 Months and VL<50 Combined

Bangsberg et al JID in press
Constructing The Adherence-Resistance Curve DRM Over 12 Months and VL<50 Combined

Bangsberg et al JID in press
Abbott 863: Probability of Nelfinavir Resistance by Adherence

Adapted from King et al., 2nd IAS (2003), #798
What About More Potent Regimens or a Treatment Naïve Population?
Partially vs Fully Suppressive Regimens

Bangsberg et al JID in press
**Partially vs Fully Suppressive Regimens**

![Graph showing adherence vs viremic DRM rate](image)

- **Legend:**
  - Green: VL > 50
  - Pink: Viremic DRM Rate
  - Yellow: DRM Rate
  - Gray: 95% VL < 50

*Bangsberg et al JID in press*
Partially vs Fully Suppressive Regimens

![Graph showing adherence and viral load](Bangsberg et al JID in press)
Why NNRTI Might Have A Different Adherence-Resistance Relationship

- NNRTI potent and exert high selective pressure
- NNRTI act distant to the active site – little impact on fitness
- NNRTI resistance seen with single dose therapy
Hypothesized Resistance Risk by Adherence and Regimen Class

- Single PI
- Boosted PI

Percent Adherence

Resistance Risk
Hypothesized Resistance Risk by Adherence and Regimen Class
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Leading Views on Adherence and Resistance in Resource-Poor Settings

Africans “don’t know what Western time is,” and “do not know what you are talking about,” when asked to take drugs at specific times.

Andrew Natsios  USAID Administrator
Adherence to HIV Therapy in the Industrialized North

San Francisco 67%
Bangsberg AIDS 2000

Pittsburgh 74%
Paterson Annals Int Med 2000

Los Angeles 63%
Liu Annals Int Med 2001

New York City 57%
Arnsten CID 2001

Hartford 53%
McNabb CID 2001

Philadelphia 79%
Gross AIDS 2001
Adherence in Patients Purchasing Generic D4T/3TC/NVP in Kampala, Uganda
N=36

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<tr>
<th>Method</th>
<th>Adherence</th>
<th>(SD)</th>
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<tr>
<td>MEMS</td>
<td>93%</td>
<td>16%</td>
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<tr>
<td>Unannounced Pill Count</td>
<td>92%</td>
<td>16%</td>
</tr>
<tr>
<td>Self Report</td>
<td>94%</td>
<td>16%</td>
</tr>
</tbody>
</table>

Oyugi et al *JAIDS* (in press)
Adherence Studies in Resource Constrained Settings

- Orrel C, Bangsberg, Badri, Wood. Adherence is not a barrier to successful antiretroviral therapy in South Africa. AIDS 2003
- Leon MP Niccolal L Determining risk factors associated with nonadherence in HIV patients in Costa Rica IAS 2003 #675
- May SB, Cardoso GCP, Costa ER, Barroso PF HUCFF High adherence in a resource poor setting in Banzil IAS 2003 #657
Africans Outdo U.S. Patients
In Following AIDS Therapy

By DONALD G. MCNEIL Jr.

Contradicting long-held prejudices that have clouded the campaign to bring AIDS drugs to millions of people in Africa, evidence is emerging that AIDS patients there are better at following their pill regimens than Americans are.

Some doctors, politicians and pharmaceutical executives have argued that it is unsafe to send millions of doses of antiretroviral drugs to Africa, for fear that incomplete pill-taking will speed the mutation of drug-resistant strains that could spread around the world.

The danger already exists: nearly 10 percent of all new HIV infections in Europe are resistant to at least one drug.

For Africa, the issue is particularly touchy because it is tinged with racism. In 2001, for example there was an outcry when the director of the United States Agency for International Development said that AIDS drugs "wouldn't work" in Africa because many Africans don't use clocks and "don't know what Western time is."

Now surveys done in Botswana, Uganda, Senegal and South Africa have found that on average, AIDS patients take about 90 percent of their medicine. The average figure in the United States is 70 percent, and it is worse among subgroups like the homeless and drug abusers.

Compliance has become easier because drugmakers from India and elsewhere are beginning to make triple-therapy cocktails that come in as few as two pills a day. These are not available in the United States yet because of patent problems — no Western company makes all three drugs for an ideal cocktail.

After nearly a decade of watching Africans die because AIDS drugs cost $10,000 or more a year per patient, rich nations began pledging aid after generic competition in 2001 drove prices down to about $300 a year. Last week the World Trade Organization agreed to alter its rules to give poor nations more access to lifesaving medicines.

But as with any epidemic moving...
• 34 yo policeman
• Salary $60/month
• Therapy $30/month
• HIV+ wife
• Lost one child
• CD4 50 to 97
• VL 750,000 to <400
• Adherence 100%
Triomune

D4T/3TC/Nevirapine
27 USD per month
Matching Regimen, Resistance and Population-Specific Adherence

San Francisco  Kampala
Matching Regimen, Resistance and Population-Specific Adherence

Bangsberg et al J. Antimicrob Chem; May 2002
Adherence-Resistance Summary

• Better adherence reduces risk of progressing to AIDS and death regardless of the regimen
• To date, most resistance has occurred in highly adherent patients on partially suppressive regimens
• More potent regimens will reduce resistance at all levels of adherence
• NNRTI regimens may lead to resistance at lower levels of adherence than PI regimens
Outline

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Adherence and AIDS-Free Survival

10% Adherence difference = 21% reduction in risk of AIDS

Bangsberg D, et al. AIDS. 2001:15:1181
HIV+ Urban Poor Death Rate: 6% Per Year
REACH Cohort

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<tr>
<th>#</th>
<th>Cause of Death</th>
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<tr>
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<td>Cardiopulmonary arrest Possibly AIDS</td>
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<td>AIDS nephropathy AIDS</td>
<td>27</td>
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<td>COPD Non AIDS</td>
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<td>7</td>
<td>MAC AIDS</td>
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<td>End stage liver disease Non AIDS</td>
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<td>Metastatic Laryngeal Carcinoma Non AIDS</td>
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<td>Myocardial Ischemia Non AIDS</td>
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<td>Bacterial Endocarditis Possibly AIDS</td>
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Riley et al CROI 2003
Outline

• The bell shaped adherence-resistance curve
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• Global priorities to prevent drug resistance
Socioeconomic Ladder

San Francisco

Africa
Leading Views on Adherence and Resistance in Resource-Poor Settings

[In sub-Saharan Africa]….the potential short term gains from reducing individual morbidity and mortality may be far outweighed by the potential for the long term spread of drug resistance…. In developed countries the number of people likely to be poor adherers is relatively small. Treatment of this group is seen as beneficial not only to the individual but also to the wider community because it gives increased protection against spread of infection. In Africa, a higher proportion of patients are likely to fall into the category of potential poor adherers unless resource intensive adherence programmes are available.

Antiretroviral therapy in Africa
<table>
<thead>
<tr>
<th>Name</th>
<th>Department/Institution</th>
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<tr>
<td>Andrew Moss, PhD</td>
<td>UCSF Epi/Biostat</td>
</tr>
<tr>
<td>Joshua Bamberger, MD, MPH</td>
<td>SF Department of Public Health</td>
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<tr>
<td>Edwin Charlebois, MPH, PhD</td>
<td>UCSF EPI Center</td>
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<td>Margaret Chesney, PhD</td>
<td>UCSF Center for AIDS Prevention</td>
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<td>Richard Clark, MPH</td>
<td>UCSF Epi/Biostat</td>
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<td>Steven Deeks, MD</td>
<td>UCSF Positive Health Program</td>
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<td>Robert Grant, MD, MPH</td>
<td>UCSF Gladstone Institute</td>
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<td>Gwen Hammer, PhD</td>
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<td>Rick Hecht, MD</td>
<td>UCSF Positive Health Program</td>
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<td>Mark Holodniy, MD</td>
<td>Palo Alto VA</td>
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<td>Kathleen Nugent Conroy</td>
<td>Stanford School of Medicine</td>
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<td>Travis Porco, PhD</td>
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<tr>
<td>Sharon Perry, PhD</td>
<td>UCSF Epi/biostat</td>
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<td>Elise Riley, PhD</td>
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<td>Marjorie Robertson, PhD</td>
<td>Alcohol Research Group</td>
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<tr>
<td>Lewis Sheiner, MD</td>
<td>UCSF Dept of Pharmacology</td>
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<tr>
<td>Jacqueline Tulsky, MD</td>
<td>UCSF Positive Health Program</td>
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<tr>
<td>Andrew Zolopa, MD</td>
<td>Stanford Positive Care Program</td>
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<td><strong>Funding:</strong></td>
<td>The Doris Duke Charitable Foundation, NIMH, University-Wide AIDS Research Program, UCSF Center for AIDS Research</td>
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Family Treatment Fund

Securing Therapy Today For a Better Tomorrow

Mission

– Provide low cost and effective antiretroviral therapy within an existing infrastructure to families who would not otherwise afford therapy.

Mechanism

– Direct purchase of monthly low cost ARV therapy with a 5 year treatment goal
– Medical care delivered free to patient at the Makerere and Mbarara University HIV Clinics
– One patient initiated on therapy for every $2000 raised
– UCSF overhead as fiscal agent: 6%

Online Tax Deductible Donations

– http: familytreatmentfund.ucsf.edu