Views on ARV Adherence in Promoting Domestic and International Health Disparities

- Misinterpreted relationship between adherence and resistance
- Mistaken views on adherence and poverty
- Misplaced priority on the 95% threshold
Doctors Withhold H.I.V. Pill Regimen From Some

Failure to Follow Rigid Schedule Could Hurt Others, They Fear

By DEBORAH SONTAG and LYNDI RICHARDSON

Tyrese Ross, an 18-year-old who has H.I.V., is street smart but childishly innocent. She does not understand the full impact of the virus that she carries, believing that it requires only a "minor adjustment," in her everyday life. So she often misses doctor's appointments and fails to take medications.

Through her Medicaid coverage, Ms. Ross, who lives in the Bronx, can afford the costly new drugs that might halt her progress toward AIDS. But her doctor will not prescribe them to her. She does not think that Ms. Ross can handle a complex drug-taking regimen, in which missing doses could have serious consequences, making her virus resistant to future treatment.

"I don't trust her ability to stick to a schedule," said Dr. Jeanne Carey, a physician at Beth Israel Medical Center's H.I.V. clinic in Manhattan.

With the early successes of drug cocktails built on a new class of drugs called protease inhibitors, national concern has focused on whether their high cost puts them out of the reach of many AIDS patients. But in New York State, which has the most comprehensive drug assistance program in the nation, everyone is covered for the new AIDS drugs.

But not everyone can get them. And cost is not the deciding factor; doctors are. Since the exacting regimens

Eddie Ramos, a counselor to the homeless, says some H.I.V.-infected addicts cannot keep to the pattern of pill-taking he follows himself.
Bell-shaped Adherence and Resistance Curve

- Increasing Adherence
- Complete Viral Suppression
- Inadequate Drug Pressure To Select Resistant Virus
- Drug Pressure Selects Resistant Virus

Increasing probability of selecting mutation
Vanhoue, 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 1990 and a rate for the city's
Cross-sectional Adherence and Resistance
Bangsberg DR, et al. AIDS. 2000:14:357

Pill count percent adherence vs. Log_{10} HIV RNA copy numbers

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

![Graph showing relationship between pill count percent adherence and Log10 HIV RNA copy numbers. Points are color-coded: green for Sensitive and orange for Resistant. The graph includes a note indicating *Primary Drug Resistant Mutation IAS-USA.*]
Correlation = 0.59
p = 0.001
Adherence and Prospective Accumulation of Drug Resistance Mutations in The REACH Cohort

>7 mo HAART w/o change in regimen

>1 mo 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
New PI Drug Resistance Mutations/6mo in Patients with VL>50 on Single PI Therapy by Adherence

- PI total: N=44, p<0.0001
- PI primary: N=44, p<0.0001
- PI secondary: N=44, p=0.03

Colors represent adherence levels:
- 0-39%
- 40-58%
- 59-75%
- 76-87%
- 88-100%
Proportion VL>50 copies/ml by Adherence Quintile
n=148

Adherence Quintile

- 0-41%
- 42-57%
- 58-78%
- 79-91%
- 92-100%

p=<0.0001

Bangsberg et al AIDS 2003:17:1325
Constructing The Adherence-Resistance Curve
DRM Over 12 Months

Adapted from Bangsberg et al JID 2004:190:162-165
Constructing The Adherence-Resistance Curve
DRM Over 12 Months and VL<50

Adapted from Bangsberg et al JID 2004:190:162-165
Constructing The Adherence-Resistance Curve
DRM Over 12 Months and VL<50 Combined

Adapted from Bangsberg et al JID 2004:190:162-165
Constructing The Adherence-Resistance Curve
DRM Over 12 Months and VL<50 Combined

Adapted from Bangsberg et al JID 2004:190:162-165
Abbott 863: Probability of Nelfinavir Resistance by Adherence

Adapted from King et al., 2nd IAS (2003), #798
Partially vs Fully Suppressive Regimens

Bangsberg et al JID June 15, 2004
Partially vs Fully Suppressive Regimens

Bangsberg et al JID June 15, 2004
Partially vs Fully Suppressive Regimens

Bangsberg et al JID June 15, 2004
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
Resistance Risk by Adherence and Regimen Class

Views on ARV Adherence in Promoting Domestic and International Health Disparities

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- Mistaken views on adherence and poverty
- Misplaced priority on the 95% threshold
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
[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 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**
Warren Stevens, Steve Kaye, Tumani Corrah BMJ 2004;328:280-282
## Adherence to HIV Therapy in the Industrialized North

<table>
<thead>
<tr>
<th>Location</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>San Francisco</td>
<td>67%</td>
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<tr>
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*San Francisco: Bangsberg AIDS 2000*

*Pittsburgh: Paterson Annals Int Med 2000*

*Los Angeles: Liu Annals Int Med 2001*

*New York City: Arnsten CID 2001*

*Hartford: McNabb CID 2001*

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

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

Oyugi et al *JAIDS* 2004 36:1100-1102
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 Bazil IAS 2003 #657
Africans Outdo U.S. Patients
In Following AIDS Therapy

By DONALD G. MCEIL 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 H.I.V. 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 80 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 life-saving medicines.

But as with any epidemic moving...
Matching Regimen, Resistance and Adherence Distribution in Kampala
Laurent et al  Effectiveness and safety of a generic fixed-dose combination of nevirapine, stavudine, and lamivudine in HIV-1-infected adults in Cameroon: open-label multicentre trial. Lancet. 2004 Jul 3;364(9428):29-34

24 Week Outcomes

VL <400 90%

# resistance mutations 7 per 100 person years

Self reported adherence 99%

Survival 85%
Socioeconomic Ladder

San Francisco

Africa
Views on ARV Adherence in Promoting Domestic and International Health Disparities

• Misinterpreted relationship between adherence and resistance
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MEMS Adherence and Incomplete Viral Suppression

## Adherence to HIV Therapy in the Industrialized North

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*References:
- Bangsberg AIDS 2000
- Paterson Annals Int Med 2000
- Liu Annals Int Med 2001
- Arnsten CID 2001
- McNabb CID 2001
- Gross AIDS 2001*
Adherence and AIDS-Free Survival
10% Adherence difference = 21% reduction in risk of AIDS

Bangsberg D, et al. AIDS. 2001:15:1181
Time to All-Cause Mortality by CD4 Cell Count and 75% Adherence

> 75% Adherent

< 75% Adherent

Probability of Survival (%)

CD4 Cell Count
- ≥ 350
- 300 - 349
- 250 - 299
- 200 - 249
- < 200

Log-rank
All p > 0.1

Time from Start of ARVs (months)

Is Average Adherence Enough?
Bangsberg and Deeks JGIM 2004;17:812-13


- Unintentional injury
- Cancer
- Heart disease
- Suicide
- HIV infection
- Homicide
- Chronic liver disease
- Stroke
- Diabetes

Note: For comparison with data for 1999-2000, data for 1987-1998 were modified to account for ICD-10 rules instead of ICD-9 rules.

<table>
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<th>#</th>
<th>Cause of Death</th>
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Riley et al. JAIDS in press
# Prevalence of ARV Resistance

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<tr>
<th>ARV Class</th>
<th>SF Urban Poor</th>
<th>Nationally</th>
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<tr>
<td></td>
<td>n=301</td>
<td>n=2864</td>
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<tr>
<td>Any ARV</td>
<td>27%</td>
<td>50%</td>
</tr>
<tr>
<td>PI</td>
<td>18%</td>
<td>26%</td>
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<tr>
<td>NNRTI</td>
<td>8%</td>
<td>16%</td>
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<tr>
<td>RTI</td>
<td>8%</td>
<td>46%</td>
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Summary

• Most resistance has occurred in highly adherent patients on partially suppressive regimens
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• Potent regimens reduce resistance at all levels of adherence
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• Poverty is not an international risk factor for incomplete adherence
Summary

- Most resistance has occurred in highly adherent patients on partially suppressive regimens
- Potent regimens reduce resistance at all levels of adherence
- Poverty is not an international risk factor for incomplete adherence
- Average adherence is sufficient to impact morbidity and mortality
Andrew Moss, PhD  
Joshua Bamberger, MD, MPH  
Tom Coates, PhD  
Edwin Charlebois, MPH, PhD  
Margaret Chesney, PhD  
Richard Clark, MPH  
Steven Deeks, MD  
Robert Grant, MD, MPH  
Reena Gupta  
Gwen Hammer, PhD  
Rick Hecht, MD  
Mark Holodniy, MD  
Kathleen Nugent Conroy  
Travis Porco, PhD  
Sharon Perry, PhD  
Elise Riley, PhD  
Marjorie Robertson, PhD  
Lewis Sheiner, MD  
Jacqueline Tulsky, MD  
Andrew Zolopa, MD  

UCSF Epi/Biostat  
SF Department of Public Health  
UCLA  
UCSF EPI Center  
UCSF Center for AIDS Prevention  
UCSF Epi/Biostat  
UCSF Positive Health Program  
UCSF Gladstone Institute  
Harvard Medical School  
UCSF EPI Center  
UCSF Positive Health Program  
Palo Alto VA  
Stanford School of Medicine  
SF Department of Public Health  
UCSF Epi/biostat  
UCSF EPI Center  
Alcohol Research Group  
UCSF Dept of Pharmacology  
UCSF Positive Health Program  
Stanford Positive Care Program  

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