Antiretroviral Therapy Administration and Adherence

David Bangsberg, MD, MPH

Associate Professor of Medicine
Epidemiology and Prevention Interventions Center
Division of Infectious Diseases
The Positive Health Program
San Francisco General Hospital
AIDS Research Institute, UCSF

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April, 2007
Doctors Withhold H.I.V. Pill Regimen From Some

Failure to Follow Rigid Schedule Could Hurt Others, They Fear

BY DEBORAH SONTAG and LYNDA RICHARDSON

Tyeshia Ross, an 18-year-old who has H.I.V., is street smart but childishly innocent. She does not understand the full import 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 regimen requires two to four drugs daily, doctors often decide that their patients simply cannot manage the pill-taking regimen.

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.
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?”

Bell-shaped Adherence and Resistance Curve

- Increasing probability of selecting mutation
- Inadequate Drug Pressure To Select Resistant Virus
- Drug Pressure Selects Resistant Virus
- Complete Viral Suppression

Increasing Adherence
MEMS Adherence and Viral Suppression

Ritonavir Boosted PIs Lead to Better Viral Suppression at Moderate Adherence Levels

Viral Suppression <50 Copies for RTV Boosted and Unboosted PI

Bangsberg et al Int Conference on Adherence to HIV Treatment 2007
NNRTI Lead to Better Viral Suppression (<400 copies/ml) than Unboosted PIs at Moderate Electronic Medication Monitor Adherence

n=65

Bangsberg CID 2006:43:939-41
Prevalence of NNRTI and PI Resistance by Adherence

Bangsberg AIDS 2006 20:223-232

N=107

% Resistant

11-53% 54-79% 80-94% 95-100%

Adherence Quartile
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

Replicative Capacity

Patient Plasma

Purify Viral RNA

AAAA
AAAA
AAAA

RT-PCR

HIV PR and RT Sequences

Pool of Patient-Derived Recombinant Viruses Containing Luciferase

Transfection

PR-RT
Luciferase
A-MLV env
Luciferase Activity (Replication) of Sensitive “Wild-Type” Virus Decreases at Higher Drug Levels
Replication of Sensitive vs. Resistant Virus

Drug concentration, nM

Luciferase

WT Control (NL4-3)

Resistant (pt-derived)
Sensitive HIV is More Fit than Resistant HIV at Lower Drug Concentrations and Becomes Less Fit at Higher Drug Concentration

Comparing Resistant Subject Isolates With Sensitive Reference Strain

Resistant: Wildtype Replication Ratio

Methods

Derive average resistant/WT fitness curve

Convert adherence adjusted predicted in vivo concentrations to comparable in vitro concentrations
Level of adherence above which the resistant virus is more fit than the wild-type virus is ~ 2% for efavirenz and nevirapine and ~ 85% for nelfinavir.
[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.
Adherence to HIV Therapy in the Industrialized North

<table>
<thead>
<tr>
<th>City</th>
<th>Percentage</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>San Francisco</td>
<td>67%</td>
<td>Bangsberg AIDS 2000</td>
</tr>
<tr>
<td>Pittsburgh</td>
<td>74%</td>
<td>Paterson Annals Int Med 2000</td>
</tr>
<tr>
<td>Los Angeles</td>
<td>63%</td>
<td>Liu Annals Int Med 2001</td>
</tr>
<tr>
<td>New York City</td>
<td>57%</td>
<td>Arnsten CID 2001</td>
</tr>
<tr>
<td>Hartford</td>
<td>53%</td>
<td>McNabb CID 2001</td>
</tr>
<tr>
<td>Philadelphia</td>
<td>79%</td>
<td>Gross AIDS 2001</td>
</tr>
</tbody>
</table>
Mbarara, Uganda
Adherence in Patients Purchasing Generic D4T/3TC/NVP in Uganda
N=36

<table>
<thead>
<tr>
<th></th>
<th>MEMS</th>
<th>Unannounced Pill Count</th>
<th>Self Report</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>93%</td>
<td>92%</td>
<td>94%</td>
</tr>
<tr>
<td>(SD 16%)</td>
<td>(SD 16%)</td>
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<td>(SD 16%)</td>
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Oyugi et al *JAIDS* 2004 36:1100-1102
Meta-Analysis of Barriers to Adherence in Africa and North America
Mills and Bangsberg JAMA 2006:296:679-690

• Systematic review of adherence
  – 28,689 patients in 228 studies
    • North America
    • Brazil, Uganda, Cote d’Ivoire, South Africa, Malawi, Bostwana, Costa Rica, Romania
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 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 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 life-saving medicines.

But as with any epidemic moving...
Adherence Declines Over Time in A Resource-Limited Setting
Oyugi AIDS (in press)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean (SD) 0-12 Week</th>
<th>Mean (SD) 13-24 Week</th>
<th>P-value</th>
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<tbody>
<tr>
<td>3-day SR</td>
<td>0.93 ± 0.179</td>
<td>0.91 ± 0.216</td>
<td>0.04</td>
</tr>
<tr>
<td>30-day VAS</td>
<td>0.95 ± 0.101</td>
<td>0.90 ± 0.175</td>
<td>0.008</td>
</tr>
<tr>
<td>PC</td>
<td>0.90 ± 0.164</td>
<td>0.87 ± 0.197</td>
<td>0.002</td>
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<tr>
<td>MEMS</td>
<td>0.91 ± 0.152</td>
<td>0.82 ± 0.271</td>
<td>&lt;0.001</td>
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<tr>
<td>VL ≤400</td>
<td>71 (71/88) 80.7%</td>
<td>70 (70/86) 81.4%</td>
<td>NS</td>
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N=97

VL: Virus Load
Triomune

D4T/3TC/Nevirapine
17 USD per month
Stopping drugs with different half lives

Drug concentration

Zone of potential replication

Last Dose

Day 1

Day 2

MONOTHERAPY

IC_{90}

IC_{50}

S. Taylor et al. 11th CROI Abs 131
Genetic polymorphisms and EFV metabolism


- Homozygous T/T genotype common in African-Americans (20%) than Caucasians (3%)
Genetic polymorphisms and EFV metabolism


- Homozygous T/T genotype common in African-Americans (20%) than Caucasians (3%)
- TT genotype 50% prevalence in Ghana (Klein, Pharm Genomic 2005)
NNRTI Resistance and Treatment Discontinuation
Parienti et al CID 2004:38:1311-6

No. patients at Risk
≤1 drug holiday  52  47  38  30  19  4
>= 2 drug holidays 19  17  13  10  6  1
Patient reported 48 hr treatment interruptions are associated with virologic failure in Uganda
Spacek CID 2006 15:252

- 23% of patients
- 63% due to financial difficulty
- Median duration 30 days
- Association with virologic failure
  - OR 0.2, 95%CI 0.1-0.5
### Frequency and Duration of Treatment

**Interruptions >48hrs over 24 weeks on Self-pay ART**

Oyugi and Bangsberg AIDS (in press)

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<td>±2.9 (S.D)</td>
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Correlates: Financial difficulty securing ARVs and pharmacy stockouts
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Correlates: Financial difficulty securing ARVs and pharmacy stockouts

90% of all missed doses occur during an interruption
MEMS-Defined 48 Hour Treatment Interruptions Predict Resistance to Self-pay ART in Uganda
Oyugi and Bangsberg AIDS (in press)

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<td>&gt;48 hours</td>
<td>8/32 (63%)</td>
<td>0/56 (0%)</td>
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P=0.04
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
How to Take ARVs on Time Rural Uganda Without a Watch: John’s Adherence Story
Maier, Mwebesa, Emenyonu, Pepper, Bangsberg
PLOS 2006

• No education
• Works as a farmer.
• Lives with his brother, sister-in-law, and three nieces in a three room mud-walled house without electricity.
• Owns a lantern, bed, sofa, bike, and a radio, but no watch.
• HIV in April 2005 and started generic D4T/3TC/NVP (Triomune) after disseminated herpes zoster and Kaposi’s sarcoma
• CD4 count of 151
Electronic medication monitor record of time of bottle openings for am and pm doses.
Adherence

- 90% of doses within 10 minutes of 7:20
- 90% of doses within 17 minutes of 7:20 pm
- Overall adherence 98.9%
John’s Adherence: 0-9 and 10-18 months

Initial MEMS assessment (August 2005 to April 2006 (9 months))

Subsequent MEMS assessment (May 2006 to January 2007 (9 months))
Obstacles to Adherence in RLC

• Distance from health center/transport costs
• Stock-outs
• Stigma/disclosure
• Long waiting lines at the clinic
  – “feel rushed in conversations with the doctors because of the other people waiting”
• Adverse effects
Summary

• Most resistance has occurred in highly adherent patients on partially suppressive regimens

• Potent regimens reduce resistance at all levels of adherence

• NNRTI resistance: low adherence and treatment discontinuation

• Internationally: stable drug supply and distribution
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Andrew Moss, PhD
Ed Acosta
Huyen Cao, MD
Tom Coates, PhD
Edwin Charlebois, MPH, PhD
Barry Bredt, PhD
Richard Clark, MPH
Steven Deeks, MD
Nneka Emenyonu
Robert Grant, MD, MPH
Norma Ware, PhD
Gwen Hammer, PhD
Rick Hecht, MD
Mark Holodniy, MD
Jeff Martin, MD
Neil Parkin, PhD
Jennifer Free
Travis Porco, PhD
Irene Andia, MMed
Elise Riley, PhD
Neil Parkin
Richard Harrigan
Andrew Zolopa, MD

UCSF Epi/Biostat
Univ of Alabama
Ca Sate Health Department
UCLA
UCSF EPI Center
UCSF Center for AIDS Prevention
UCSF Epi/Biostat
UCSF Positive Health Program
UCSF Epi Center
UCSF Gladstone Institute
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Palo Alto VA
UCSF Epidemiology
Monogram Bioscience
UCSF Epi Center
SF Department of Public Health
Mbarara University
UCSF EPI Center
Virologic
University of British Columbia
Stanford Positive Care Program

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