Antiretroviral Adherence in sub-Saharan Africa: Acute and Chronic

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Doctors Withhold H.I.V. Pill Regimen From Some

Failure to Follow Rigid Schedule Could Hurt Others, They Fear

By DEBORAH SONTAG
and LYNDIA RICHARDSON

Tyeisha 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 say. Since the existing plans...
[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

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 Sub-Saharan Africa

### Objective Measures

<table>
<thead>
<tr>
<th>Author</th>
<th>Measure</th>
<th>Location</th>
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<tr>
<td>Orrel AIDS 2001</td>
<td>Clinic pill count</td>
<td>S. Africa</td>
<td>91%</td>
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<td>Frick Int J STD AIDS 2001</td>
<td>MEMS</td>
<td>Kenya</td>
<td>93%</td>
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<tr>
<td>Oyugi JAIDS 2004</td>
<td>MEMS Unannounced pill count</td>
<td>Uganda</td>
<td>91-94%</td>
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<td>Oyugi AIDS 2007</td>
<td>MEMS Unannounced pill count</td>
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<tr>
<td>Weidle Lancet 2006</td>
<td>Pharmacy refill</td>
<td>Uganda</td>
<td>97% &gt;95%</td>
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<td>Stringer JAMA 2006</td>
<td>Pharmacy refill</td>
<td>Zambia</td>
<td>1 day late</td>
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<td>Etard Trop Med Hygiene 2007</td>
<td>Pharmacy refill</td>
<td>Senegal</td>
<td>91%</td>
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<td>Nachega AIDS 2010</td>
<td>Pharmacy refill</td>
<td>Southern Africa</td>
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<td>Vrissendorp Eur J Clin Pharm 2007</td>
<td>MEMS</td>
<td>Botswana</td>
<td>85%</td>
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<td>Muller Ped ID 2008</td>
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<td>S. Africa</td>
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<td>Bell JAIDS 2007</td>
<td>MEMS</td>
<td>Malawi</td>
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<td>Muyingo JAIDS 2008</td>
<td>Pharmacy Refil</td>
<td>Uganda</td>
<td>87-95%</td>
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<tr>
<td>Abassa BMC Health Services Res 2008</td>
<td>Clinic based pill count</td>
<td>Uganda</td>
<td>78% people &gt;95%</td>
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<tr>
<td>San Lio CID 2008</td>
<td>Pharmacy refill</td>
<td>Mozambique</td>
<td>72% of people &gt;95%</td>
</tr>
<tr>
<td>Beyene Pharmacoepi 2009</td>
<td>Unannounced pill count</td>
<td>Etiopia</td>
<td>88%</td>
</tr>
</tbody>
</table>
Meta-Analysis of Barriers to Adherence in Africa and North America
Mills et al 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, Botswana, Costa Rica, Romania

Resource-Rich Country Summary
54.7% (95CI: 48.0-61.3%)

Resource-Poor Country Summary
77.1% (95CI:67.3%-85.6%)
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 a mistake to send millions of doses of anti-retroviral 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 seems remote: nearly 16 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 medication. 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...
Modest Decline in Adherence Over Time in MTCTP-Plus Program in Uganda
Byakika-Tusiime et al AIDS Behavior 2009

- 177 participants followed for 6 months with a mean of 11 months prior treatment
  - (75 new starts, 102 on treatment)
- Unannounced pill count adherence 98.3%
- Decline in adherence: each month 0.93 odds of sustaining >95% adherence; p=0.003
Improving Health
Improving Health

Resource Scarcity

Resource Scarcity

A Social Model of Adherence for sub-Saharan Africa
Ware et al PLoS Medicine 2009
A Social Model of Adherence for sub-Saharan Africa
Ware et al PLoS Medicine 2009

Improving Health

Adherence

Resource Scarcity

Relationships as resources to overcome economic obstacles to adherence

Resource Scarcity
Improving Health

Relationships as resources to overcome economic obstacles to adherence

Resource Scarcity

Adherence fulfills responsibility to helpers and preserve relationships as a resource

Resource Scarcity

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Improving Health

Resource Scarcity

Relationships as resources to overcome economic obstacles to adherence

Social Capital

Adherence fulfills responsibility to helpers and preserve relationships as a resource

Resource Scarcity

Presented at the 4th INTEREST Workshop
25-28 May 2010, Maputo Mozambique
A Social Model of Adherence for sub-Saharan Africa
Ware et al PLoS Medicine 2009

Improving Health

Social Structural:
Patterns of Inequality, e.g., stigma, gender inequality

Resource Scarcity

Infrastructural:
Few treatment sites
Distance to care
Cost/Availability of Transportation

Social Capital

Relationships as resources to overcome economic obstacles to adherence

Adherence fulfills responsibility to helpers and preserve relationships as a resource

Resource Scarcity

Cultural:
Religious Beliefs
Respect for Authority
Importance of having children

Individual:
HIV knowledge
Med side effects
Cognitive function
Mental health
Alcohol Use

Presented at the 4th INTEREST Workshop
25-28 May 2010, Maputo Mozambique
Barriers to Adherence in sub-Saharan Africa

• Routine
  – ETOH/substance use
  – Depression
  – Side effects
  – Pill burden/dosing frequency
  – Memory
  – Adolescence

• Priority
  – Transportation to clinic
  – Food security
  – Stock-outs and substitutions
  – Stigma

Priority Adherence Barrier: Transportation

- Cost to pick up medications: 30-50% income
- 40% of missed doses: insufficient funds for transportation.
- Interventions
  - Cash transfer
  - Mobile pharmacy
  - Accompagneur/DOT

Priority Adherence Barrier: Transportation
Cash Transfers Improve Adherence Among Patients Living >20 km from Clinic
Emenyonyu et al CROI 2010
n=149

Unannounced Home Pill Count Adherence
0-6 months 6-12 months

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Intervention</th>
<th>Control</th>
<th>Intervention</th>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Std Dev</td>
<td>Mean</td>
<td>Std Dev</td>
</tr>
<tr>
<td>Adherence</td>
<td>0.83</td>
<td>±0.18</td>
<td>0.88</td>
<td>±0.14</td>
</tr>
<tr>
<td>p=0.07</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(0-6 months)</td>
<td></td>
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Cash Transfer 10,000-15,000 USh (5-7 USD)
Priority Adherence Barrier: Transportation
Cash Transfers Improve Retention in Care
Emenyonyu et al CROI 2010

Loss to follow-up >3 months

Survival Distribution Function

- Intervention

- Control

P=0.05
Priority Adherence Barrier: Food Insecurity

- ARVs increased appetite and intolerable hunger
- ARV side effects exacerbated by hunger
- Participants believed they should skip doses if they could not afford the added nutritional burden
- Give up buying food to cover cost of transportation
- Forgot medication doses while working for long days to secure food.

Ware PLOS Medicine 2009
Weiser SD PLoS One. 2010
Weiser S JAIDS 2003
Hordon AIDS Care. 2007

Presented at the 4th INTEREST Workshop
25-28 May 2010, Maputo Mozambique
Priority Adherence Barrier: Stigma
HIV Stigma and Missed Medications in HIV-Positive People in Five African Countries
Priscilla S. Dlamini AIDS Patient Care STDS. 2009
Stigma, Social Capital, Structural Barriers, and Adherence
Bangsberg and Deeks Ann Int Med 2010

- Stigma
- Social Capital
- Routine Barriers: Medication side effects, Depression, Substance use, Memory
- Structural & economic barriers
- Treatment Adherence
Priority Adherence Barrier: Stock-outs

• 65% of missed doses due pharmacy stock-outs at University of Nigeria Teaching Hospital

Uzochukwu BS, Health Policy Plan. 2009 May;24(3):189-96.
**Priority Adherence Barrier: Stock-outs**  
**Frequency and Duration of Treatment**  
**Interruptions >48hrs over 24 weeks on Self-pay ART**  
Oyugi et al AIDS 2007

<table>
<thead>
<tr>
<th>Interruptions ≥ 48 hours</th>
<th>199 interruptions</th>
<th>62 people (64%)</th>
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<tbody>
<tr>
<td>Mean # interruptions/person</td>
<td>2.0</td>
<td>±2.9 (S.D)</td>
</tr>
<tr>
<td>Mean duration (days) for those who have interruptions</td>
<td>11.5</td>
<td>±9.2 (S.D)</td>
</tr>
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Correlates: Financial difficulty securing ARVs and pharmacy stockouts

90% of all missed doses occur during an interruption  
Most missed doses: cost or non-availability during stock-out
Priority Adherence Barrier: Stock-outs

Frequent Regimen Switches due to Inconsistent Drug Supply among HIV-infected Patients Starting Antiretroviral Therapy in a Rural Ugandan University-based Clinic
Megan McCurdy et al CROI 2010

- 453 participants assessed q3 months after ART initiation
- Median FU=24 months
- 867 total person-years observation

<table>
<thead>
<tr>
<th>Type of ARV Change</th>
<th>Incidence per 100 person-yrs</th>
</tr>
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<tbody>
<tr>
<td>Total Clinical Changes</td>
<td>15</td>
</tr>
<tr>
<td>Total Non-Clinical Changes</td>
<td>125</td>
</tr>
<tr>
<td>Manufacturer only</td>
<td>61</td>
</tr>
<tr>
<td>Pill Burden</td>
<td>59</td>
</tr>
<tr>
<td>Active Component</td>
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</table>
Priority Adherence Barrier: Stock-outs

Frequent Regimen Switches due to Inconsistent Drug Supply among HIV-infected Patients Starting Antiretroviral Therapy in a Rural Ugandan University-based Clinic

Megan McCurdy et al CROI 2010

Total Antiretroviral Therapy Changes

Percent of Study Participants

Time on ARVs (months)

- Orange line: Non-Clinical Change
- Purple line: Clinical Change
At Front Lines, AIDS War Is Falling Apart
Donald McNeil Jr, May 9, 2010

Dinavance Kamukama, 28, front right, with her cousins in Kampala, Uganda. She is on a waiting list for AIDS medication.
Stopping drugs with different half lives

Last Dose

Day 1

Day 2

MONOTHERAPY

Zone of potential replication

Drug concentration

Time (hours)

0 12 24 36 48

IC₉₀ IC₅₀

Presented at the 4th INTEREST Workshop 25-28 May 2010, Maputo Mozambique

S. Taylor et al. 11th CROI Abs 131
Duration of MEMS Defined Treatment Interruption and Probability of NNRTI Virologic Failure
n=72

Estimated 95% confidence interval

Estimated probability of viral control

Longer interval of treatment discontinuation in days

+ Controls
O Cases
Estimated
95% confidence interval
Real-time Adherence Monitoring
Bangsberg and Deeks Annal Int Med 2010
Existing Mobile Network Covers >90% of Ugandan Population

http://www.rent-mobile-phone.com/images/maps/uganda_map.jpg
Perfect adherence: does this patient need a HIV viral load?
MBISS19

96 hour interruption

Missed dose

Maybe a VL in this person when s/he comes to clinic?
48 hour interruption starting yesterday

Missed evening dose 6 days ago

Time to check in with this patient to prevent VL rebound if s/he does not take his/her dose today and device “heartbeat” confirms the device is in working and in range.
Pharmacy Refill Adherence is Better Than CD4 Response as a Surrogate to HIV RNA Monitoring

Detecting VL Rebound
CD4 Monitoring vs Pharmacy Refill Adherence
What is the most important adherence outcome?

• Traditional measures
  – % people who take more than 80, 90 or 95% doses
  – Mean/median adherence

• New measures
  – Frequency of several day interruption
  – Duration of interruption
  – Minimum adherence
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 in Rural Uganda Without a Watch: John’s Adherence Story
Maier et al 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))
Conclusions

• ARV adherence in sub-Saharan Africa is excellent
• Fragile balance of social capital to overcome routine structural and economic barriers to care.
• Stigma neutralizes moderating effects of social capital
• Return of treatment ARV waitlists will have an unpredictable impact on adherence
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