Adherence to HIV Treatment and Prevention

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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 LYNTA RICHARDSON

Tyceisha Ross, 18, 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 regi-

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

Improving Health

Resource Scarcity

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

Improving Health

Resource Scarcity

Relationships as resources to overcome economic obstacles to adherence

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Improving Health

Adherence fulfills responsibility to helpers and preserve relationships as a resource

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Improving Health

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Relationships as resources to overcome economic obstacles to adherence

Social Capital

Adherence fulfills responsibility to helpers and preserve relationships as a resource

Resource Scarcity
Stigma, Social Capital, Structural Barriers, and Adherence in Resource-Limited Settings

Bangsberg and Deeks Ann Int Med 2010
Frequency and Duration of Treatment

Interruptions >48hrs over 24 weeks

Oyugi et al AIDS 2007

<table>
<thead>
<tr>
<th>Interruptions &gt; 48 hours</th>
<th>199 interruptions</th>
<th>62 people (64%)</th>
</tr>
</thead>
<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>
</tbody>
</table>

Interruptions account for 90% of all missed doses
Interruptions Independently Predict Virologic Failure

Adjusted odds ratios of detectable HIV-RNA by categories of total non-covered days and longest interruption 28 days prior to HIV RNA

Genberg et al AIDS 2012

* P ≤ 0.05  ** p ≤ 0.01
Duration of MEMS Defined Treatment Interruption and Probability of NNRTI Virologic Failure


n=72

Estimated Probability and Observed case

Estimated probability of viral control

Longer interval of treatment discontinuation in days
Real-time Adherence Monitoring
Haberer et al AIDS and Behavior 2010

Wisepill Adherence Monitor
www.wisepill.com
Real-time Adherence Monitoring
Haberer et al AIDS and Behavior 2010
Real-time Adherence Monitoring

Haberer et al AIDS and Behavior 2010
The 2013 Guidelines Development Group recommends that national HIV programmes provide ART to all people with a confirmed HIV diagnosis with a CD4 count of 500 cells/mm3 or less.
Early Treatment (CD4>250) is Associated with More Frequent Treatment Interruptions and Incomplete Virologic Suppression

Adakun et al JAIDS 2013

- Average MEMS adherence <90%: OR=1.54 p=0.19
- Any MEMS >72 hr interruptions OR=2.21 p=0.05
- HIV RNA >400 OR=2.52 p=0.04
- Controlling for: age, sex, marital status, education, employment, socioeconomic status, clinic travel time, Hopkins Depression score, and AUDIT-C alcohol screen, and ARV regimen
Stigma, Social Capital, Structural Barriers, and Adherence in Resource-Limited Settings

Bangsberg and Deeks Ann Int Med 2010

- Stigma
- Social Capital
  - Routine Barriers
    - Medication side effects
    - Depression
    - Substance use
    - Memory
  - Structural & economic barriers
- Treatment Adherence
Stigma, Social Capital, Structural Barriers, and Adherence in Resource-Limited Settings

Bangsberg and Deeks Ann Int Med 2010

Stigma

Social Capital

Decline in health and economic status

Structural & economic barriers

Routine Barriers
- Medication side effects
- Depression
- Substance use
- Memory

Treatment Adherence
The Leaky Cascade of HIV/AIDS Care Programs in Resource Limited Settings

HIV Infected

HIV Diagnosed

Staged

ART eligible

ART ineligible

ART Initiation

ART eligibility

Retention on ART

40%

59%

68%

70%

46%

Antiretroviral therapy refusal among newly diagnosed HIV-infected adults

Ingrid T. Katz\textsuperscript{a,b}, Thandekile Essien\textsuperscript{c}, Edmore T. Marinda\textsuperscript{d}, Glenda E. Gray\textsuperscript{c}, David R. Bangsberg\textsuperscript{b,e,f,g}, Neil A. Martinson\textsuperscript{c,h,*} and Guy De Bruyn\textsuperscript{c,*}

**Objective:** To determine rates and predictors of treatment refusal in newly identified HIV-infected individuals in Soweto, South Africa.

**Design:** It is designed as a cross-sectional study.

**Methods:** We analyzed data from adult clients (>18 years) presenting for voluntary counseling and testing (VCT) at the Zazi Testing Center, Perinatal HIV Research Unit to determine rates of antiretroviral therapy (ART) refusal among treatment-eligible, HIV-infected individuals (CD4\(^+\) cell count < 200 cells/\mu l or WHO stage 4). Multiple logistic regression models were used to investigate factors associated with refusal.

**Results:** From December 2008 to December 2009, 7287 adult clients were HIV tested after counseling. Two thousand, five hundred and sixty-two (35\%) were HIV-infected, of whom 743 (29\%) were eligible for immediate ART. One hundred and forty-eight (20\%) refused referral to initiate ART, most of whom (92\%) continued to refuse after 2 months of counseling. The leading reason for ART refusal was given as ‘feeling healthy’ (37\%), despite clients having a median CD4\(^+\) cell count of 110 cells/\mu l and triple the rate of active tuberculosis as seen in nonrefusers. In adjusted models, single clients [adjusted odds ratio (AOR) 1.80, 95\% confidence interval (CI) 1.06–3.06] and those with active tuberculosis (AOR 3.50, 95\% CI 1.55–6.61) were more likely to refuse ART.

**Conclusion:** Nearly one in five treatment-eligible HIV-infected individuals in Soweto refused to initiate ART after VCT, putting them at higher risk for early mortality. ‘Feeling healthy’ was given as the most common reason to refuse ART, despite a suppressed CD4\(^+\) count and comorbidities such as tuberculosis. These findings highlight the urgent need for research to inform interventions targeting ART refusers.

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**AIDS 2011, 25:2177–2181**

**Keywords:** Africa, HIV, refusal, treatment, voluntary counseling and testing
PrEP is a new HIV prevention method in which people who do not have HIV infection take a pill daily to reduce their risk of becoming infected.
# Pre-exposure Prophylaxis: ART in HIV negatives to Prevent HIV Acquisition

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>N</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx</td>
<td>MSM</td>
<td>2499</td>
<td>44% efficacy</td>
</tr>
<tr>
<td>TDF2 Study</td>
<td>Young men and women</td>
<td>1200</td>
<td>62% efficacy</td>
</tr>
<tr>
<td>Partners PrEP Study</td>
<td>Heterosexual couples</td>
<td>4758</td>
<td>67% efficacy TDF</td>
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<tr>
<td>FEM-PrEP</td>
<td>Women</td>
<td>2021</td>
<td>No efficacy</td>
</tr>
<tr>
<td>VOICE</td>
<td>Women</td>
<td>3021 (oral arms)</td>
<td>No efficacy</td>
</tr>
<tr>
<td>Bangkok Tenofovir Study</td>
<td>IDUs</td>
<td>2400</td>
<td>62% efficacy FTC/TDF</td>
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</tbody>
</table>
## Efficacy

<table>
<thead>
<tr>
<th>Study</th>
<th>% of blood samples with tenofovir detected</th>
<th>HIV protection efficacy in randomized comparison</th>
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</thead>
<tbody>
<tr>
<td>Partners PrEP FTC/TDF arm</td>
<td>81%</td>
<td>75%</td>
</tr>
<tr>
<td>TDF2</td>
<td>79%</td>
<td>62%</td>
</tr>
<tr>
<td>iPrEx</td>
<td>51%</td>
<td>44%</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>26%</td>
<td>6%</td>
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Donnell et al. CROI 2012
Grant et al. N Engl J Med 2010
Van Damme et al. CROI 2012
Paxton et al. FDA 2012
Adherence to Antiretroviral Prophylaxis for HIV Prevention: A Substudy Cohort within a Clinical Trial of Serodiscordant Couples in East Africa

Jessica E. Haberer¹,²*, Jared M. Baeten³,⁴,⁵, James Campbell⁶, Jonathan Wangisi⁶, Elly Katabira⁷, Allan Ronald⁸, Elioda Tumwesigye⁹, Christina Psaros¹⁰,¹¹, Steven A. Safren¹⁰,¹¹, Norma C. Ware¹², Katherine K. Thomas³, Deborah Donnell³,¹³, Meighan Krows³, Lara Kidoguchi³, Connie Celum³,⁴,⁵, David R. Bangsberg¹,²,¹⁴
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<table>
<thead>
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<th></th>
<th>N</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
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<th>Median (IQR)</th>
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<th>Median (IQR)</th>
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<tbody>
<tr>
<td>Overall</td>
<td>1,039</td>
<td>97.6 (6.3)</td>
<td>99.1 (96.9-100)</td>
<td>86.9 (16.4)</td>
<td>92.1 (85.9-94.2)</td>
<td>96.6 (6.7)</td>
<td>98.8 (96-99.8)</td>
<td>98.2 (3.8)</td>
<td>99.4 (98-100)</td>
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<tr>
<td>By gender</td>
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<tr>
<td>Female</td>
<td>490</td>
<td>98.2 (5.1)</td>
<td>99.3 (97.5-100)</td>
<td>89.6 (12.4)</td>
<td>92.9 (88.4-94.6)</td>
<td>97.4 (6.1)</td>
<td>99.1 (97-100)</td>
<td>98.4 (3.9)</td>
<td>99.5 (98.3-100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>549</td>
<td>97.1 (7.2)</td>
<td>98.8 (96.2-100)</td>
<td>84.6 (19)</td>
<td>91.2 (83.5-93.6)</td>
<td>95.9 (7.2)</td>
<td>98.4 (95.5-99.6)</td>
<td>97.9 (3.8)</td>
<td>99.2 (97.6-100)</td>
<td></td>
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</tr>
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</table>
PrEP Efficacy

- HIV-1 infections
  - 14 in 404 participants on placebo (333 person-years)
  - 0 infections in 750 participants on active drug (616 person-years)
- PrEP efficacy within this adherence sub-study was 100% (95% CI 87-100%)
Excellent Adherence PrEP Adherence Explained by Relationship Dynamics Ware et al JAIDS 2012

PrEP Resolves Tension in a Committed HIV Discordant Sexual Relationship

“Discordance dilemma”

PREP adherence is opportunity to mitigate tension and strengthen relationship
Excellent Adherence PrEP Adherence Explained by Relationship Dynamics Ware et al JAIDS 2012

PrEP Resolves Tension in a Committed HIV Discordant Sexual Relationship

Love

“Discordance dilemma”

PREP adherence is opportunity to mitigate tension and strengthen relationship
Corollary: Relationship Discord Threatens PrEP Adherence
Ware et al JAIDS 2012

PrEP Can Create Tension in a Previously Committed HIV Discordant Sexual Relationship

PREP is a reminder of “discordance dilemma” in setting of mistrust or threat to the relationship

Discord and Distrust

PREP nonadherence becomes mechanism to express discord
PrEP Adherence During Relationship Discord and Distrust
Relationship Support and PREP Adherence
Ware and Bangsberg JAIDS 2011

Stigma

Structural & economic barriers

Routine Barriers
Medication side effects
Depression
Substance use
Memory

Treatment Adherence
Relationship Support and PREP Adherence
Ware and Bangsberg JAIDS 2011

Stigma

Routine Barriers
- Medication side effects
- Depression
- Substance use
- Memory

Relationship Support

Structural & economic barriers

Treatment Adherence
What's Love Got to Do With It? Explaining Adherence to Oral Antiretroviral Pre-Exposure Prophylaxis for HIV-Serodiscordant Couples

Norma C. Ware, PhD,* Monique A. Wyatt,* Jessica E. Haberer, MD, MS,† Jared M. Baeten, MD, PhD,‡ Alexander Kintu, MD,§ Christina Psaros, PhD,|| Steven Safren, PhD,|| Elioda Tumwesigye, MD,§ Connie L. Celum, MD, MPH,†¶ and David R. Bangsberg, MD, MPH†∗
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 pm
• 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

• Humility
  – (we were wrong most of the time)
Conclusions

- Humility
  - (we were wrong most of the time)
- Social context matters
  - Strength of social ties to partner, family, friends
  - Impact of HIV on close social ties
Conclusions

• Humility
  – (we were wrong most of the time)

• Social context matters
  – Strength of social ties to partner, family, friends
  – Impact of HIV on close social ties

• Reliable PrEP adherence by engaging stable committed partners
Conclusions

• Humility
  – (we were wrong most of the time)
• Social context matters
  – Strength of social ties to partner, family, friends
  – Impact of HIV on close social ties
• Reliable PrEP adherence by engaging stable committed partners
• Early ARV treatment may introduce new challenges
”In sum, a well designed study and important contribution to the field of nosocomial transmission of TB, but I strongly recommend that the author find an editor whose first language is English.”
Anonymous reviewer
Commentary

Protease Inhibitors in the Homeless

Homeless people are often thought not to adhere to therapy. Should we try to make protease inhibitors available to them? The new therapies for human immunodeficiency virus (HIV) infection are expensive, and their use may lead to the development of drug resistance. Do these drawbacks outweigh the ethical imperative to make effective drugs available to an underserved population?

In late 1995, the first protease inhibitor was licensed by the Food and Drug Administration for persons infected with HIV. In combination with reverse transcriptase inhibitors, protease inhibitors give unprecedented improvements in CD4+ cell count, viral load, morbidity, and mortality.1 One press report used the term “Lazarus effect”10 to describe the return to functional status of some patients with end-stage acquired immunodeficiency syndrome (AIDS). Driven by both science and enthusiasm, the standard of care for HIV-infected patients has quickly become combination antiretroviral therapy with a protease inhibitor.10 The price of treatment is $12,000 to $15,000 per year11.

But there are reasons for caution in prescribing protease inhibitors for the homeless. First, adherence to treatment is thought to be poor enough that effectiveness is in doubt. Second, poor adherence may lead not just to low effectiveness but also to problems of drug resistance. And third, the costs of protease inhibitors might be better spent on other interventions. In the first section of this essay we consider these issues. In the second section we make a series of recommendations for physicians who treat the homeless and marginally housed.

Adherence

Adherence to protease inhibitor treatment is the central issue. Questions about the effectiveness of protease inhibitors in the homeless revolve around the belief that homeless people will not adhere to medical regimens that include 29 pills per day in 2 or 3 divided doses. Combination chemotherapy with protease inhibitors must be designed around compliance with once-daily regimens.
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