

Adherence to HIV Treatment and Prevention

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September, 2014



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

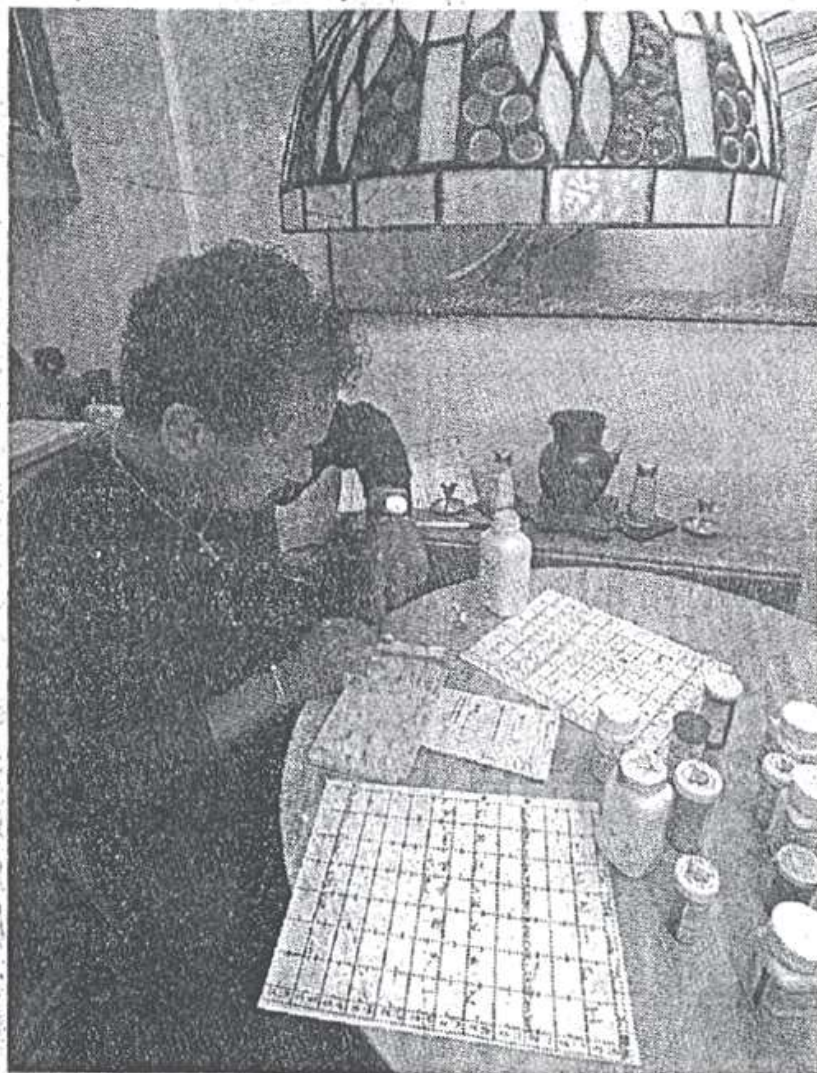
Tyeisha Ross, an 18-year-old who has H.I.V., is street smart but childishly innocent. She does not understand the full import of the virus that she carries, believing that it requires only a "minor adjustment" in her everyday life. So she often misses doctor's appointments and fails to take medications.

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 are. Since the exacting regi-



Michelle V. Agins/The New York Times

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.

Antiretroviral therapy in Africa

Warren Stevens, Steve Kaye, Tumani Corrah BMJ 2004;328:280-282

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

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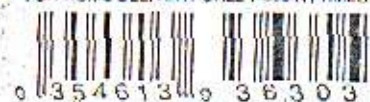
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graduates.

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A Social Model of Adherence for sub-Saharan Africa

Ware et al PLoS Medicine 2009

Improving Health

A Social Model of Adherence for sub-Saharan Africa

Ware et al PLoS Medicine 2009

Improving Health

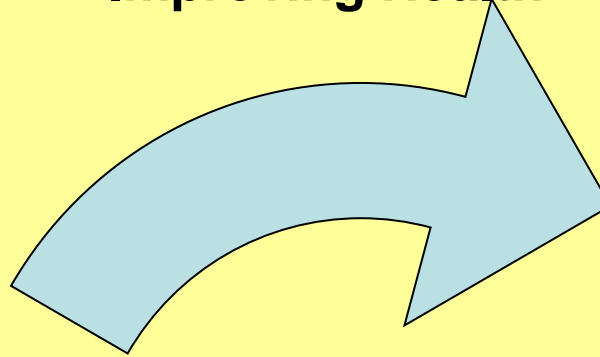
*Resource
Scarcity*

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Improving Health



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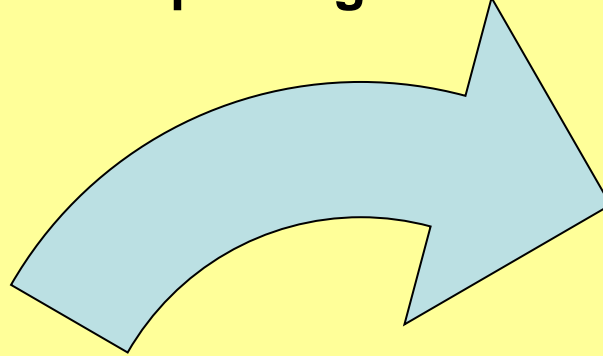
Relationships
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overcome
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adherence

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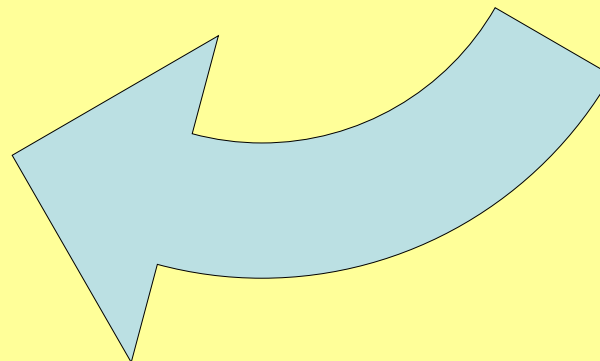


Adherence
fulfills
responsibility to
helpers and
preserve
relationships
as a resource

*Resource
Scarcity*

Relationships
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adherence

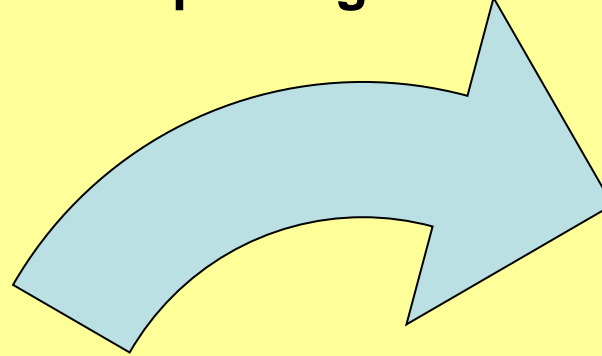
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Improving Health



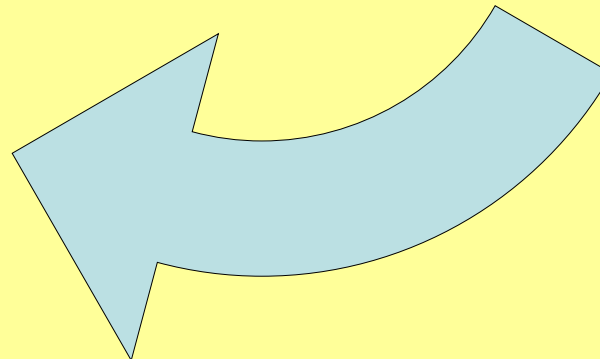
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Relationships
as resources to
overcome
economic
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adherence

**Social
Capital**

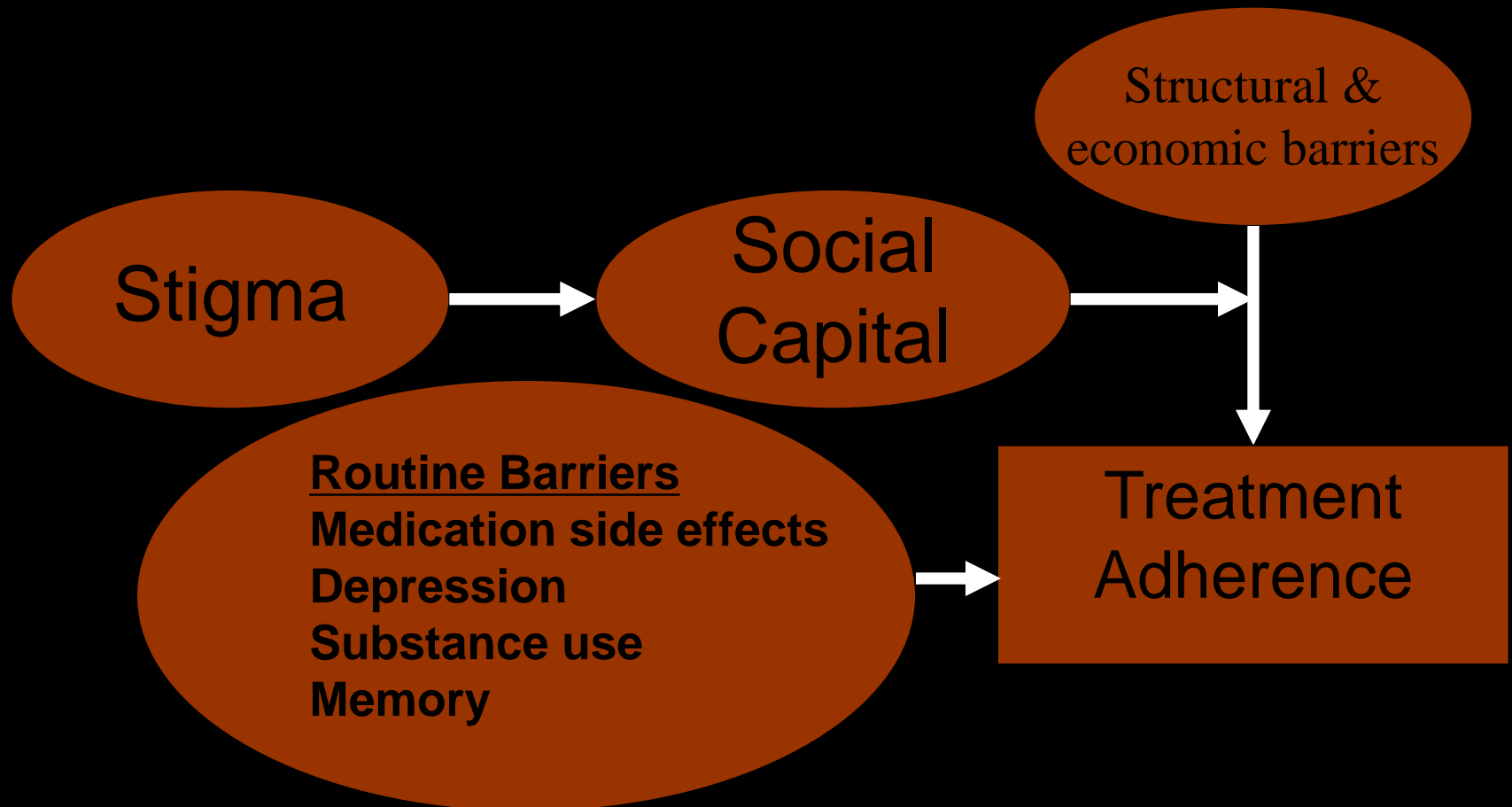
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*Resource
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Stigma, Social Capital, Structural Barriers, and Adherence in Resource-Limited Settings

Bangsberg and Deeks Ann Int Med 2010



Frequency and Duration of Treatment Interruptions >48hrs over 24 weeks

Oyugi et al AIDS 2007

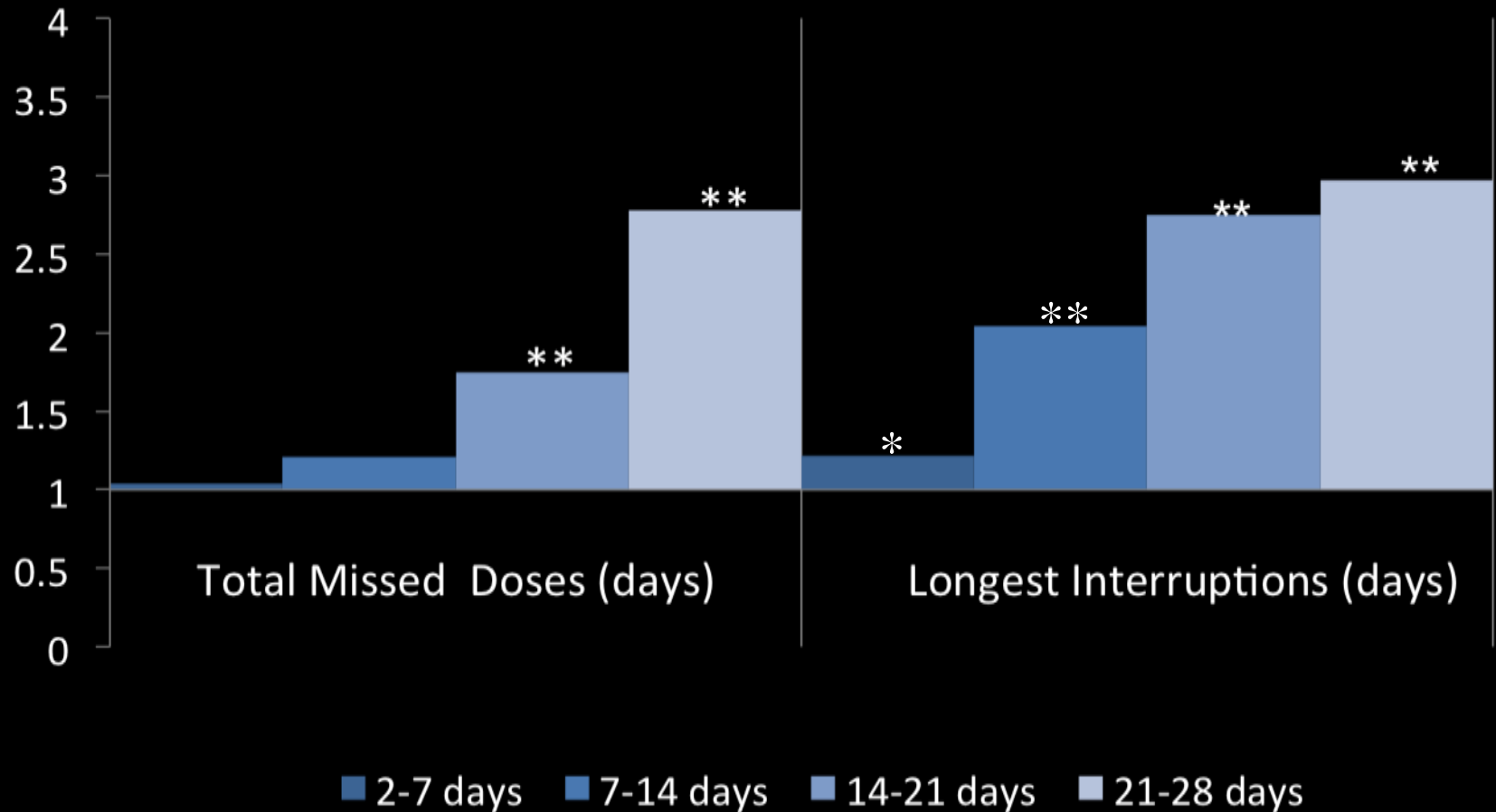
Interruptions > 48 hours	199 interruptions	62 people (64%)
Mean # interruptions/person	2.0	±2.9 (S.D)
Mean duration (days) for those who have interruptions	11.5	±9.2 (S.D)

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

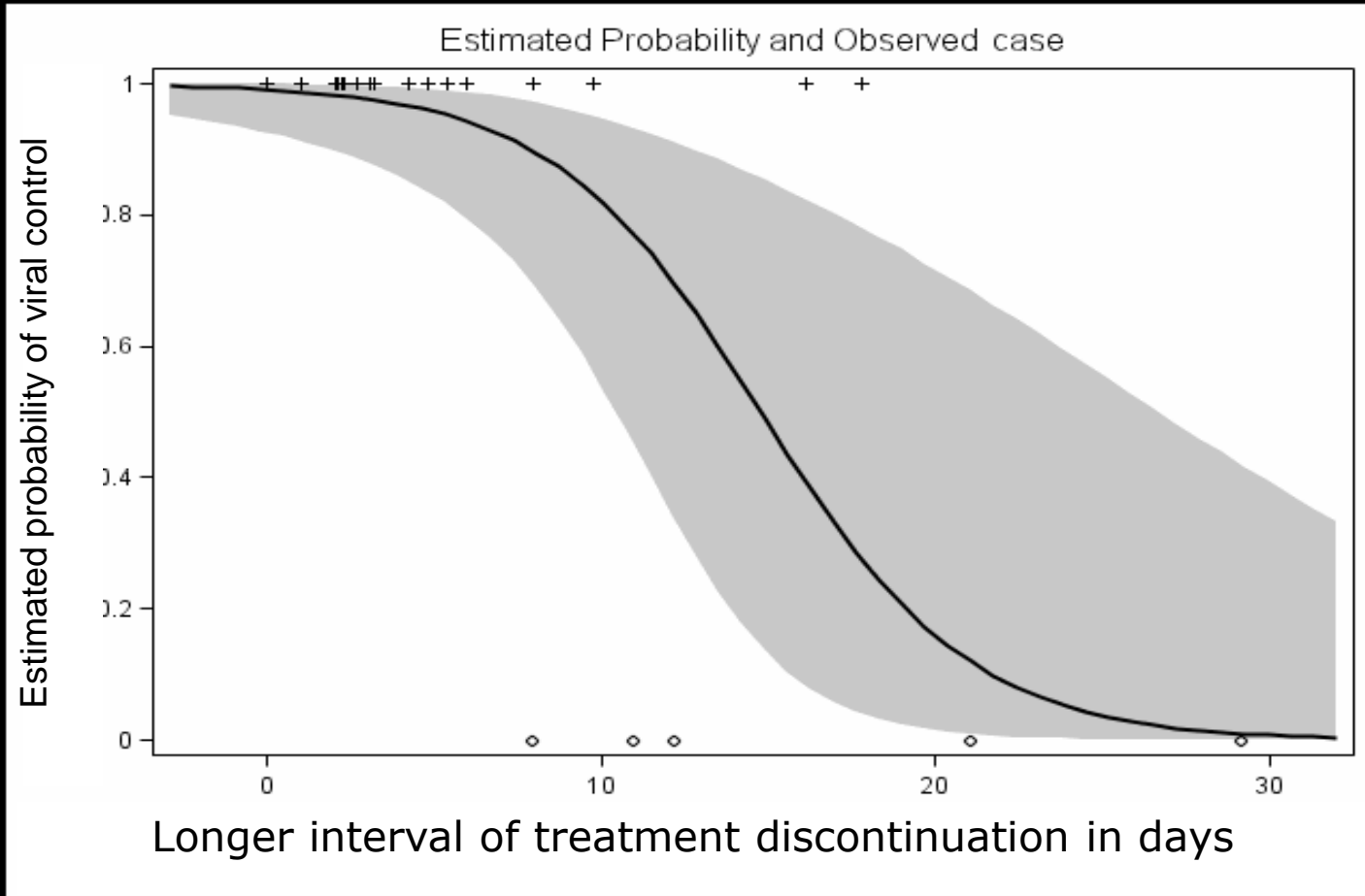


* $P \leq 0.05$ ** $p \leq 0.01$

Duration of MEMS Defined Treatment Interruption and Probability of NNRTI Virologic Failure

Parienti et al PLoS One 2008

n=72

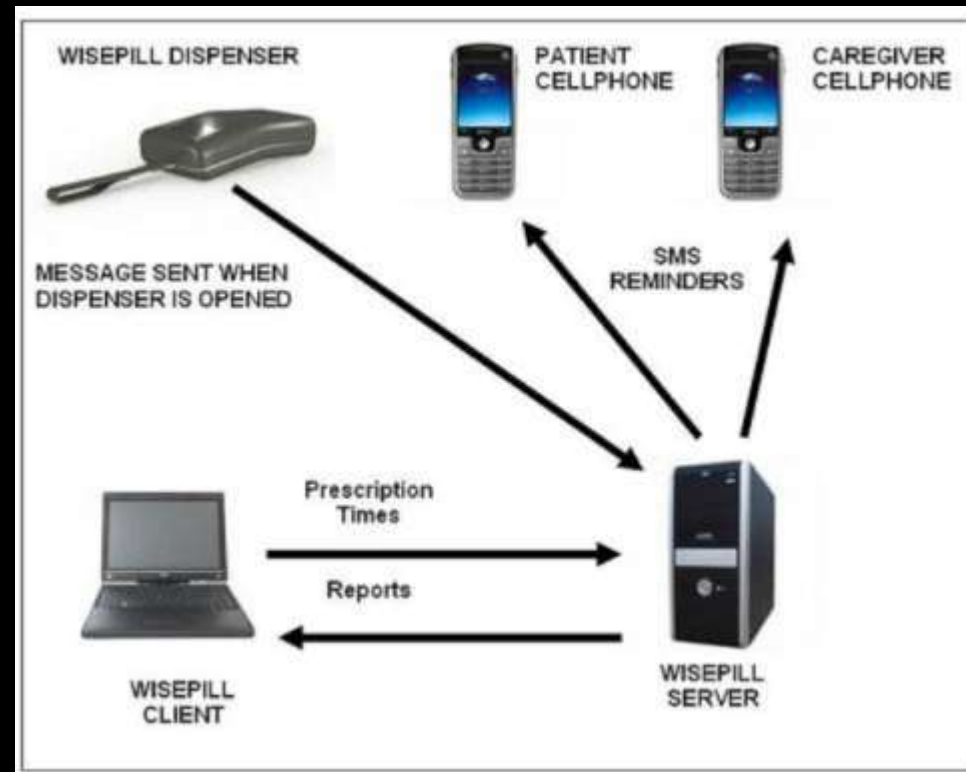


Real-time Adherence Monitoring

Haberer et al AIDS and Behavior 2010



Wisepill Adherence Monitor
www.wisepill.com



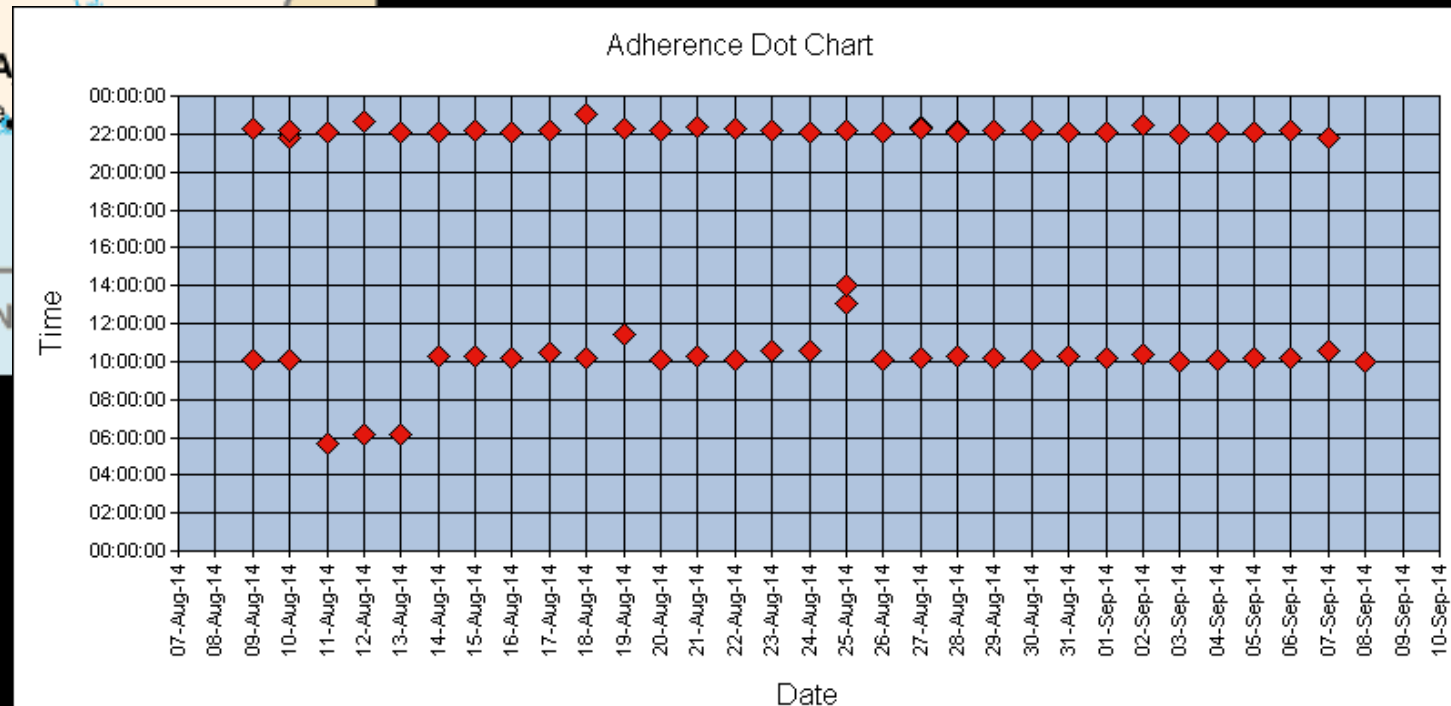
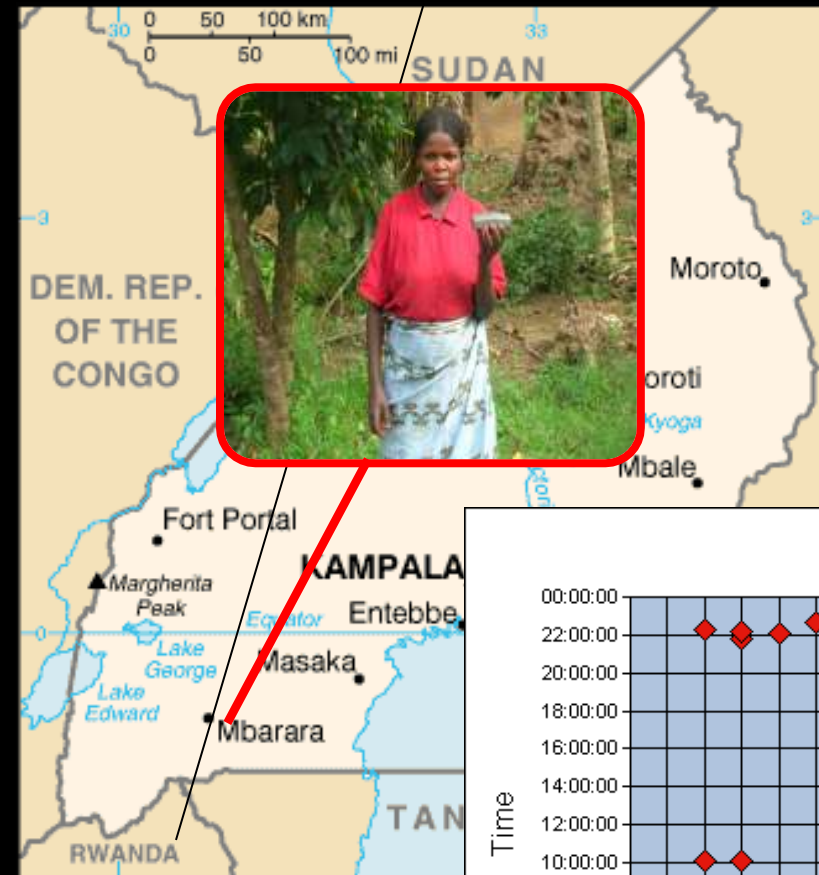
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Real-time Adherence Monitoring

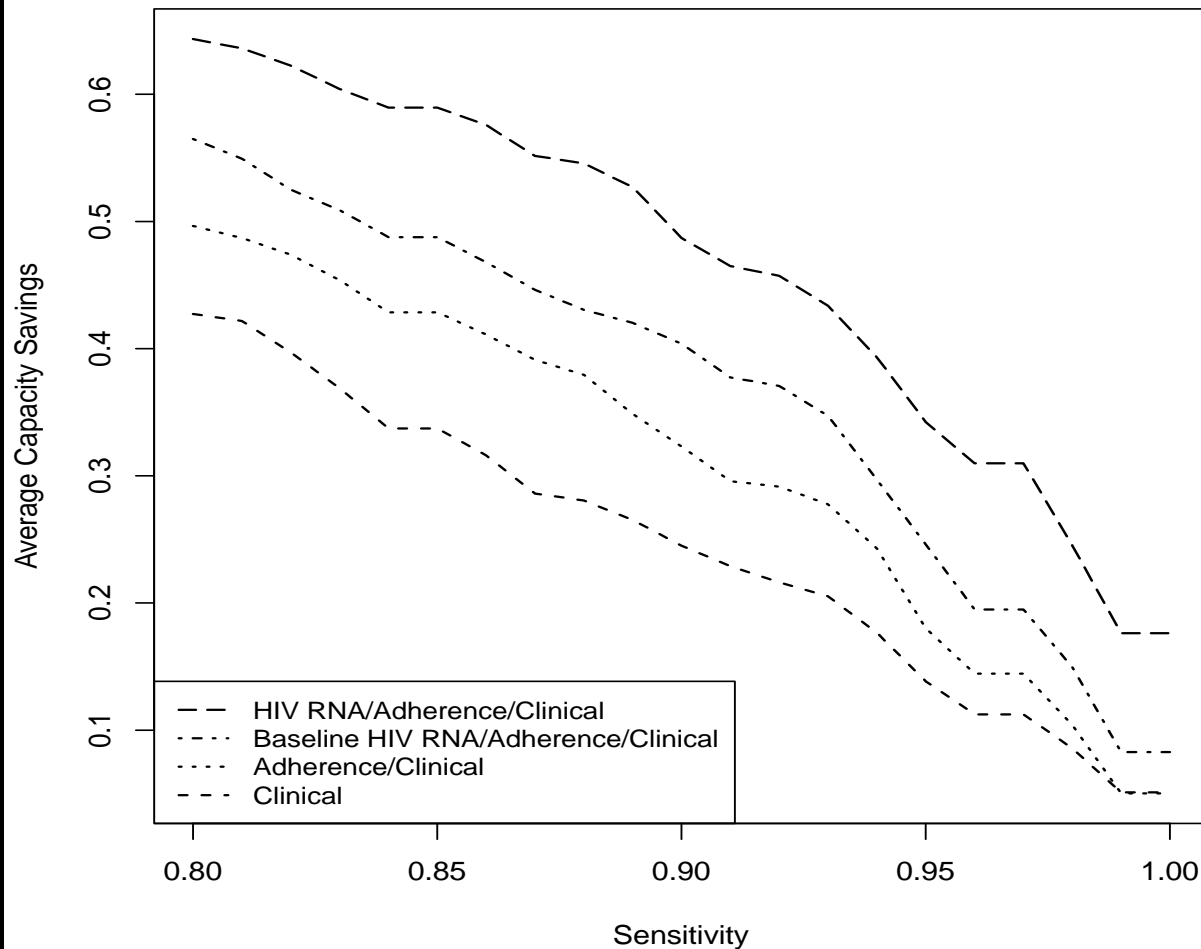
Haberer et al AIDS and Behavior 2010



30% Laboratory Monitoring Savings

Machine “Super” Learner Targeted RNA Testing

Petersen et al CROI 2013





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.

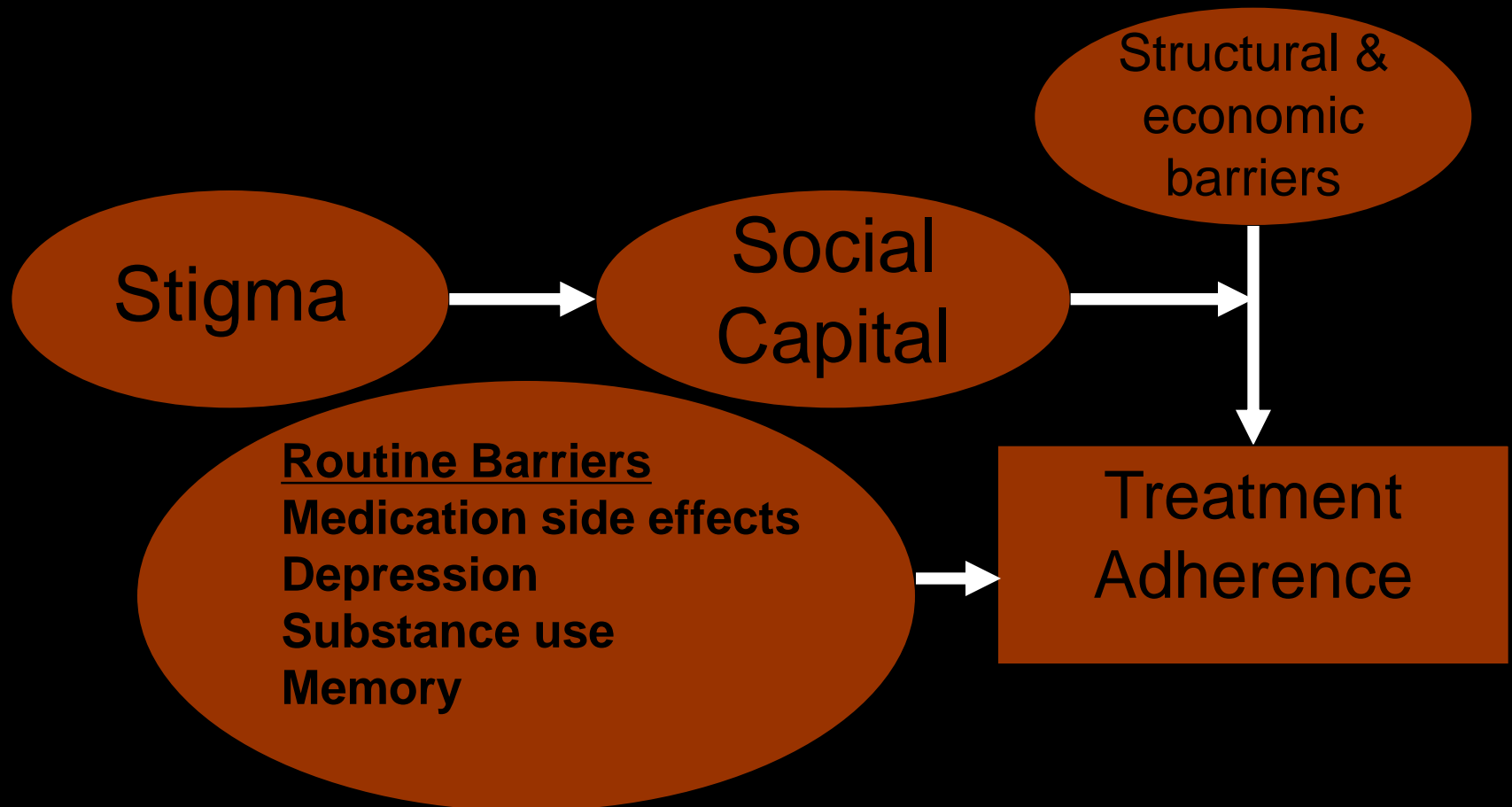
Early Treatment (CD4>250) is Associated with More Frequent Treatment Interruptions and Incomplete Virologic Suppression

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

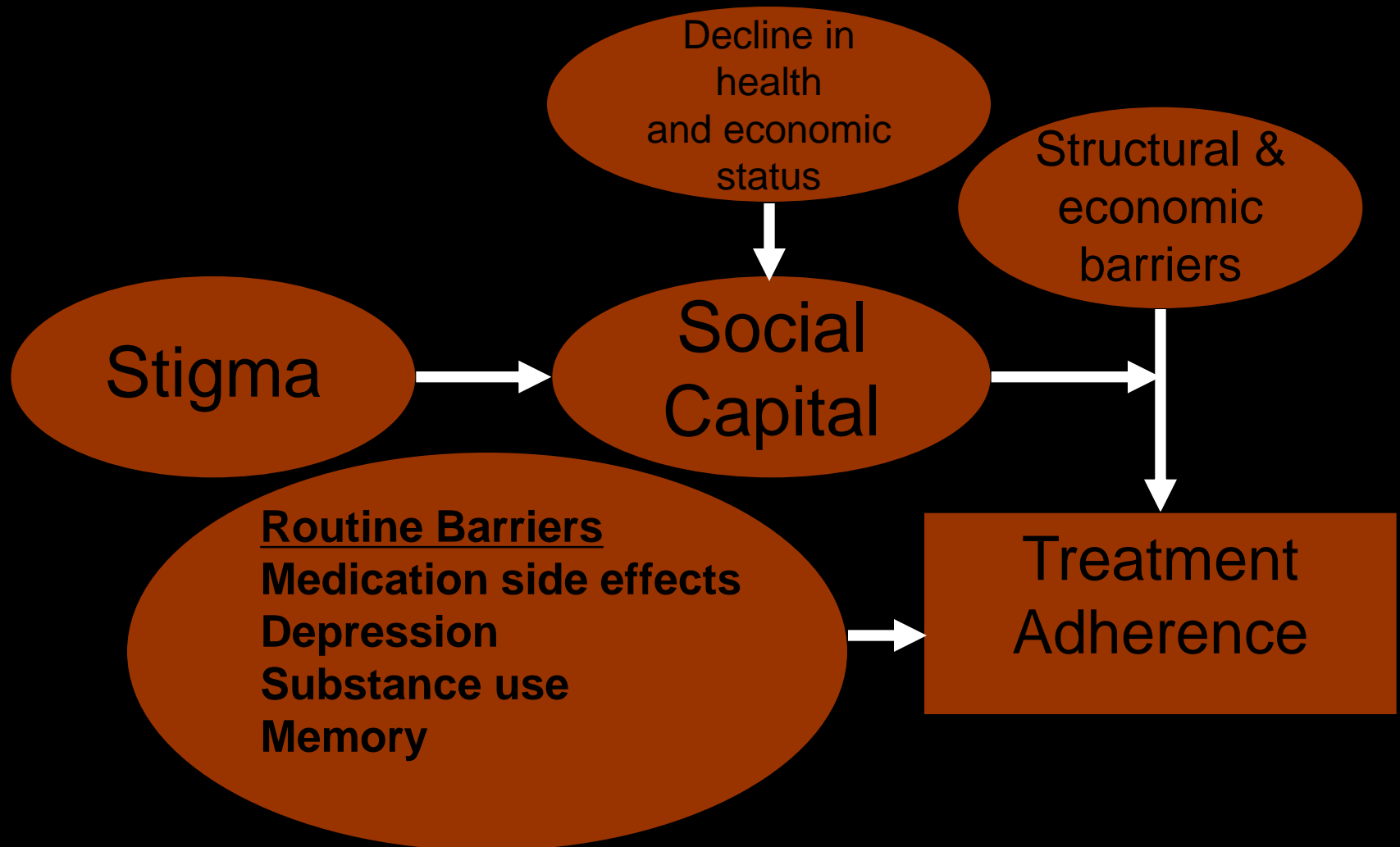
Stigma, Social Capital, Structural Barriers, and Adherence in Resource-Limited Settings

Bangsberg and Deeks Ann Int Med 2010

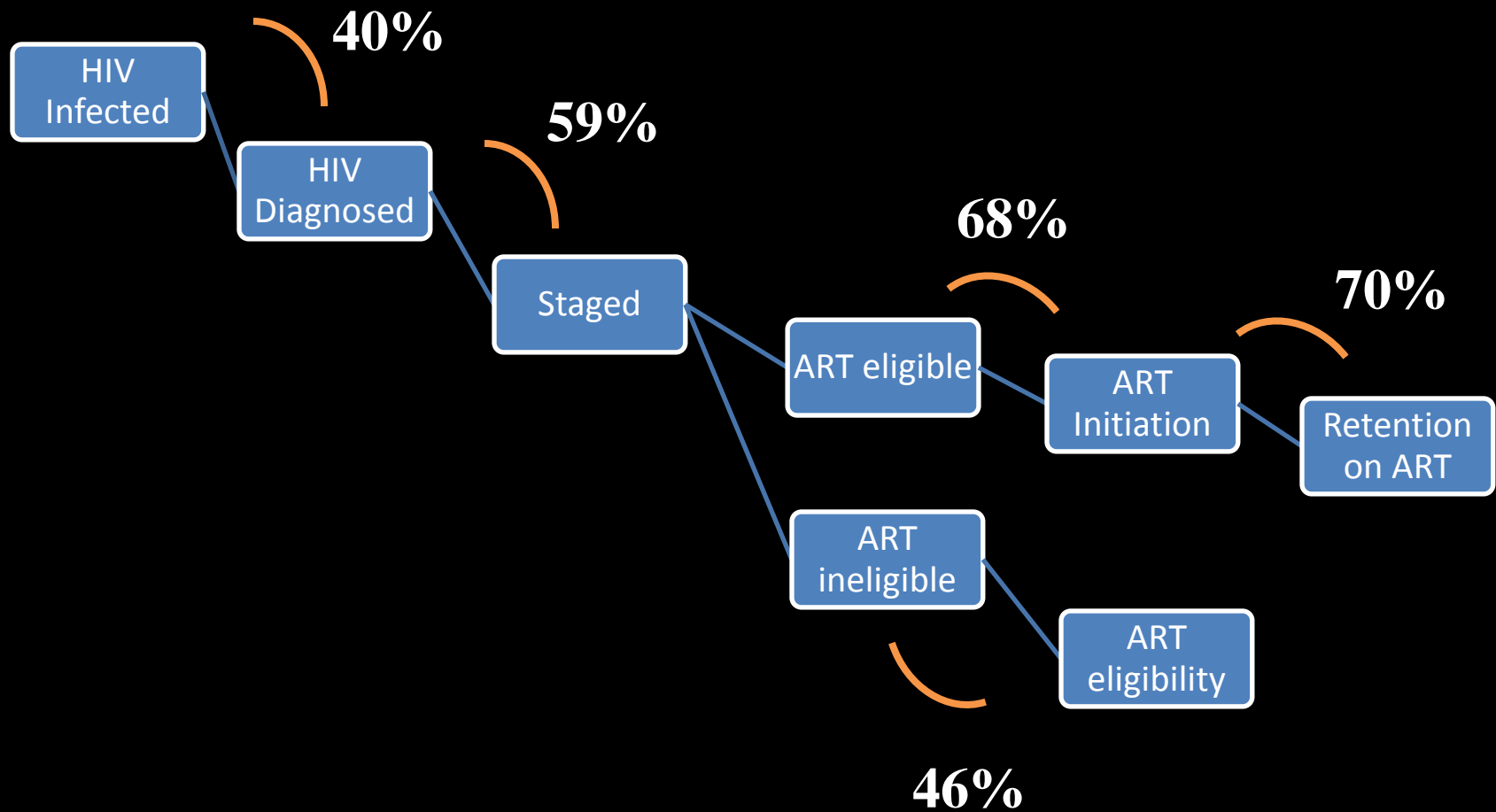


Stigma, Social Capital, Structural Barriers, and Adherence in Resource-Limited Settings

Bangsberg and Deeks Ann Int Med 2010



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



Rosen, PLoS Med 2011; Gardner CID 2011Fox, TMIH 2010; Giordano AIDS Care 2005; Giordano Current HIV/AIDS Reports 2005

Antiretroviral therapy refusal among newly diagnosed HIV-infected adults

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

Study	Population	N	Results
iPrEx	MSM	2499	44% efficacy
TDF2 Study	Young men and women	1200	62% efficacy
Partners PrEP Study	Heterosexual couples	4758	67% efficacy TDF 75% efficacy FTC/TDF
FEM-PrEP	Women	2021	No efficacy
VOICE	Women	3021 (oral arms)	No efficacy
Bangkok Tenofovir Study	IDUs	2400	62% efficacy FTC/TDF

Efficacy

	% of blood samples with tenofovir detected	HIV protection efficacy in randomized comparison
Partners PrEP FTC/TDF arm	81%	75%
TDF2	79%	62%
iPrEx	51%	44%
FEM-PrEP	26%	6%

Adherence to Antiretroviral Prophylaxis for HIV Prevention: A Substudy Cohort within a Clinical Trial of Serodiscordant Couples in East Africa

Jessica E. Haberer^{1,2*}, Jared M. Baeten^{3,4,5}, James Campbell⁶, Jonathan Wangisi⁶, Elly Katabira⁷, Allan Ronald⁸, Elioda Tumwesigye⁹, Christina Psaros^{10,11}, Steven A. Safren^{10,11}, Norma C. Ware¹², Katherine K. Thomas³, Deborah Donnell^{3,13}, Meighan Krows³, Lara Kidoguchi³, Connie Celum^{3,4,5}, David R. Bangsberg^{1,2,14}

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	N	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Overall	1,039	97.6 (6.3)	99.1 (96.9-100)	86.9 (16.4)	92.1 (85.9-94.2)	96.6 (6.7)	98.8 (96-99.8)	98.2 (3.8)	99.4 (98-100)
By gender									
Female	490	98.2 (5.1)	99.3 (97.5-100)	89.6 (12.4)	92.9 (88.4-94.6)	97.4 (6.1)	99.1 (97-100)	98.4 (3.9)	99.5 (98.3-100)
Male	549	97.1 (7.2)	98.8 (96.2-100)	84.6 (19)	91.2 (83.5-93.6)	95.9 (7.2)	98.4 (95.5-99.6)	97.9 (3.8)	99.2 (97.6-100)

PrEP Efficacy

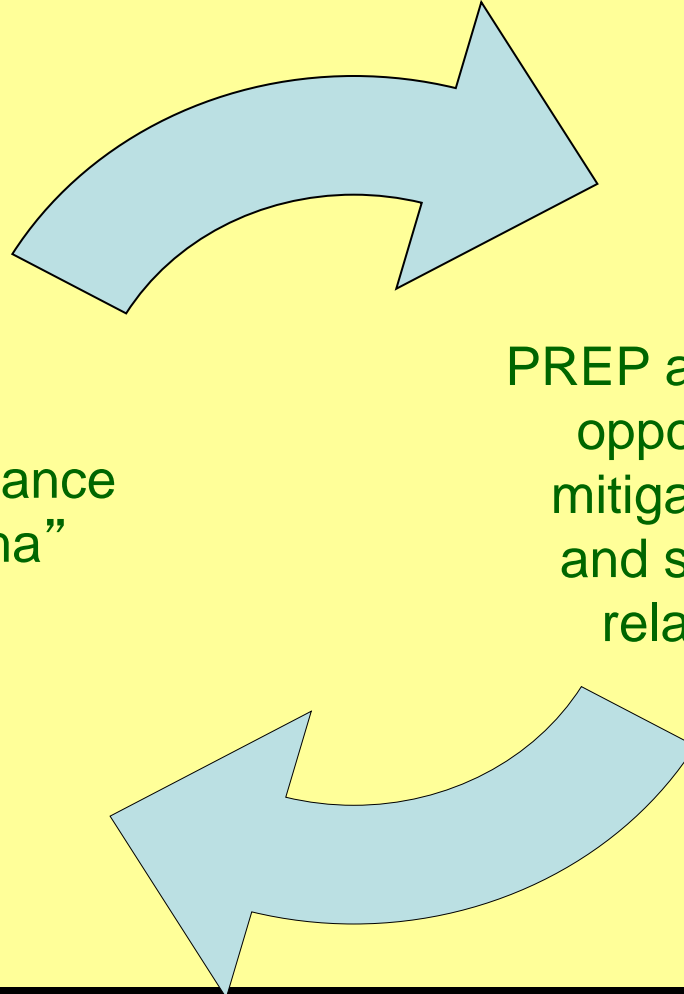
- HIV-1 infections
 - 14 in 404 participants on placebo (333 person-years)
 - 0 infections in 750 participants on active drug (616 person-years)
- PrEP efficacy within this adherence sub-study was 100% (95% CI 87-100%)

Excellent Adherence PrEP Adherence Explained by Relationship Dynamics Ware et al JAIDS 2012

PrEP Resolves Tension in a Committed HIV Discordant Sexual Relationship

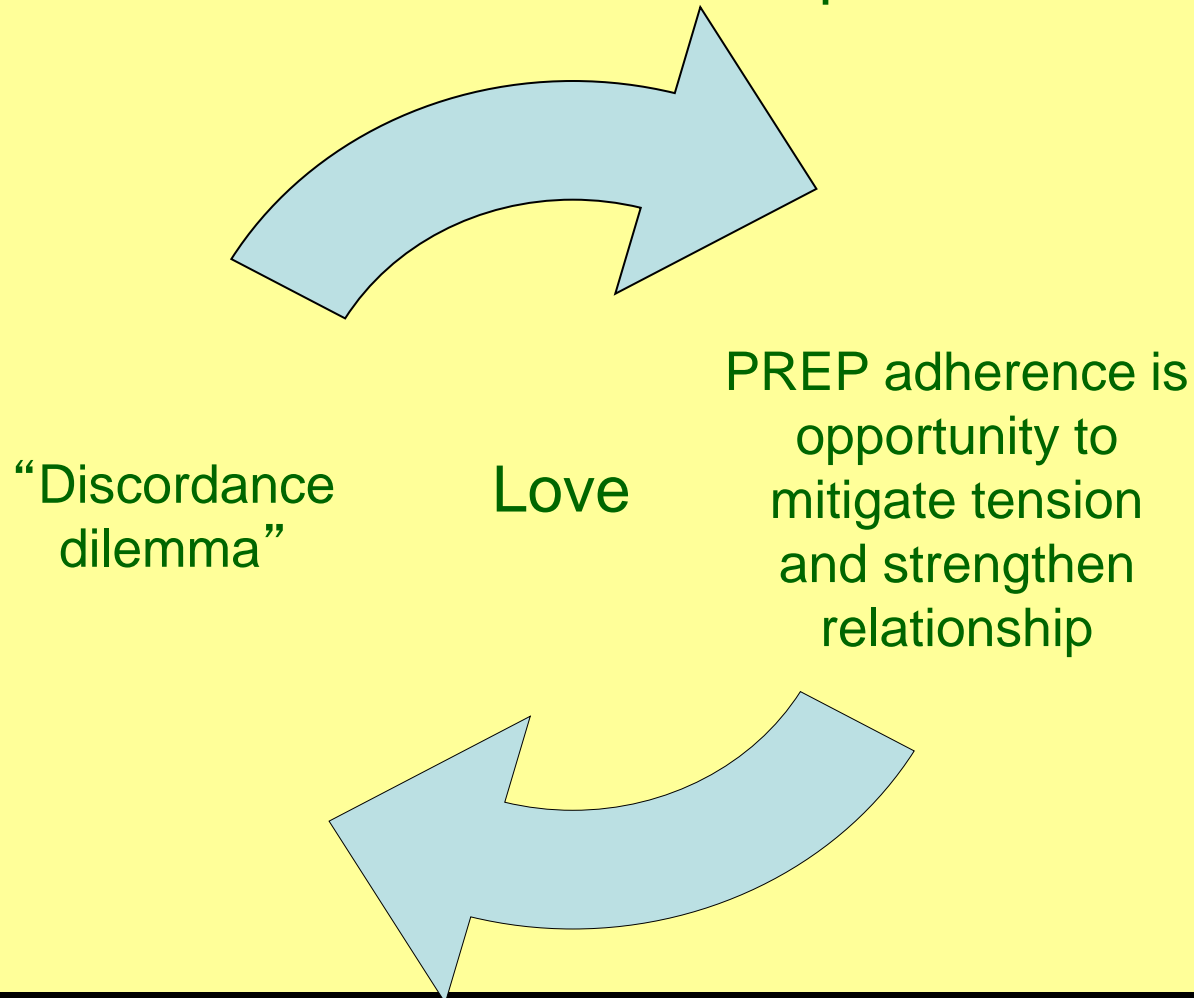
“Discordance dilemma”

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



Corollary: Relationship Discord Threatens PrEP Adherence

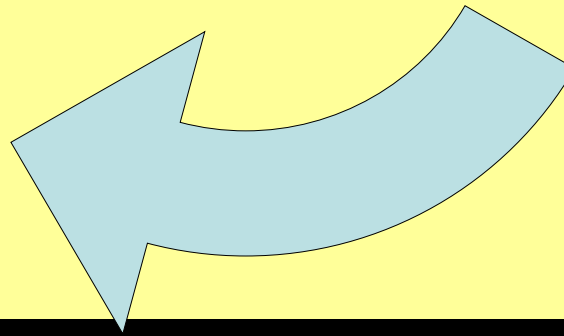
Ware et al JAIDS 2012

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

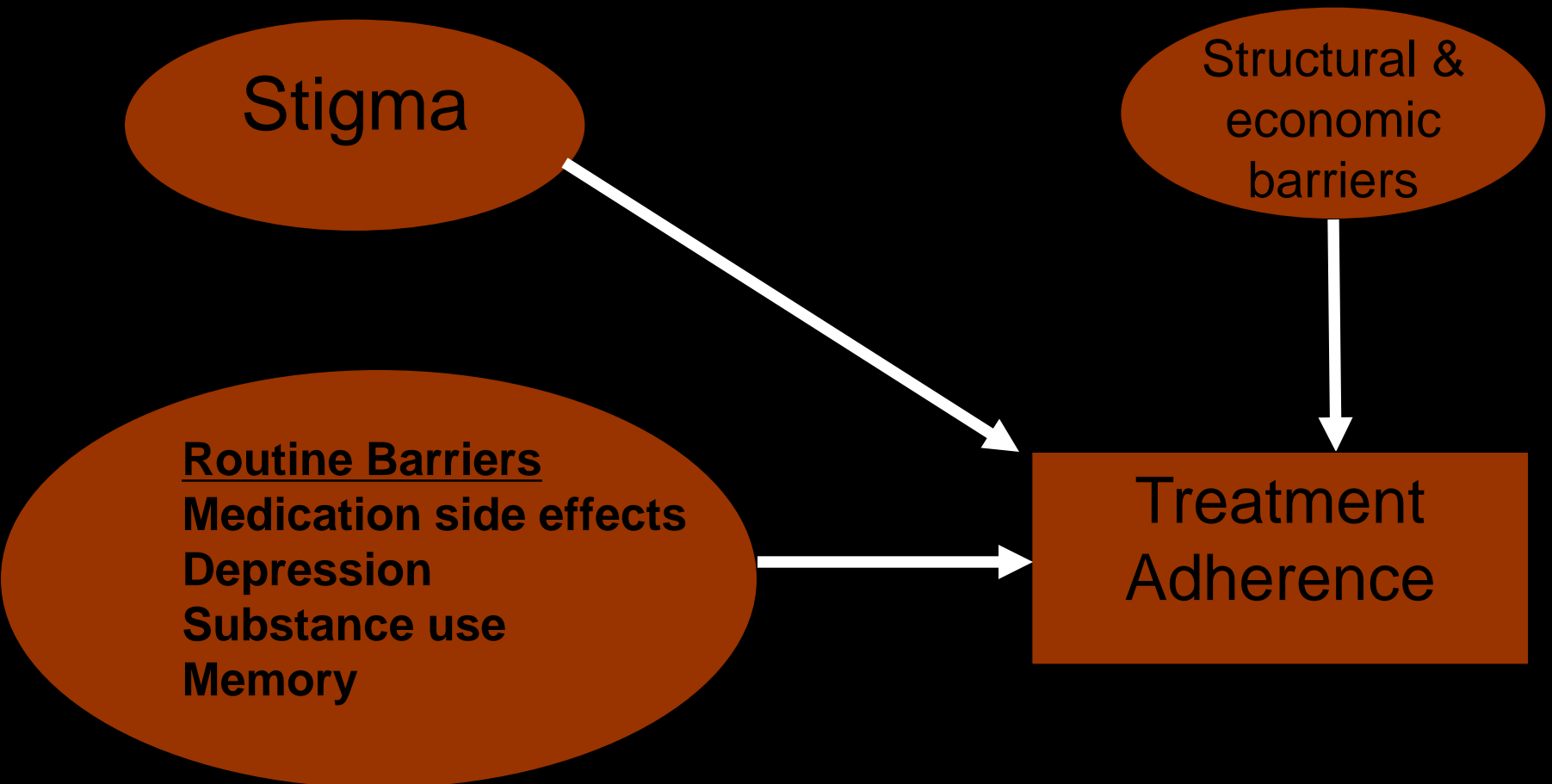


PrEP Adherence During Relationship Discord and Distrust



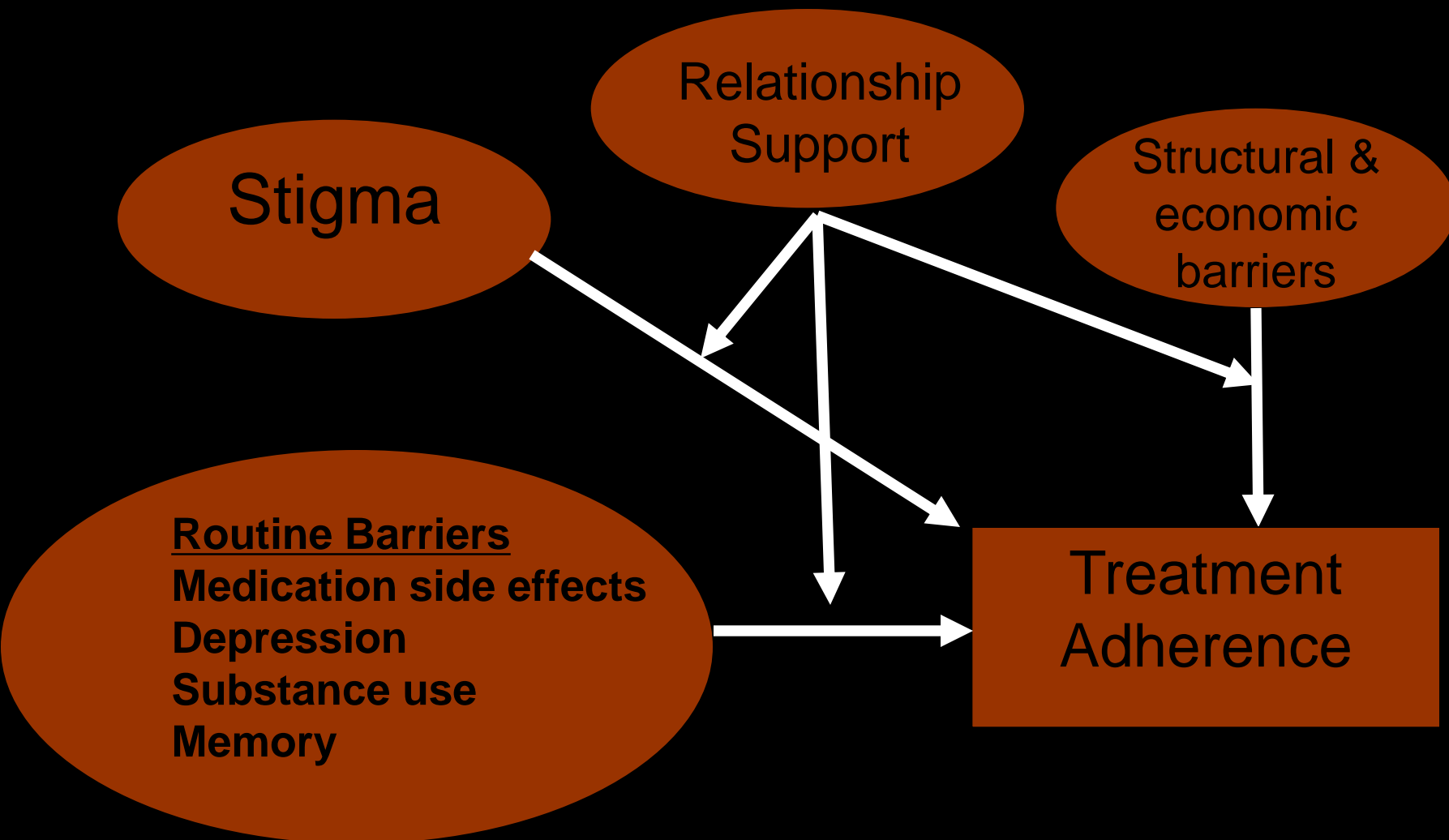
Relationship Support and PREP Adherence

Ware and Bangsberg JAIDS 2011



Relationship Support and PREP Adherence

Ware and Bangsberg JAIDS 2011



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

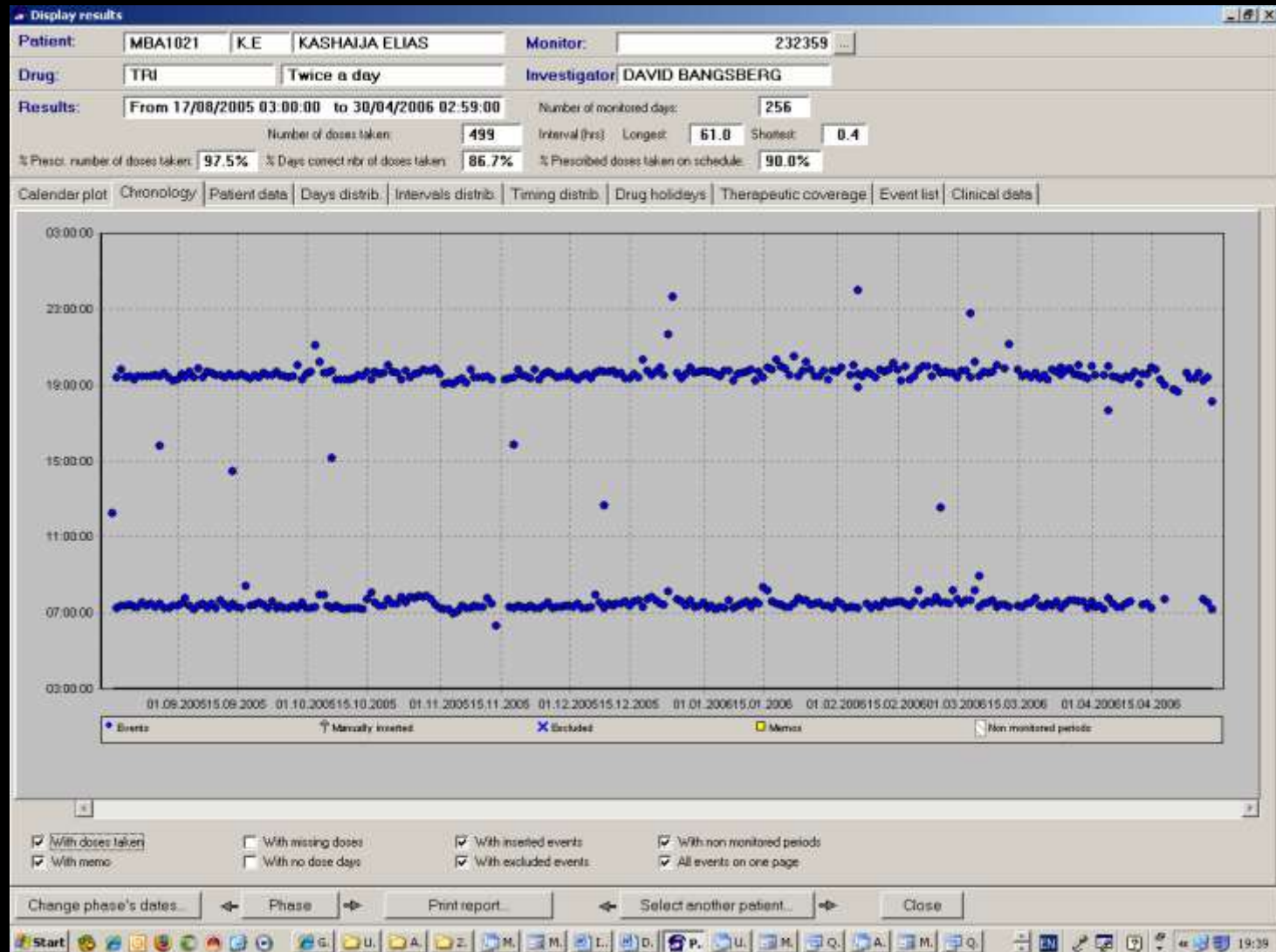
Maier et al PLOS 2006

- 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



APREX
The Patient Compliance
Experts

Electronic medication monitor record of time of bottle openings for am and pm doses.

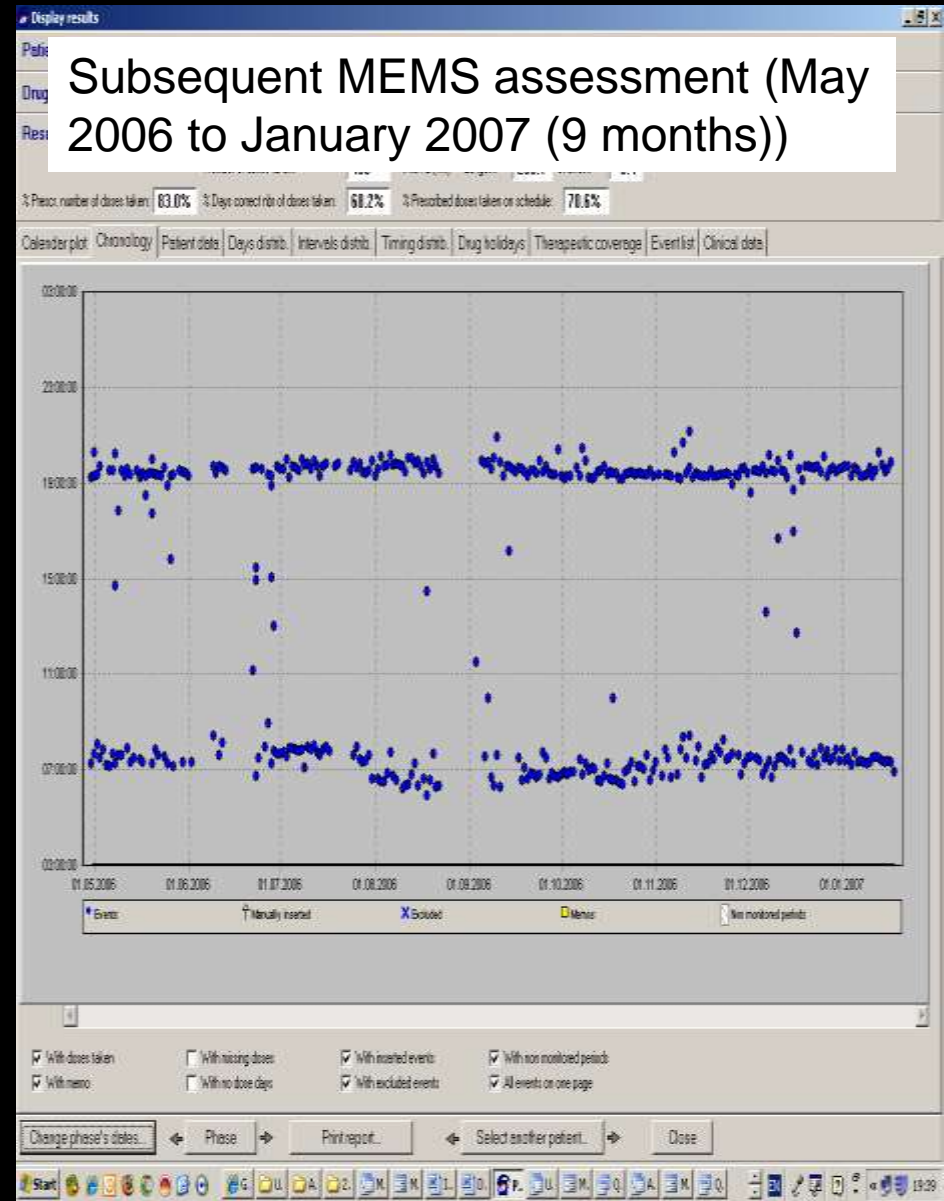
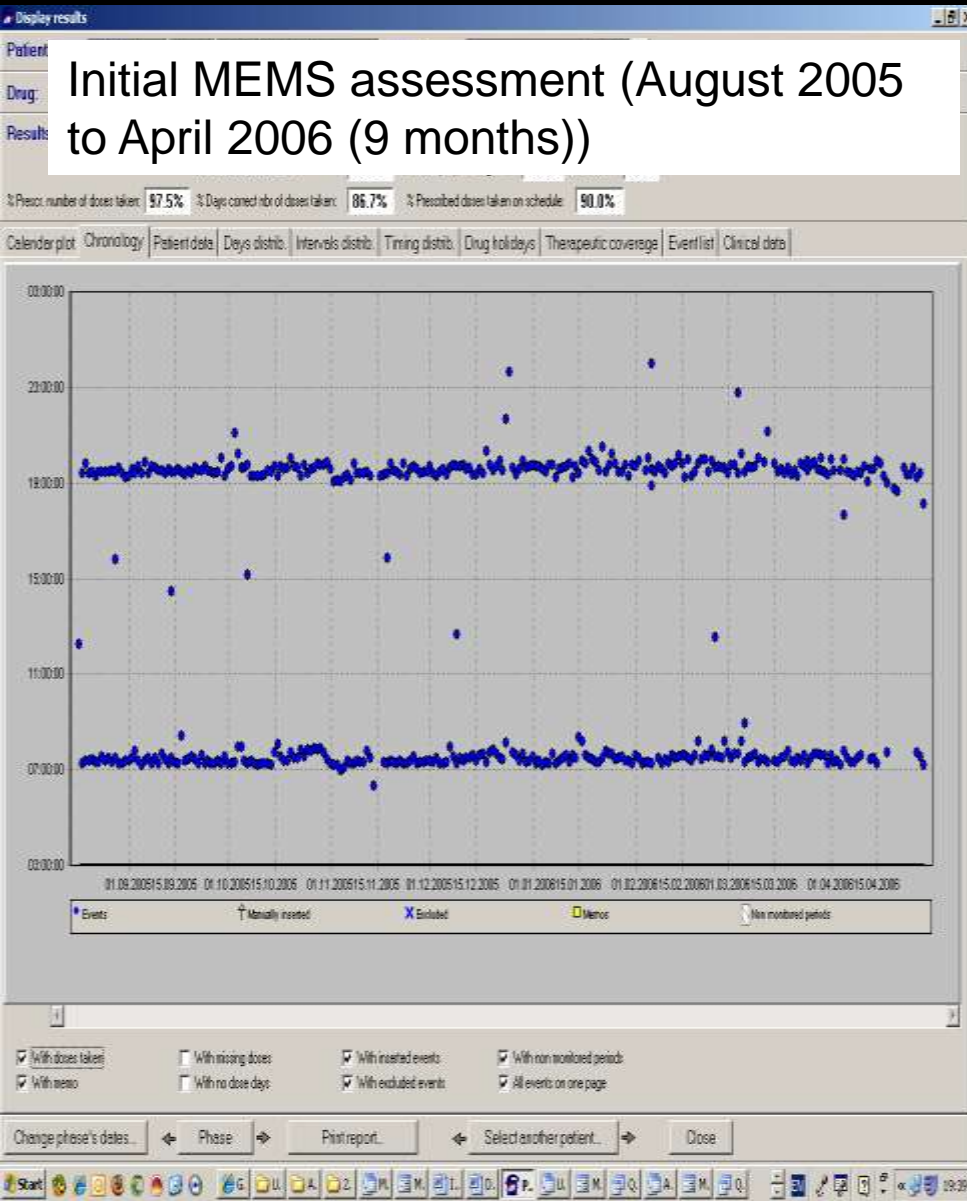


Adherence

- 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



Conclusions

- Humility
 - (we were wrong most of the time)

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

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Conclusions

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 - (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







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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"² 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.³ The price of treatment is \$12 000 to \$15 000 per year.⁴

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 20 pills per day in 2 or 3 divided doses. Combination chemotherapy with protease inhibitors must be timed around meals, with some drugs taken with

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