A multi-faceted approach to adherence – a broader perspective

Wits Institute (formerly RHRU and ECHO)

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Adherence in HIV prevention trials

- Adherence to investigational product is critical in trials of biomedical interventions to prevent HIV (Padian, 2008)
- Without adequate adherence, the true efficacy of these interventions cannot be determined (Weiss, 2008)
- The majority of current or ongoing HIV prevention trials rely on user-dependent adherence
- Despite high levels of HIV treatment adherence in our setting, these levels may not be translated to high levels of adherence to preventive interventions in healthy volunteers

HIV prevention trials face particular prevention challenges

- Trials recruit healthy volunteers who may have little incentive to adhere to products of unknown efficacy
  - Altruism, access to personal health and behavioural benefits have been reported previously as main reasons for participation (Colfax, 2005; Kenyon, 2006)
  - Compensation is also more important in some settings (Shaffer, 2006)
- Measurement of adherence still relies largely on user-dependent measures e.g. self-report, pill count
  - Also require adherence to pharmacy refill visits and return of pill bottles
- Protocol often require adherence to additional preventive behaviours e.g. condom use, avoidance of genital cleansing, coital use of product
  - Links between product adherence and sexual behaviour create additional challenges

Research questions

- What motivates trial participation in South African women and how does this influence trial participation?
- How good are our existing adherence measures?
- Can we do more to predict who will adhere well and who will require support?

Methods

A proof-of-concept, randomised, double-blind, placebo-controlled trial of daily acyclovir 400mg BD vs. placebo for 3 months among co-infected women not requiring HAART

- During the trial
  - Monthly visit data collected on adherence by pill count and self-report
- Post-trial
  - in-depth interviews with trial participants (n=32)
  - Analysis of trial data to assess baseline predictors of poor adherence (<90% doses taken) (n=300)

What motivates trial participation in South African women and how does this influence trial participation?

Reasons for participation

- Participants motivated by desire to access health information and to gain control of their health
  - Access to information, testing and treatment were all mentioned
- Although women did discuss HIV and HSV-2 specifically, they were more likely to speak of wanting to improve their health more generally
- Compensation was not a motivating factor for most women

Reasons for participation

" I joined the study because I wanted to know about my health; it was not because of the money" (Participant #20)

"My aim for coming to the clinic was to get something to help me. I found what I was looking for because the medication that I received helped my problem. My aim was not to receive money when I came here. If it was just because I wanted the money then it would have been better if I had just stayed at home" (Participant #16)

Reasons for participation

- **Altruism** was not a major determining factor for trial participation
  - Only a single participant noted that she was motivated to assist the research process
- Overall, the decision to participate was a **rational health decision** in the face of perceptions of general reproductive ill-health in the community
- While most said their **partners** were aware of their participation, few mentioned that male partners had assisted in decision to participate
- Participants more often sought advice about participation from **female relatives** or friends
- **Perceived personal benefits** outweighed any negative attitudes towards research in the community
  - Many specifically said that they would not listen to anyone who attempted to sabotage their participation

How good are our existing adherence measures?

Measuring adherence during the trial

	Month 1 N=299 n (%)	Month 2 N=298 n (%)	Month 3 N=298 n (%)
Missed visits	**20 (7)**	**26 (9)**	**28 (9)**
Adherence data from pill counts			
No. of pill boxes returned at follow up	261 (94)	258 (95)	253 (94)
Percentage of expected doses taken			
<90%	41 (14)	36 (12)	36 (12)
90-100%	232 (84)	232 (85)	224 (83)
Not returned	6 (2)	4 (1)	10 (3)
Self-reported adherence data from questionnaire			
No. of consecutive doses missed			
<9	258 (87)	250 (84)	253 (85)
>=10	20 (7)	19 (6)	15 (5)

[1] 3 participants (2%) at month 2 and 2 participants (1%) at month 3 did not provide a measure of self-reported adherence

Post-trial interviews confirmed reported adherence during the trial

- Participants reported missing a few doses and compensation strategies
- Reasons for missed doses matched reasons reported during the trial viz. Change in routine, travel, side effects

- A small number linked their motivation to adhere to study drugs to a perception that their health had improved since enrolment in the study
- No participants reported pill sharing and many noted that it was an unwise strategy if one was concerned about one's own health and that of partners, family or friends
- Participants reflected that lying about their adherence would limit the degree to which they could measure health improvements or manage health problems

Post-trial interviews confirmed reported adherence during the trial

“I was scared [to tell clinic staff I had missed a dose].I thought they would shout at me but they did not shout at me - they showed me how to take them so I could see if they were going to help”. (Participant #6)

”I was honest because I told them [clinic staff] I was taking my pills and I was honest about it. The other thing is that I never missed to take my pills and my husband used to set the alarm so the time it started to go off I knew it was the time for me to take my pills”. (Participant #19)

”I think the nurses helped me to take my pills because they used to encourage me to take my medication if I want to become better. Moreover, the nurses were fine by me. (Participant #8)”

Can we do more to predict who will adhere well and who will require support?

Predictors of poor adherence

- Poor adherers (<90% doses taken)
  - 58% aged 25-34 years
  - 83% single
  - 84% secondary/tertiary education
  - 57% >1 week outside JHB in past year
  - 14% >1 current partner
  - 70% condom use at last sex act
  - 12% history of GUD in past 3 months
  - 47% <6 months since HIV diagnosis

Predictors of poor adherence

Risk factor	Adjusted OR	95% CI	p
Age (years)	0.95	0.91 – 1.00	0.038
Mobility			
<=1 week outside JHB in past year	1.00	Ref	
>1 week outside JHB in past year	2.44	1.41 – 4.21	0.001
Number of current sexual partners			
<=1	1.00	Ref	
>1	2.51	1.03 – 6.09	0.043
Time since HIV diagnosis			
<6m prior to enrolment	1.00	Ref	
>=6m & <3yrs prior to enrolment	0.52	0.27 – 1.01	0.054
>=3 years prior to enrolment	0.74	0.38 – 1.42	0.363

Conclusions

- Women's participation in this clinical trial was overwhelmingly motivated by a desire to better manage and understand their health while accessing quality healthcare
- High levels of drug adherence can be achieved when study activities are highly applicable to participants or fill an unmet need
- Women's motivation to improve their health influenced their adherence to study visits and study drug which in turn enhanced adherence assessments
  - Adherence measures observed in the trial were corroborated in post-trial interviews
- It is important to appreciate the linkages between visit adherence and product adherence

Conclusions

- Trial staff play a critical role in supporting adherence through quality care and knowledge
- Participants who are less likely to adhere to study drug can be identified on demographic factors alone
  - Younger age, travel >1 week, having >1 sex partner predict poor adherence
  - Importantly neither clinical indicators nor randomisation arm were associated with poor adherence
- Future trials that involve daily dosing may benefit from the lessons learned in the acyclovir trials, despite some differences in trial populations

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