Episodic medication adherence in adolescents and young adults with perinatally acquired HIV: a within-participants approach

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ABSTRACT

Due to the success of antiretroviral (ART) medications, young people living with perinatally acquired HIV (PHIV+) are now surviving into adolescence and young adulthood. Understanding factors influencing ART non-adherence in this group is important in developing effective adherence interventions. Most studies of ART adherence in HIV-positive populations assess differences in adherence levels and adherence predictors between participants, over a period of time (global adherence). Many individuals living with HIV, however, including PHIV+ young people, take medication inconsistently. To investigate this pattern of adherence, a within-participants design, focussing on specific episodes of adherence and non-adherence, is suitable (episodic adherence). A within-participants design was used with 29 PHIV+ young people (17 female, median age 17 years, range 14–22 years), enrolled in the UK Adolescents and Adults Living with Perinatal HIV cohort study. Participants were eligible if they could identify one dose of medication taken and one dose they had missed in the previous two months. For each of the two episodes (one adherent, one non-adherent), behavioural factors (whom they were with, location, routine, day, reminders) and psychological factors at the time of the episode (information about medication, adherence motivation, perceived behavioural skills to adhere to medication – derived from the Information-Motivation-Behavioural Skills (IMB) Model – and affect) were assessed in a questionnaire. Non-adherence was significantly associated with weekend days (Friday to Sunday versus Monday to Thursday, \( p = .001 \)), lack of routine (\( p = .004 \)), and being out of the home (\( p = .003 \)), but not with whom the young person was with or whether they were reminded to take medication. Non-adherence was associated with lower levels of behavioural skills (\( p < .001 \)), and lower positive affect (\( p = .005 \)). Non-adherence was not significantly associated with negative affect, information about ART, or ART motivation. The use of situationally specific strategies to enhance adherence in young people who take their medication inconsistently is proposed.

Introduction

Mortality in HIV-positive people aged 10–19 years, many of whom are living with perinatally acquired HIV (PHIV+), is increasing (UNICEF, 2015). This may partly be due to low levels of antiretroviral (ART) adherence (Kim, Gerver, Fidler, & Ward, 2014). It is, therefore, important to investigate factors influencing ART non-adherence in young PHIV+ people.

PHIV+ young people face many challenges, including the HIV-related death or serious illness of parents, hospitalisations, missed school and social opportunities, and pain (Mellins & Malee, 2013). PHIV+ young people often have long histories of medication use with sub-optimal regimens and treatment failure (Sohn & Hazra, 2013). Some young PHIV+ individuals also have cognitive functioning (Laughton, Cornell, Boivin, & Van Rie, 2013) and mental health (Mellins & Malee, 2013) difficulties that may affect ART adherence.

A number of individual psychological and behavioural factors are associated with ART non-adherence in young people living with HIV. These include: the perceived difficulty of medication routine (Chandwani et al., 2012); depression (Kacanek et al., 2015; Kang, Delzell, Chhabra, & Oberdorfer, 2015; Sheth et al., 2015); substance use (Chandwani et al., 2012); lower treatment self-efficacy (Kang et al., 2015; Rudy, Murphy, Harris, Muenz, & Ellen, 2009); negative treatment outcome expectancies (Rudy et al., 2009); and forgetting (Chandwani et al., 2012). A number of additional individual “reasons” for non-adherence have been cited, including side effects (Macdonell, Naar-King, Murphy, Parsons, & Huszti,
fearing HIV disclosure and anticipated stigma (Buchanan et al., 2012; Denison et al., 2015; Rao, Kekwetswe, Hosek, Martinez, & Rodriguez, 2007), not feeling like taking medication and not wanting to be reminded of HIV (Macdonell, Naar-King, Huszti, & Belzer, 2013).

Forty to 50% of patients across various medical conditions are “inconsistently adherent”, intentionally or unintentionally skipping doses or taking unplanned breaks (WHO, 2003). Similar rates of inconsistent ART adherence have been reported in HIV-positive samples (Carrieri et al., 2001). Within-participant designs allow the investigation of factors which may vary according to specific contexts, enable static demographic factors to be controlled for and help to explain variability within individuals (Wagner & Ryan, 2004). Variation in actual or perceived barriers to or facilitators of adherence can also be measured episodically, relating to specific medication events. Such designs have been used to investigate self-efficacy and smoking cessation behaviour (Van Zundert, Engels, & Kuntsche, 2011) and medication adherence in adults with Beta Thalassaemia Major (Vosper, Evangeli, Porter, & Shah, 2013).

The Information-Motivation-Behavioural Skills (IMB) model describes behavioural and psychological determinants of ART adherence (Fisher, Fisher, Amico, & Harmon, 2006). It includes: information, or understanding of the regimen and side effects; motivation, both personal motivation, or treatment outcome expectancies and their perceived importance, and social motivation, or the perception and importance of others’ wishes in relation to ART adherence; and behavioural skills, objective skills in taking medication as well as perceived self-efficacy in using those skills (Fisher, Fisher, & Shuper, 2014). Moderating variables are included (e.g., mental health issues) (Amico et al., 2009). Each IMB construct might vary according to situation, making this model suited to researching differences within individuals across contexts.

This study focuses on situational behavioural and IMB-derived psychological factors and ART adherence in young people with PHIV+. It responds to calls for theory-informed ART adherence research with young people living with HIV (Simoni et al., 2007). The study also addresses a gap in the literature concerning situational determinants of non-adherence. It aims to investigate which psychological and behavioural variables differentiate episodes of ART adherence and non-adherence in young PHIV+ people.

Method

Design and setting

An event-level within-participant design was used. Participants completed the same measure for one adherent and one non-adherent event. Recruitment was from three clinics (two in London, one in Manchester) and a London voluntary-sector organisation.

Participants

Participants had previously enrolled in the UK Adolescents and Adults Living with Perinatal HIV Infection (AALPHI) cohort study, attending one of the four sites. AALPHI samples systematically from 20 sites across the UK. Inclusion criteria are a history of UK paediatric care; perinatally acquired HIV; 13–21 years at time of enrolment; and UK resident >6 months. A systematic sampling approach was also used for this study. All eligible participants were approached between December 2014 and April 2015. Inclusion criteria for the current study were as for AALPHI. In addition, participants needed to be on ART, and able to recall a taken and missed dose in the preceding two months.

Thirty-six young people were approached, of whom 29 participated. The seven who refused to participate cited insufficient time as the reason for not taking part. Anonymous identifiers were linked to the AALPHI database for demographic and behavioural characteristics.

Ethical approval

Ethical approval was granted by Berkshire B NHS Ethics Committee and Royal Holloway University of London Psychology Departmental Ethics Committee.

Measures

A self-report questionnaire (available in both paper and pencil and online format) was used. Participants were asked how they thought and felt at a time when they did or did not take their medication. The questionnaire construction was guided by the Day Reconstruction Method to reduce recall bias (Kahneman, Krueger, Schkade, Schwarz, & Stone, 2004).

Behavioural variables

The following behavioural factors were assessed (prior to ratings of situational psychological states, to enhance episodic memory detail) for each of the two events:

- Day;
- Location (home; a friend’s home; partner’s home; public place, for example, work, school or college; family member’s home);
- Who was with them (alone; with friend; partner; family; acquaintance; work colleague);
Table 1. Demographic information (n = 29).

| Variable     | Value |
|--------------|-------|
| Age          | Median 17, IQR 16–18.5 |
| Gender       | Female 17 |
| Birthplace   | UK/Europe 9, Africa 20 |
| Ethnicity    | Black African 25, Other 3, Prefer not to say 1 |

- Whether activity was routine (yes/no, if no, was activity planned or unplanned);
- Whether someone else reminded them to take their medication (yes/no);
- Use of street drugs or alcohol (yes/no).

**Psychological variables**

The questionnaire measured constructs from the IMB model, adapting the *LifeWindows Information Motivation Behavioural Skills ART Adherence Questionnaire* (LW-IMB-AAQ) (Life Windows Project Team, 2006). This 33-item scale measures ART adherence barriers. The LW-IMB-AAQ has not been used with adolescents (Amico, personal communication). The measure was, therefore, adapted for the target group and to be situationally specific. Items not satisfying these criteria were removed and/or adapted. The omitted items were presented to a focus group (12 young people from the UK Children’s HIV Association (CHIVA) Youth Committee) to corroborate that they had not been erroneously excluded. Three information items (from 9), 7 motivation items (from 10) and 10 behavioural skills items (from 14) remained after this process. Extra items were added based on other factors found to predict between-participant ART adherence in young PHIV+ people or to have been elicited as reasons for non-adherence (Agwu & Fairlie, 2013; Macdonell et al., 2011; Rudy, Murphy, Harris, Muenz, & Ellen, 2010). Four information (e.g., “I knew what medication to take”), 10 motivation (e.g., “I thought other people would notice I was taking my medication, which concerned me”), and 8 behavioural skills items (e.g., “I felt confident I could take my medicines however I was feeling”) were included in the final 22-item questionnaire. Responses were rated on a five-point Likert scale (strongly disagree to strongly agree). Cronbach’s alpha was calculated for subscales for each episode. Further analysis assessed whether subscales could be refined to improve psychometric properties. For the motivation subscale, alpha improved from 0.79 to 0.85 for non-adherent episode and 0.76–0.87 for adherent episode, if two items were dropped. The item-total correlations for these items were low. An eight-item Personal Motivation scale was, therefore, used for analysis. One of the two dropped items measured social motivation (“People around me that I care about were supportive about my medication”). This was analysed separately. The behavioural skills and information subscales did not require modifications (information adherent episode $\alpha = 0.98$; information non-adherent $\alpha = 0.71$; behavioural skills adherent $\alpha = 0.71$; behavioural skills non-adherent $\alpha = 0.83$).

Affect was assessed by adapting the *Positive and Negative Affect Schedule* (PANAS-C) – 10 item Children’s Version (Ebesutani et al., 2011), to be relevant to a specific event. This scale has two five-item subscales (positive and negative affect). In our sample, internal consistency was excellent (adherent episode: positive affect $\alpha = 0.91$, negative affect $\alpha = 0.86$; non-adherent episode: positive affect $\alpha = 0.94$, negative affect $\alpha = 0.93$). An additional four negative affect items were suggested by the focus group: feeling blamed, helpless, out of control and weak. To avoid bias towards negative affect items, an additional four positive affect items were added, derived from a critique of the PANAS (Peterson et al., 2013) (calm, content, at ease and satisfied) measuring non-activated positive affect.

Intentional adherence for the adherent episode was measured with the item, “Taking the medicines was my choice”. Non-intentional non-adherence was measured with the item, “I forgot”. Somatic symptoms (both episodes) were measured with a single item, “I felt ill”. These items used five-point Likert scales (strongly disagree to strongly agree).

**Procedure**

AALPHI research nurses introduced the study to eligible participants whom had already enrolled and completed their first AALPHI interview. Occasional ART non-adherence was normalised. People wishing to participate could consent and complete the questionnaire in writing or online. Online consent was carried according to national guidelines (BPS, 2013). Event order was counter-balanced to control for order effects. Participants received £10 for taking part.

**Analysis**

Skewed continuous variables were transformed for parametric analysis. Bivariate analysis compared adherent and non-adherent episodes. Variables meeting assumptions for parametric statistics were analysed using paired-samples $t$-tests. Categorical variables were analysed using McNemar’s chi square tests (using Fisher’s exact estimates for expected frequencies $<$5). Effect sizes were calculated using Cramer’s phi ($\phi$) for categorical variables.
Results

Demographic information is presented in Table 1. Participants were predominantly female (17/29: 59%), born in Africa (20/29: 69%), of Black African ethnicity (25/28: 89%), with a median age of 17 years. These characteristics are similar to UK national data on paediatric HIV (51% female; 52% born abroad; 79% Black African) (CHIPS, 2014). Table 2 presents clinical and behavioural characteristics at AALPHI enrolment (median days prior to this study = 468).

Participants were mostly on once a day regimens (24/25). Self-reported adherence was predominantly excellent or good (23/25). The majority had shared their HIV status with 2 or fewer individuals (21/26). One participant had been referred to child mental health services. The majority did not drink alcohol (18/28).

The median rating of “Taking the medicines was my choice” for adherent episode was 5 (interquartile range [IQR] 3.75–5). The median rating of “I forgot” for non-adherent episode was 4 (IQR = 2.25–5).

Relationships between psychological variables and adherence

Table 3 presents descriptive statistics for information, motivation and behavioural skills subscales.

There were no significant differences between adherent and non-adherent episode on the information subscale (reverse log transformed due to negative skew) ($p = .28, d = 0.06$) or personal motivation subscale ($p = .78, d = 0.04$). The relationship between higher social motivation and non-adherence approached significance ($p = .07; d = 0.38$, small to medium effect). The difference in behavioural skills between episodes was highly significant, with participants rating their abilities in taking medication lower for the non-adherent episode ($p < .001; d = 0.91$, large effect).

Relationships between behavioural variables and non-adherence

Table 3 presents descriptive statistics for behavioural variables and adherence.

There was a significant relationship between non-adherence and weekend days (Friday to Sunday) ($p = .001; \phi = 0.65$, large effect size). Participants were significantly more likely to be non-adherent on a day when the routine was different to normal ($p = .004, \phi = 0.59$, large effect). The non-adherent event was more likely when participants were out of the home ($p = .003, \phi = 0.58$, large effect). Non-adherence was neither associated with whom the young person was with ($p = .34, \phi = 0.24$) nor having someone to remind them to take medication ($p = .63, \phi = 0.19$). Substance use difference between episodes were not analysed due to very low levels of substance use.

| Variable | Non-adherent episode (frequencies) | Adherent episode (frequencies) | $p$ value* |
|----------|----------------------------------|-------------------------------|-----------|
| Weekday  | Mon–Thu 11 | 22 | .001 |
|          | Fri–Sun 16 | 5  |     |
|          | Missing 2  | 2  |     |
| Routine  | Normal 12  | Same 24 | .004 |
|          | Unexpected 8 | Different 2 |     |
|          | Planned 7  | 15  |     |
|          | Missing 2  | 1  |     |
| Location | At home 15 | 25  | .003 |
|          | Not at home 14 | 3  |     |
|          | Missing 0  | 1  |     |
| Who with at time of dose/missed dose | Alone 8 | 12 | .34 |
|          | Friend 10  | Not 0 |     |
|          | Partner 2  | alone 0 |     |
|          | Family 9  | 16  |     |
|          | Missing 0  | 1  |     |
| Someone there to remind you | Yes 11 | 9  | .63 |
|          | No 18  | 19  |     |
| Substance use | Yes 4  | 2  |     |
|          | Missing 0  | 1  |     |

*p value of difference between non-adherent and adherent episode.
Table 4. Descriptive statistics for Information, Motivation, and Behavioural Skills.

| Variable                      | Episode          | Mean  | SD  | p value* |
|-------------------------------|------------------|-------|-----|----------|
| Information                   | Non-adherent     | 18.04 | 3.64| .28      |
| (4–20)                        | Adherent         | 19.04 | 1.64|          |
| Personal motivation           | Non-adherent     | 21.14 | 8.59| .78      |
| (8–40)                        | Adherent         | 21.54 | 8.06|          |
| Social motivation             | Non-adherent     | 2.52  | 1.33| .07      |
| (1–5)                         | Adherent         | 2     | 1.28|          |
| Behavioural skills            | Non-adherent     | 29.75 | 9.52| <.001    |
| (10–50)                       | Adherent         | 37.92 | 7.29|          |

*p value of difference between non-adherent and adherent episode.

Table 5 presents descriptive statistics for affective and somatic variables.

Young people rated their positive emotions (measured by the PANAS-C Positive Affect five-item scale) more highly for adherent episode (p = .005, d = 0.61, medium to large effect). All additional positive affect items: feeling calm (p = .01, d = 0.63); at ease (p = .03, d = 0.49); content (p = .03, d = 0.48); and satisfied (p = .02, d = 0.51), were rated significantly higher for adherent episode (medium or medium to large sized effects).

Negative affect (measured by the PANAS-C Negative Affect five-item scale) was not associated with non-adherence (p = .08 d = 0.36, small to medium effect). Of the additional negative affect items, feeling weak (p = .40, d = 0.12), log transformed helpless (p = .13, d = 0.27), and out of control (p = .11, d = 0.29) were not rated differently between episodes. Feeling blamed, however, was significantly higher for non-adherent episode (p = .004, d = 0.73, medium to large effect).

There was no significant difference in reports of feeling ill between episodes (p = .76, d = 0.06).

Discussion

This study represents an initial exploration of situational medication adherence amongst young PHIV + people. Non-adherence was strongly associated with lower perceived behavioural skills at the time of the episode. The behavioural skills construct in the IMB model includes having the confidence and skill to self-cue and self-administer ART, incorporate ART into daily routines, manage possible unwanted effects and reinforce oneself for ongoing adherence (Fisher et al., 2014). Our findings are consistent with the model, which proposes that behavioural skills are the most proximal factor to adherence (Fisher, Amico, Fisher, & Harman, 2008). Our findings also suggest that perceived behavioural skills vary situationally. Relationships between higher levels of self-efficacy (closely related to perceived behavioural skills) and ART adherence have been demonstrated between participants in the PHIV+ population (Kang et al., 2015; Rudy et al., 2010). Bandura suggested that higher self-efficacy produces greater effort and persistence in solving problems when facing challenges (Bandura, 1986). Our participants may have faced different situational challenges, which subsequently impacted on effort and self-confidence in adhering to ART at that time.

Non-adherence was not associated with the other central constructs of the IMB model (information and motivation). The lack of difference in information scores between episodes may have been due to a ceiling effect. In the IMB model, information is essential for adequate adherence (Fisher et al., 2014). ART-related knowledge may be necessary but not sufficient for adherence. Non-adherence was also not associated with ART motivation, consistent with findings with adults with Beta Thalassaemia Major using a similar within-participant methodology (Vosper et al., 2013) but in contrast to between-participant findings in young people with PHIV+ (Rudy et al., 2009).

Non-adherence was associated with lower activated (e.g., “I feel happy”) and non-activated (e.g., “I feel calm”) positive affect. Examining positive affect in relation to adherence is rarely reported in the literature. Non-adherence was not significantly associated with negative affect, although this may be due to low statistical power. Studies in adults have also failed to find a relationship between negative affect and ART adherence (Gonzalez et al., 2007). There was an association between feeling blamed and non-adherence, although it is not

Table 5. Descriptive statistics for affective and somatic variables.

| Variable                      | Episode          | Mean (SD) | p value* |
|-------------------------------|------------------|-----------|----------|
| PANAS-C 5 item Positive affect|                 |           |          |
| (5–25)                        | Non-adherent     | 8.55 (5.55)| .005   |
|                              | Adherent         | 12.15 (6.62)|         |
| Calm                          | Non-adherent     | 2.34 (1.32)| .01     |
| (1–5)                         | Adherent         | 3.33 (1.49)|         |
| At ease                       | Non-adherent     | 2.28 (1.31)| .03     |
| (1–5)                         | Adherent         | 3.07 (1.54)|         |
| Content                       | Non-adherent     | 2.14 (1.19)| .03     |
| (1–5)                         | Adherent         | 2.85 (1.43)|         |
| Satisfied                     | Non-adherent     | 2.17 (1.34)| .02     |
| (1–5)                         | Adherent         | 3.00 (1.54)|         |
| PANAS-C 5 item Negative Affect|                 |           | .08     |
| (5–25)                        | Non-adherent     | 8.96 (5.25)|         |
|                              | Adherent         | 11.34 (5.97)|        |
| Weak                          | Non-adherent     | 2.10 (1.21)| .40     |
| (1–5)                         | Adherent         | 2.00 (1.44)|         |
| Helpless                      | Non-adherent     | 2.17 (1.47)| .13     |
| (1–5)                         | Adherent         | 1.77 (1.07)|         |
| Out of control                | Non-adherent     | 2.21 (1.40)| .11     |
| (1–5)                         | Adherent         | 1.93 (1.36)|         |
| Blamed                        | Non-adherent     | 2.17 (1.39)| .004    |
| (1–5)                         | Adherent         | 1.41 (0.80)|         |
| Somatic symptoms              | Non-adherent     | 2.52 (1.37)| .76     |
|                              | Adherent         | 2.54 (1.38)|         |

*p value of difference between non-adherent and adherent episode.
clear whether feeling blamed occurred before or after non-adherence. Non-adherence was significantly associated with weekend days, lack of routine and being out of the home. Being away from home has been cited as a reason for non-adherence (Denison et al., 2015), and having a routine has been cited as a reason for ART adherence in HIV+ adolescents (Kim, McDonald, Kim, Foster, & Fidler, 2015). Lower adherence levels at weekends have prompted trials of regimens that do not include weekend doses (Butler, 2015). The differences between episodes on behavioural variables suggest difficulty in adhering in particular contexts. Different daily activity may have interfered with adherence planning and cueing. Psychological variables found to vary between episode (behavioural skills and positive affect, in particular) may have mediated the relationship between situation and adherence. For example, young people might feel more confident in particular contexts, which then facilitates adherence. This could not be tested statistically due to our small sample.

This study was limited by the use of non-standardised measures, whose psychometric properties should be established in larger samples. The small sample size meant that there was limited statistical power to detect significant differences and precluded any multivariable analysis. The study benefited from systematic sampling and a good response rate (81%). There may, however, have been differences between those who participated and those who chose not to take part which biased the findings.

Future research could assess whether companions at the time of the episode are aware of the young person’s HIV status. PHIV+ young people have reported not taking ART to avoid disclosing their diagnosis (Denison et al., 2015). Associations between onward disclosure and less hiding of medication have been found in PHIV+ children and adolescents (Calabrese et al., 2012). Larger samples could enable analysis of adherence predictors between ages, support multivariable analysis and allow comparison of predictors of intentional versus unintentional non-adherence. Forgetting may be a particularly pertinent factor in episodic non-adherence in this population. With changes to usual routine and location, an absence of relied-upon cues would necessitate a greater reliance on working memory, which may be impaired in the PHIV+ population (Laughton et al., 2013). Prospective studies, using ecological momentary assessment of adherence episodes, could enhance measurement reliability and validity (Shiffman, Stone, & Hufford, 2008).

Clinically, assessments of barriers to and facilitators of adherence could focus on situational variations in cognitions and affect. A greater understanding of situational factors implicated in non-adherence would help clinicians and young people in considering strategies to manage situations with a greater risk of non-adherence. This work could use the concepts of action planning (developing when, where and how elements of goal-directed behaviour) and coping planning (anticipating barriers and planning alternative actions to attain one’s goals) (Sniehotta, Scholz, & Schwarzer, 2006).

A focus on facilitators (as well as barriers) to adherence is consistent with psychological interventions, including Motivational Interviewing and Cognitive Behaviour Therapy (Mbuagbaw et al., 2015). This study highlights perceived behavioural skills as potentially critical for episodic ART adherence, suggesting that key areas for intervention could be: improving confidence to overcome barriers, promoting abilities in acquiring personal and social support, incorporating ART into daily life, self-cueing and self-reinforcement to adhere to ART (Fisher et al., 2006).

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