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A Systematic Review of Treatment Fatigue among HIV-infected Patients Prescribed Antiretroviral Therapy

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Abstract

HIV treatment requires lifelong adherence to medication regimens that comprise inconvenient scheduling, adverse side effects, and lifestyle changes. Antiretroviral adherence and treatment fatigue have been inextricably linked. Adherence in HIV-infected populations has been well investigated; however, little is known about treatment fatigue. This review examines the current state of the literature on treatment fatigue among HIV populations and provides an overview of its etiology and potential consequences. Standard systematic research methods were used to gather published papers on treatment fatigue and HIV. Five databases were searched using PRISMA criteria. Of 1,557 studies identified, 21 met the following inclusion criteria: (a) study participants were HIV-infected, (b) participants were prescribed antiretroviral medication, (c) the article referenced treatment fatigue, (d) the article was published in a peer-reviewed journal, and (e) text was available in English. Only seven articles operationally defined treatment fatigue, with three themes emerging throughout the definitions: (1) pill burden, (2) loss of desire to adhere to the regimen, and (3) nonadherence to regimens as a consequence of treatment fatigue. Based on these studies, treatment fatigue may be defined as “decreased desire and motivation to maintain vigilance in adhering to a treatment regimen among patients prescribed long-term protocols.” The cause and course of treatment fatigue appear to vary by developmental stage. To date, only structured treatment interruptions have been examined as an intervention to reduce treatment fatigue in children and adults. No behavioral interventions have been developed to reduce treatment fatigue. Further, only qualitative studies have examined treatment fatigue conceptually. Studies designed to systematically assess treatment fatigue are needed. Increased understanding of the course and duration of treatment fatigue is expected to improve adherence interventions, thereby improving clinical outcomes for individuals living with HIV.

Keywords

treatment fatigue; HIV; review; adherence

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Introduction

HIV treatment requires strict adherence and lifestyle changes, including integration into daily routine, coping with side effects, consistently obtaining prescription refills and attending medical appointments, and remembering to take medications throughout the patient's life (Chesney et al., 2000; Friedland, 2006). Treatment fatigue has been identified as a consequence of long-term regimens resulting in a decline in adherence over time and with subsequent regimens (Arem et al., 2011; Ostrop, Hallett, & Gill, 2000; Cook et al., 2011; Gardner, Burman, Maravi, & Davidson, 2006; Ickovics & Meade, 2002; Johnson, Stallworth, & Neilands, 2003; Paterson et al., 2000). Although we have extensive knowledge on mechanisms associated with nonadherence and have developed interventions to promote adherence, little is known about the development and course of treatment fatigue. This systematic literature review aimed to examine treatment fatigue among people living with HIV (PLWH) by (a) identifying factors contributing to the etiology and maintenance of treatment fatigue, (b) examining the extent to which treatment fatigue is systematically measured, and (c) identifying methods of intervention.

Methods

Search strategy and selection of studies

Studies published through August 2013 that examined treatment fatigue among PLWH prescribed ART were reviewed based on PRISMA guidelines. Searches were conducted within PsycINFO, PubMed, CINAHL, Medline, and Web of Science databases using the following terms: ("*treatment*" OR "*pill*" OR "*medication*" OR "*regimen*") AND "*fatigue*" AND "*HIV*." After deleting duplicate references ($n = 1,020$), 537 articles were identified. Articles were excluded if the work (a) represented an unpublished thesis or dissertation; (b) was not peer-reviewed; (c) was unavailable in English; (d) study participants were HIV seronegative; (e) study participants were not prescribed ART; (f) the study comprised animal research; (g) made no reference to fatigue or cited only physiological fatigue. Twenty-one studies were included in the final review (see Figure 1). Data extracted included: (a) definition of the construct; (b) developmental factors; (c) potential etiological factors, (d) potential consequences; (e) developmental factors; (g) method of measurement; and (h) interventions.

Results

Definition

A variety of terms were used to describe the targeted concept, including "pill fatigue," "medication fatigue," "treatment fatigue," "regimen fatigue," "dosing fatigue," "drug fatigue," and "injection fatigue" (see Table 1). Only seven articles provided a definition (see Table 2), resulting in three primary themes: (1) "pill burden," (2) "loss of desire" or "tiring" of adhering to treatment, and (3) nonadherence. The most thorough definition was provided by Miramontes (2001), who characterized treatment fatigue by (a) patient characteristics (e.g., life stressors, cultural/health beliefs), (b) patient-provider relationship (e.g., respect, trust, communication), and (c) regimen issues (dosing restrictions, impact on lifestyle).

Etiology

Among children/adolescents, pharmacological properties, including the number of pills, hospital visits required, side effects, dosing restrictions, and time since regimen initiation, were noted as etiological factors (Marhefka, Tepper, Brown, & Farley, 2006; Merzel, VanDevanter, & Irvine, 2008; Saitoh et al., 2008; and Van Dyk, 2010). Treatment fatigue tends to fluctuate over time and may occur more frequently within the first year of treatment among children/adolescents (Marhefka et al., 2006).

Developmental characteristics have been identified as contributing factors. As children move into adolescence, adherence tends to decrease (Mellins, Brackis-Cott, Dolezal, & Abrams, 2004). Most children become aware of their HIV status after age eight or nine (Pinzón-Iregui, Beck-Sagué, & Malow, 2013) and begin to take over medication responsibilities during adolescence (Merzel et al., 2008). Challenges noted among caregivers of HIV-infected adolescents included children's lying about taking medications and difficulty monitoring adherence during the school hours and summer months (Merzel et al., 2008; Saitoh et al., 2008). Consequently, caregivers appear to experience treatment fatigue. Among the adult population, risk and protective factors included patient characteristics (e.g., quality of life, cultural/health beliefs, life stressors) and the patient-provider relationship (e.g., mutual respect and trust, provider accessibility, communication, patient satisfaction).

Consequences

Among children/adolescents, the most commonly reported consequence is nonadherence. Among adults, pharmacological properties were identified most frequently as contributing factors (see Table 1 for citations), including pill/treatment burden and intensity of treatment, continuous daily treatment, complicated regimens, time since treatment initiation, prolonged treatment, and side effects.

Interventions

Only one study aimed to decrease treatment fatigue among children/adolescents through planned treatment interruption (PTI; Noguero et al., 2010). Significant decreases in CD4 counts and increased viral loads were reported after 12 months, suggesting PTIs are not an effective method of intervention. Within the adult population, PTIs have been used to prevent treatment fatigue (Eron et al., 2008); however, routine PTIs are discouraged due to viral replication and disease progression (Lundgren et al., 2008; Danel et al., 2006). No behavioral interventions were identified to decrease treatment fatigue among adults or children/adolescents.

Measurement

Only three studies reported quantitative or qualitative measurement of treatment fatigue. One study assessed reasons for nonadherence among children via survey administered to the primary care provider (Saitoh et al., 2008). Merzel and colleagues (2008) examined treatment fatigue among caregivers of HIV-infected children through qualitative interviews, noting that "regimen fatigue" emerged as a result of children's opposition to taking medications as they grow older. Van Dyk (2010) surveyed 439 HIV-infected individuals via

a semi-structured interview and assessed treatment fatigue using a single item labeled “treatment fatigue (i.e., taking ‘treatment holidays’)”.

Discussion

This review examined the potential causes, consequences, and characteristics of treatment fatigue among PLWH. Twenty-one relevant studies were identified. A variety of terminology was used interchangeably to address this same construct within the literature (see Table 1), the most frequent being “treatment fatigue.” However, the literature lacks consensus of an operational definition (see Table 2). Based on this review, treatment fatigue is separate from and should not be equated with nonadherence, as treatment fatigue seems to evoke its own consequences. This demonstrates the importance of developing an adequate definition of and valid and reliable measurements to assess treatment fatigue.

Developmental factors appear to be associated with treatment fatigue (see Table 1). Specifically, these studies highlighted pill burden (e.g., number/size of pills) as contributing to treatment fatigue in children. As children move into adolescents it appears that increased autonomy may play a stronger role in treatment fatigue. Among caregivers of HIV-infected children/adolescents, oppositional behaviors such as lying, refusing to take medications, and difficulty monitoring adherence contribute to caregivers’ experience of treatment fatigue. Finally, among adults, the literature suggests that pill burden and patient-provider interaction play a role in the development of treatment fatigue.

To date, only pharmacological interventions using structured treatment interruptions have been examined to decrease treatment fatigue; however, these interventions are not recommended due to increased morbidity and mortality risk. Behavioral interventions, tailored to developmental stage, may provide a platform to address factors associated with treatment fatigue. Further, patients newly prescribed treatment regimens may benefit from education about treatment fatigue and development of skills to prevent its occurrence. Timing, delivery method, and dose response should be considered prior to intervention development. Treatment fatigue is not a one-time, static experience, but occurs at multiple times throughout the patient’s life.

This review highlights the paucity of research on and understanding of treatment fatigue. Synthesis of existing terminology describing this construct is needed. The most widely used term that described this concept was “treatment fatigue.” Unfortunately, this term frequently represents the physiological construct of fatigue as a consequence of disease or medication side effects and may result in confusion among disciplines. The authors propose use of the term “treatment regimen fatigue” to represent the psychological fatigue associated with long-term treatment. Consolidation of a definition is an important foundation for future investigations. The authors propose the following operational definition of treatment regimen fatigue: decreased desire and motivation to maintain vigilance in adhering to a treatment regimen as prescribed by a provider.

Several limitations should be acknowledged. First, this review only targeted PLWH in order to minimize confounding variables in the development of the concept. Second, this review is

not intended to be an exhaustive review of the literature. The lack of consistent terminology used to identify treatment fatigue in the literature makes it plausible that some articles were not identified that examined this construct. However, the authors used a variety of search terms that are commonly used in the HIV literature related to this construct, consulted with healthcare providers regarding terms used within the clinic setting, and examined literature from other chronic illness populations to determine appropriate search terms in an effort to include as many relevant studies as possible. Third, the lack of established research resulted in a small number of studies meeting inclusion criteria for the current study, which limits the ability to draw conclusions. Finally, the quality of construct measurement, either qualitatively or quantitatively, in the included studies is not optimal for accurately defining treatment regimen fatigue.

This review details the emergence of treatment fatigue in the HIV literature and takes the first step towards defining and identifying its etiology and consequences. Future research should seek to develop a valid and reliable measure of treatment fatigue. Examination of caregivers' experience of treatment fatigue for HIV-infected children and adults is important. Further study regarding the etiology, maintenance, and life course of treatment fatigue is expected to aid intervention efforts.

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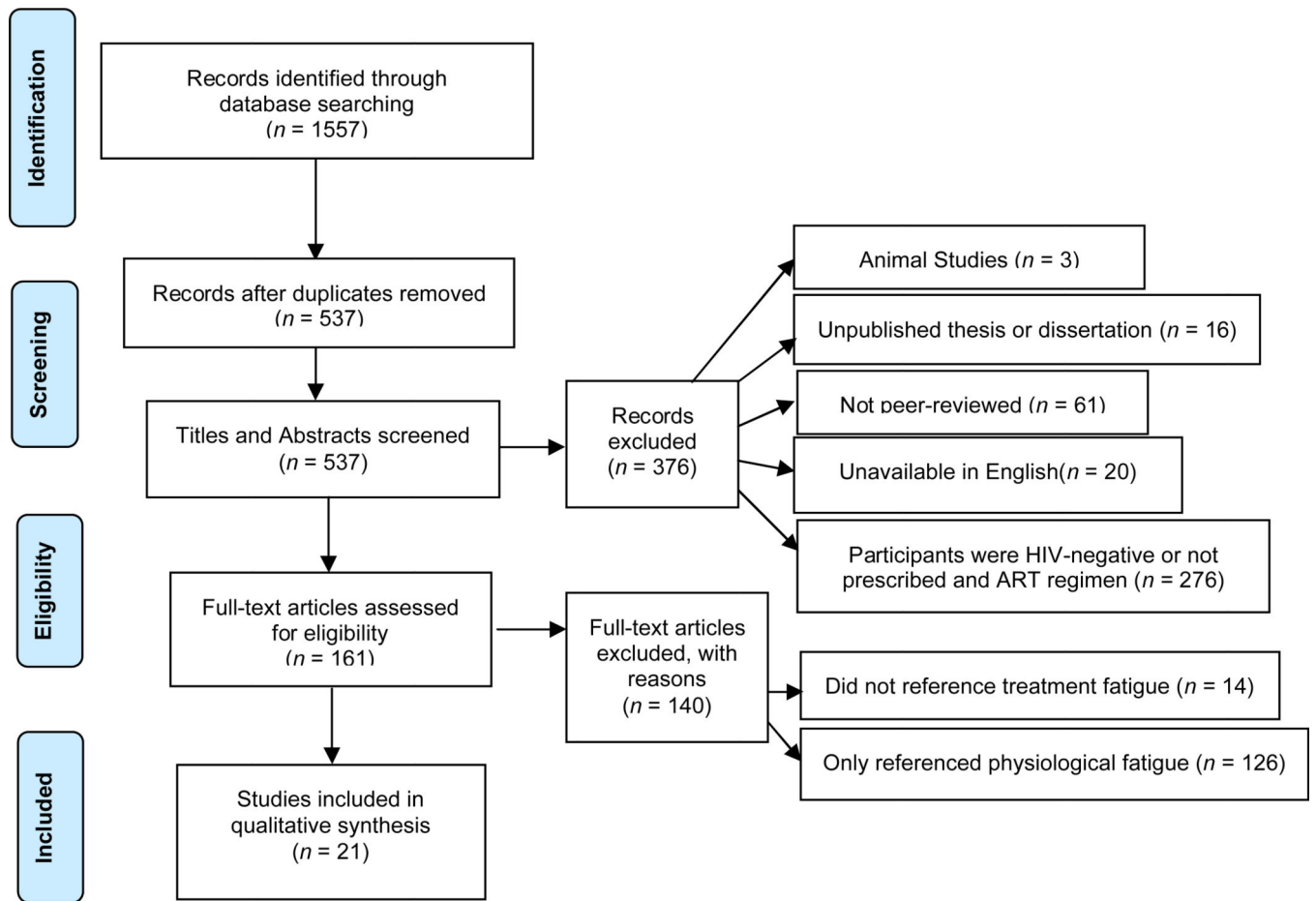


Figure 1.
Study Flow Diagram

Table 1

Summary of Content Analyses of Treatment Fatigue Grouped by Developmental Stage

Terminology	Article	Developmental Factors of Treatment Fatigue	Potential Contributing Variables	Potential Consequences of Fatigue	Fatigue Measurement
<i>Children</i>					
<i>Medication Fatigue</i>	Saitoh et al. (2008)	Treatment requirements, difficulty monitoring	Pill burden	Treatment interruption, decline in CD4 cell count	Survey of PCP ^a
<i>Treatment Fatigue</i>	Noguera et al. (2010)		---	Planned treatment interruption	---
<i>HIV-infected Children & their Caregivers</i>					
<i>Regimen Fatigue</i>	Merzel et al. (2008)	Increased autonomy and opposition	Treatment burden, increased child autonomy	Decreased adherence	Qualitative Interview
<i>Regimen Fatigue</i>	Marhefka et al. (2006)	Fluctuates over time, onset often in first year of HAART	Pill burden, time since regimen initiation, dosing, side effects	Nonadherence to HAART	---
<i>Adolescents</i>					
<i>Treatment Fatigue</i>	Van Dyk (2010)	Pharmacological properties	Treatment burden	Nonadherence, drug holidays	Qualitative interview
<i>Adults</i>					
<i>Pill Fatigue</i>	Cohen et al. (2007)	Continuous daily treatment	Continuous treatment, daily medications	Erratic adherence, treatment failure	---
<i>Pill Fatigue</i>	Miron & Smith (2010)	Treatment intensity	Intense course of treatment	Drug holidays	---
<i>Pill Fatigue</i>	Ostrop et al. (2000)		---	Nonadherence	---
<i>Pill Fatigue</i>	Skies et al. (2008)		---	Discontinuation of HAART	---
<i>Medication Fatigue</i>	Ruane et al. (2003)		Complicated regimens	Decreased willingness to adhere	---
<i>Treatment Fatigue</i>	Arem et al. (2011)	Time since treatment initiation	Length on regimen	Decreased adherence	---
<i>Treatment Fatigue</i>	Bagenda et al. (2011)	Prolonged treatment	Prolonged HAART	Nonadherence	---
<i>Treatment Fatigue</i>	DiMascio et al. (2003)	Prolonged treatment	Prolonged HAART	Decreased adherence	---
<i>Treatment Fatigue</i>	Fox et al. (2010)		---	Nonadherence	---
<i>Treatment Fatigue</i>	McMahon et al. (2007)	Side effects	Side effects	Interfere with long-term treatment	---
<i>Treatment Fatigue</i>	Miramontes (2001)	Treatment intensity, pharmacological properties, patient-provider interactions, patient characteristics	Patient characteristics, patient-provider relationship, regimen issues (e.g., dosage, side effects)	Discontinuation of treatment	---

Terminology	Article	Developmental Factors of Treatment Fatigue	Potential Contributing Variables	Potential Consequences of Fatigue	Fatigue Measurement
<i>Treatment Fatigue</i>	Pai et al. (2006)		---	Nonadherence	---
<i>Treatment Fatigue</i>	Thompson et al. (2009)	Side effects	Side effects, regimen burden	Nonadherence	---
<i>Dosing Fatigue</i>	Ruane et al. (2010)	Complicated regimens	Regimen burden	Decreased long-term adherence	---
<i>Drug Fatigue</i>	Lemiale et al. (2009)		---	---	---
<i>Injection Fatigue</i>	Lalezari et al. (2003)		Number of injections	Discontinuation of treatment	---

^aPCP = primary care provider

Table 2

Definitions of Fatigue in Relation to HIV-Medication Adherence

Terminology	Article	Definition of Fatigue
<i>Medication Fatigue</i>	Ruane et al. (2003)	"unwillingness to continue treatment due to the nuisance of having to take a multiplicity of doses and a high pill burden"; "loss of desire to take medication over time due to high pill burden"
<i>Regimen Fatigue</i>	Saitoh et al. (2008)	"patients who were unable to take antiretroviral medications because of pill burden and/or nonadherence"
	Marhefka et al. (2006)	No definition provided
	Merzel et al. (2008)	No definition provided
<i>Treatment Fatigue</i>	Arem et al. (2011)	"patients tiring of continually taking ART"
	Bagenda et al. (2011)	No definition provided
	DiMascio et al. (2003)	No definition provided
	Fox et al. (2010)	No definition provided
	McMahon et al. (2007)	No definition provided
	Miramontes (2001)	"treatment fatigue is a generic term that includes aspects from all three domains: (a) patient characteristics, such as life stresses, quality of life, and cultural and health beliefs; (b) issues stemming from the patient-provider relationship, such as respect, trust, accessibility, communication, and patient satisfaction; and (c) treatment regimen issues, such as number of medications, dosing frequency, side effects, duration of therapy, impact on lifestyle, and cost"
<i>Dosing Fatigue</i>	Noguera et al. (2010)	No definition provided
	Pai et al. (2006)	No definition provided
	Thompson et al. (2009)	No definition provided
	Van Dyk (2010)	"taking 'treatment holidays'; 'emotional tiredness of taking ARVs'"
<i>Pill Fatigue</i>	Ruane et al. (2010)	Pill fatigue: "unwillingness to continue treatment due to the nuisance of having to take a multiplicity of doses and a high pill burden" and "loss of desire to take medication over time due to high pill burden"
	Cohen et al. (2007)	No definition provided
<i>Drug Fatigue</i>	Miron & Smith (2010)	No definition provided
	Ostrop et al. (2000)	No definition provided
	Skjest et al. (2008)	No definition provided
<i>Injection Fatigue</i>	Lemiale et al. (2009)	No definition provided
	Lalezari et al. (2003)	"tired of giving injections"