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REVIEW PAPER

Impact of HIV-Status Disclosure on Adherence to Antiretroviral Therapy Among HIV-Infected Children in Resource-Limited Settings: A Systematic Review

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Abstract Pediatric HIV remains a significant global health dilemma, especially in resource-constrained nations. As access to ART increases around the world, areas of concern in pediatric HIV treatment include age-appropriate disclosure of HIV status to children and development of adherence habits over time. This review was conducted to synthesize quantitative associations reported between disclosure and adherence among children living with HIV in resource-limited settings. An electronic database search of PubMed, MEDLINE and Cochrane returned 1348 results after removal of duplicates, 14 of which were found to meet inclusion criteria. Review of these reports showed conflicting results regarding the impact of disclosure on adherence, with 5 showing no association, 4 showing a negative impact of disclosure on adherence, and 5 showing positive benefits of disclosure for adherence habits. Thus, there was no clear consensus on the effect, if any, that disclosure has on medication adherence. Longitudinal, prospective research needs to be conducted to evaluate further impacts that disclosure may have on adherence habits over time, and interventions must be structured to link the two processes together in order to maximize health benefit to the child or adolescent.

Resumen A medida que el acceso a tratamiento anti-retroviral aumenta alrededor del mundo, la revelación a un niño de su diagnóstico de VIH y el cumplimiento con el tratamiento anti-retroviral continúan siendo un reto. Esta revisión de literatura resume las asociaciones cuantitativas reportadas entre la revelación del diagnóstico y el cumplimiento del tratamiento anti-retroviral en niños viviendo con VIH en un entorno de recursos limitados. Una búsqueda en la base de datos electrónica de PubMed, MEDLINE y Cochrane, luego de descartar resultados duplicados, arrojó 1348 resultados de los cuales 14 cumplían con los criterios de inclusión. Estos estudios reportaron resultados conflictivos con respecto al impacto de la revelación del diagnóstico sobre el cumplimiento del tratamiento: 5 reportes demostraron no asociación, 4 demostraron un impacto negativo de la revelación del diagnóstico sobre el cumplimiento del tratamiento, y 5 demostraron beneficios positivos de la revelación sobre el cumplimiento. Por tanto, no hay un consenso en el efecto que tiene la revelación del diagnóstico sobre el cumplimiento del tratamiento. Se necesitan estudios prospectivos para evaluar a fondo el impacto que la revelación del diagnóstico podría tener a través del tiempo en los hábitos de cumplimiento del tratamiento y las intervenciones deben ser estructuradas para enlazar estos dos procesos, maximizando así el beneficio a la salud del niño o adolescente.

Keywords Pediatric · Adherence · Disclosure · Resource-limited · HIV

Introduction

The pediatric HIV epidemic continues to be of global health significance, particularly in resource-limited countries. Sub-Saharan Africa is disproportionally affected; it is home to over 90 % of pediatric HIV cases worldwide [1]. Although there has been increased access to antiretroviral

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therapy (ART) in resource-limited settings, pediatric HIV ART coverage still lags behind that of adults. At the end of December 2013, only 23 % of HIV-infected children were receiving ART [2]. With the recent World Health Organization (WHO) recommendation to start ART in children regardless of WHO clinical stage or CD4 cell count [3], pediatric ART coverage will increase worldwide. As ART coverage increases, two perennial challenges with treatment—HIV status disclosure and adherence to treatment—are bound to escalate [4, 5]. Treatment success depends on an unwavering cooperation of the patient and optimum adherence to treatment doses and schedules. One can speculate that when a patient does not understand the reasons for taking a prescribed medication, the cooperation needed could be compromised. This is akin to giving medication to HIV-infected children without disclosing their HIV status to them. Moreover, with HIV treatment, an optimum adherence of ≥95 % is required to achieve sustained virologic suppression and to avoid evolution of drug-resistant HIV variants [6, 7].

Since 1999, the American Academy of Pediatrics has recommended age-appropriate disclosure of HIV status to children, with full disclosure occurring by adolescence in order to achieve better disease outcomes and assist with the child's psychological adjustment to knowing his or her status [8]. In 2011, the WHO published a similar set of guidelines which recommended beginning the disclosure process at 6 years old, with full disclosure accomplished by the age of twelve [4]. However, several studies from resource-limited settings have reported unacceptably low levels of disclosure of HIV status to HIV-infected children [5, 9, 10]. Reasons that caregivers do not disclose their child's HIV-positive status to the child include fear of social rejection and isolation, parental sense of guilt, worry that the child will not keep their diagnoses to themselves, and concerns on how disclosure will affect the psychological health of the child [9, 11, 12]. There are emerging reports on the benefits of disclosure of HIV status, including psychological health, improved adherence and better clinical outcomes [13–15]. However, the prevalence of pediatric HIV disclosure is poor, ranging from 0 to 69 % in one systematic review [12].

Despite the fact that adherence is the sine qua non for successful HIV treatment and prevention of disease progression, it continues to be low in pediatric HIV, with one study in Ethiopia finding only 34.8 % of children to have an adherence rate of ≥95 % using unannounced home-based pill count [16]. The low prevalence of pediatric adherence is due to complex and inter-related factors, which are often beyond the control of the child [17–20]. Examples of factors affecting adherence in HIV-infected children are: (1) total dependence on the caregiver for procurement and administration of medication [20]; (2) lack of appropriate pediatric drug formulation and the taste of available formulations [19, 21]; and (3) socioeconomic status of the caregiver and access to service delivery [18, 20]. Moreover, in resource-limited settings where access to more expensive second-line regimens are limited, adherence to first-line regimens is critical. Thus children and their caregivers are constantly negotiating on ways to ensure optimum adherence to therapy. One factor that might help with the success of this negotiation is disclosure of HIV status to the child. Disclosure might help the child understand why he or she is taking daily medications and the benefits thereof.

There have been multiple studies in resource-poor settings seeking to find associations between disclosure status and levels of ART adherence. A number of studies have reported both psychological and medical benefits of disclosure of their HIV positive status to children and adolescents [9, 12]. However, many of these studies have been qualitative in nature and have not shown quantifiable associations of status disclosure with medication adherence, instead using caregiver and child interviews as the basis for establishing the connection between the two [21–24]. However, as disclosure becomes a more prominent focus in pediatric HIV treatment, there is a need for more longitudinal and quantitative data in order to establish the associations and effects of disclosure on adherence. In this way, interventions may be designed to utilize the disclosure process as a chance to develop better adherence habits in children and adolescents on antiretroviral treatment. This review sought to synthesize published quantitative data on the relationship between disclosure and adherence in order to better understand the impact the disclosure process is having on HIV-infected children in resource-limited countries.

Methods

Primary Search Strategies, Information Sources, and Inclusion Criteria

We conducted a systematic search of electronic medical databases, including PubMed (inception-October 2015), MEDLINE (January 1998–October 2015) and the Cochrane Database of Systematic Reviews (January 1998–October 2015). Search strategy involved the following phrases and Boolean operators: *pediatric* AND* medication* AND* adherence*, *pediatric* AND* hiv* AND* disclosure*, and *caregiver* AND* hiv* AND* disclosure*. Searches were conducted by JSN, and the final search was completed on October 13, 2015. The authors also examined the references and bibliography lists of two identified systematic reviews to maximize identification of relevant articles for inclusion

[9, 12]. Research protocols and study inclusion criteria were determined a priori by the authors, but the protocol was not previously published in a systematic review database.

Publications were eligible for selection if they included quantitative data on the association between HIV status disclosure and adherence to ART in pediatric patients in resource-limited settings. The age range considered was 0–19 years with both children (0–9 years) and adolescents (10–19 years) included. Additionally, the study had to have been conducted in a low- or middle-income nation as determined by 2015 World Bank classification [25]. Only studies published since 1999, the year of the American Academy of Pediatrics disclosure recommendation publication [8], were considered. Disclosure in the included studies was defined as the child knowing that he or she has the HIV infection, as determined by either caregiver or child report. Furthermore, the study had to have a defined measure of adherence, such as patient report, caregiver report, pill count or electronic methods. Each study included a threshold for what was considered "adherent" versus "non-adherent" based on the method of adherence determination that the authors had used. Cross-sectional and observational study designs were considered for inclusion.

Article Review and Data Extraction

Studies included in the review were obtained through a two-step screening process. Initial search results were scanned for possible inclusion. Studies that clearly did not relate to HIV, studies conducted only in an adult population, studies published prior to 1999, studies conducted in resource rich nations, and studies with only qualitative data were excluded on initial examination (Fig. 1). Publications that passed the initial screening were then more thoroughly examined for predetermined inclusion criteria by two independent researchers (JSN and ARS). Disagreements over inclusion were settled by consensus. After the second review of the articles, records were excluded [10, 13, 14, 22–24, 26–39] for lack of quantifiable associations of adherence with disclosure or conduction of the study in a "high income" setting as classified by the World Bank system [25]. Data regarding study population and setting, medication adherence measurement tools, medication adherence levels, disclosure levels and quantified associations between disclosure and adherence were extracted for review and analysis. Risk of inherent bias regarding medication adherence determination used in the studies was noted during review of the articles and is discussed further below. Quality of the studies was noted during review by evaluating study design, sample sizes, inherent study bias and publication bias. Descriptive statistics regarding sample sizes of the studies included were calculated using Microsoft Excel (2013). No statistical meta-analysis of data was performed due to different methods of measuring adherence, different age ranges in the study populations (which would skew the rates of disclosure), and, ultimately, different methods used to calculate associations between adherence and disclosure.

Results

Studies Included in the Review

Figure 1 represents search results using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart paradigm [40]. Initial keyword searches in the three databases yielded a total of 2228 results (PubMed = 1392; MEDLINE = 789; Cochrane = 47), while record retrieval from two systematic reviews [9, 12] yielded 63 results, for a total of 2291 records. After excluding repeated titles, 1348 records remained. From the initial screening of titles and abstracts, 1314 of these results were excluded due to non-HIV related topics (N = 878), publication date prior to 1999 (N = 69), conduction of the study in a resource-rich setting (N = 81), exclusively adult study population (N = 98), lack of data on disclosure rates or adherence rates (N = 110), qualitative study design (N = 76), and case report study design (N = 2). Thirty-four articles were then saved for full-text review by JSN and ARS. After the second review of the articles, studies were excluded [10, 13, 14, 22–24, 26–39] for poorly defined adherence (N = 2) [23, 38], lack of quantifiable associations of adherence with disclosure (N = 15) [10, 13, 14, 22, 24, 26–28, 30–32, 34, 35, 37, 39] or conduction of the study in a "high income" setting (N = 3) [29, 33, 36] as classified by the World Bank system [25]. Fourteen studies met all of the selection criteria (Table 1).

Study Designs and Sample Characteristics

The study designs were predominately cross-sectional (12 of 14), with only 2 studies being prospective observational cohorts (Table 1). There was a wide variation in the sample sizes of the studies included with a mean sample size of 293.93 (SD, 219.74) and a range of 57–792. The total number of children and adolescent included in the studies was 4115. The ages ranged from 2 months to 19 years old. With regard to region of study, 85.7 % were from Africa (East Africa, 7; West Africa, 2; and South Africa, 3) and 14.3 % from Asia (India, 1 and Thailand, 1). Of the studies from Africa, 4 of 12 were conducted in Ethiopia. Mother-to-child transmission and blood transfusions were the modes of HIV transmission considered in 13 of the studies,

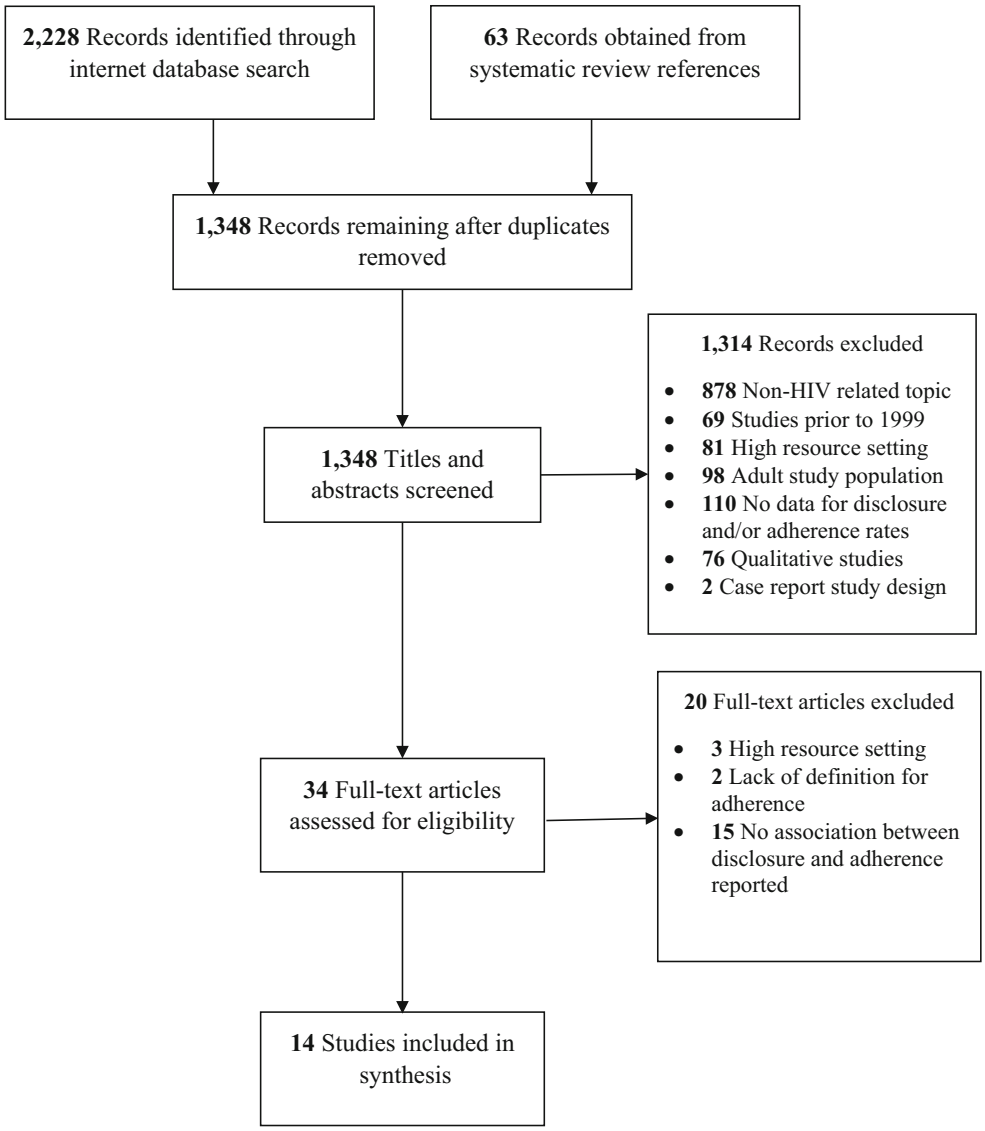

Fig. 1 Search Algorithm

while 1 study also included horizontally infected adolescents in their sample population [41].

Adherence Measures and Prevalence

Levels of adherence and methods for adherence measurement varied widely in the various studies examined (Table 2). Three of the studies used multiple methods in order to determine level of adherence [15, 42, 43]. In total, 10 studies reported adherence values based on various forms of caregiver recall or report [15, 42–50]; 3 used pharmacy or clinic-based pill count [15, 43, 51]; 2 utilized child report [41, 42]; 2 performed unannounced home-based pill count [16, 43]; 2 utilized Medication Event Monitoring Systems (MEMS, Aardex, Switzerland) [15, 32]; and 1 study used Visual Analogue Scale (VAS) [15]. Studies indicated that they considered "adherence" to involve either a patient taking ≥95 % of medication doses over a given period of time [15, 16, 32, 41, 43–45, 48, 51] or no missed doses on recall in a specified time window [42, 46, 47, 49, 50], although the length of time patients were followed differed between the studies. Most authors chose to report their data as "percentage of patients obtaining adherence" (Table 2), and data for these studies ranged from 34.8 % [16] (using announced home-based pill count) to 94.1 % [43] (using clinic-based pill count). Five of the studies reported the percentage of patients adherent separately in disclosed versus undisclosed children [16, 42, 43, 50, 51]. Three studies chose to examine adherence as a continuous variable with each

Table 1 Characteristics of study populations

Study authors	Country and setting	Study design	N = patient population	Patient ages
Arage et al. [44]	Northeast Ethiopia; three hospitals in South Wollo Zone	Cross-sectional	N = 440	2 months–14 years old
Bhattacharya et al. [49]	India: ART clinic at a hospital in North India	Cross-sectional	N = 145	>5 years old[a]
Biadgilign et al. [46]	Ethiopia; five hospitals in Addis Ababa	Cross-sectional	N = 390	3 months–14 years old
Biressaw et al. [16]	Ethiopia; urban pediatric ART clinic	Cross-sectional	N = 210	1–14 years old
Cluver et al. [41]	South Africa; stratified sample from 39 health facilities in Eastern Cape	Cross-sectional	N = 684	10–19 years old
Dachew et al. [45]	Northwest Ethiopia; Gondar Hospital and Gondar Poly Clinic	Cross-sectional	N = 314	2 months–15 years old
Haberer et al. [15]	Zambia; University Teaching Hospital in Lusaka	Prospective, observational cohort	N = 96	Median (IQR): 6 years old [2, 9][b]
Muller et al. [32]	South Africa; public hospital in Cape Town	Cross-sectional	N = 57	9–128 months old
Nabukeera-Barungi et al. [43]	Uganda; Mulago Hospital	Cross-sectional	N = 170	2–18 years old
Polisset et al. 2008	Togo; three HIV/AIDS care centers in Lome	Cross-sectional	N = 74	15 years old or younger
Sirikum et al. [51]	Thailand; Thai Red Cross AIDS Research Centre, Bangkok	Prospective, observational cohort	N = 260	6–18 years old
Turissini et al. [50]	Kenya; large referral clinic in Eldoret	Cross-sectional	N = 270	6–14 years old
Ugwu and Eneh [48]	Nigeria; pediatric infectious disease unit of the Port Harcourt Teaching Hospital	Cross-sectional	N = 213	3 month–18 years old
Vreeman et al. [31, 42]	Kenya; Four clinics	Cross-sectional	N = 792	6–14 years old

[a] Age of study participants was defined as "children aged > 5 years," but upper limit of ages was not given

[b] Overall age range not reported in this study

patient having a percentage adherence calculated. Two of these studies reported median adherence [15, 51] and one reported mean adherence [32] with a range of 81–99.2 % (Table 2).

Prevalence of Disclosure

Disclosure in the studies was defined as the child knowing that he or she is infected specifically with HIV, determined by either child or caregiver report. In these studies, disclosure was generally low, ranging from 8.4 to 79 % (Table 2). Haberer et al. did not report percentages of disclosure, but instead gave an absolute number of disclosed children within the specific age range of 9–15 years old [15]. While nine studies contained children below the age of six, the WHO threshold age for the beginning of the disclosure process [4], in their study population [15, 16, 32, 43–48], only three of these studies [15, 43, 47] explicitly stated that they corrected their statistics on disclosure to reflect only patients in their study at least 6 years of age or older.

Association of Disclosure with Adherence

The association of disclosure with adherence was found to vary widely between the studies (Table 2). Five studies showed no statistically significant relationship between disclosure and adherence [32, 43, 49–51]. Two studies found an association of disclosure with non-adherence [42, 45], while two others showed non-disclosure to be associated with adherence [16, 46]. The remaining five studies reported either a positive association of disclosure with adherence [15, 41, 44, 48] or an association of non-disclosure with non-adherence [47]. Thus, disclosure was shown to be associated with better adherence in five studies, but shown to be associated with worse adherence in four studies. Seven studies included disclosure and adherence in a multivariate logistic regression model to

Table 2 Associations of medication adherence and status disclosure

Study	Type of adherence reported	Definition of aherence	Percent adherence	Percent disclosure	Association conclusion	Statistical test	Statistical value reported
Arage et al. [44]	Percentage of patients adherent based on caregivers' report of 1-month recall	≥95 % of medication doses taken	Overall adherence: 78.6 %	55 %	Disclosure associated with adherence	Multiple logistic regression	aOR = 3.47 (2.10, 6.81) p = 0.029
Bhattacharya et al. [49]	Percentage of patients adherent to ART based on caregivers' 4 day recall	No missed doses on 4 day recall	Disclosed: 94.1 % Non-disclosed: 89.3 %	41.4 %	No statistically significant association	Not stated: comparison of disclosed vs. non-disclosed adherence	p = 0.141
Biadgilign et al. [46]	Percentage of patients adherent based on caregivers' report of 1 week recall	Patient missed no more than one dose for 1 week prior to study	Overall adherence: 86.9 %	17.4 %	Non-disclosure associated with adherence	Stepwise logistic regression	aOR = 2.53 (1.24, 5.19) p = 0.011
Biressaw et al. [16]	Percent of patients adherent based on unannounced home-based pill count	≥95 % of medication doses taken	Disclosed: 29.2 % Non-disclosed: 42.3 %	42.3 %	Non-disclosure associated with adherence	Multivariate logistic regression	aOR = 2.35 (1.09, 5.06)
Cluver et al. [41]	Percentage of patients adherent based on patient past-week, past-3 days and past-weekend recall	≥95 % of medication doses taken	Overall adherence: 64 %	70 %	Disclosure associated with adherence[a] Disclosure prior to age 12 associated with adherence	Multivariate logistic regression Multivariate logistic regression	OR = 2.18 (1.47–3.24) OR = 2.65 (1.34–5.22)
Dachew et al. [45]	Percentage of patients adherent based on caregivers' report following 1 month of treatment	≥95 % of medication doses taken	Overall adherence: 90.4 %	57.9 %	Disclosure negatively associated with adherence	Multivariate logistic regression	aOR = 0.27 (0.24, 0.32) p = 0.001
Haberer et al. [15]	Median adherence based on Medication Event Monitoring Systems (MEMS)[b]	≥ 95 % of medication doses take	Median (IQR): 94.8 % (87.8, 97.7)	26 children of those 9–15 years old	Disclosure associated with fewer non-adherent days	Multivariate logistic regression	IRR = 0.62 (0.47–0.81) p = 0.001
	Median adherence based on unannounced home-based pill count	≥95 % of medication doses taken	Median (IQR):93.4 % (90.2, 96.7)	26	N/A	N/A	N/A
	Median adherence based on pharmacy-based pill count	≥95 % of medication doses taken	Median (IQR): 96.9 % (94.5, 98.2)	26	N/A	N/A	N/A
	Median adherence calculated from caregiver report of last missed dose	≥95 % of medication doses taken	Median (IQR): 94.8 % (86.0, 100)	26	N/A	N/A	N/A
	Median adherence based on visual analog scale (VAS)[c]	≥95 % of medication doses taken	Median (IQR): 97.4 % (96.1, 98.4)	26	N/A	N/A	N/A

Table 2 continued

Study	Type of adherence reported	Definition of aherence	Percent adherence	Percent disclosure	Association conclusion	Statistical test	Statistical value reported
Muller et al. [32]	Mean adherence based on MEMS	≥95 % of medication doses taken	Mean (SD): 81 % (21.8)	N/A	No statistically significant association	Chi Square test	p = 0.18
Nabukeera-Barungi et al. [43]	Percent of patients adherent based on three day self-report by caregivers	≥95 % of medication doses taken	Overall adherence: 84 %	59 %[d]	Not calculated	N/A	N/A
	Percent of patients adherent based on clinic-based pill counts	≥95 % of medication doses taken	Overall adherence: 94.1 %	59 %	Not calculated	N/A	N/A
	Percentage of patients adherent based on home-based unannounced pill counts	≥95 % of medication doses taken	Disclosed: 72.7 % Non-disclosed: 70.8 %	59 %	No statistically significant association	Pearson's Chi square test	OR = 0.91 (0.39–2.07) p = 0.82
Polisset et al. 2008	Percentage of patients adherent based on caregiver 4 day and 1 month recall	Zero missed doses in past 4 days or 1 month	Overall adherence: 42 %	14.9 %[e]	Non-disclosure associated with non-adherence	Fisher exact test	p < 0.05[f]
Sirikum et al. 2014	Median adherence from pharmacy-based pill count	≥95 % of medication doses taken	Median (IQR): 99.2 % (94.7, 100) Disclosed: 99.2 % (95.0–100) Non-disclosed: 99 % (95–100)	70 %	No statistically significant association No statistically significant association at 6 and 12 months post-disclosure	Wilcoxon rank-sum test Wilcoxon matched-pairs signed-rank test	p = 0.61 6 months: p = 0.75 12 months: p = 0.85
Turissini et al. [50]	Percentage of patients adherent based on caregiver 30-day recall	No missed doses	Disclosed: 80.0 % Non-disclosed: 90.4 %	11.1 %	No statistically significant association	Bivariate analysis between disclosed and non-disclosed	p = 0.104
Ugwu and Eneh [48]	Percentage of patients adherent based on caregiver three-day, seven-day and 1 month recall	≥95 % of medication doses taken	Overall adherence: 76.2 %	8.4 %	Disclosure associated with adherence	Fisher's exact test	OR = undefined p = 0.008
Vreeman et al. [31, 42]	Percent of patients adherent based on caregiver 30-day recall at clinic encounter	Any missed doses reported in past 30 days	Disclosed: 91 % Non-disclosed: 92 %	26 %	No statistically significant association	Pearson's Chi square test	p = 0.504
	Percent of patients adherent based on caregiver survey	Any report of adherence difficulties on survey	Disclosed: 45 % Non-disclosed: 48 %	26 %	No statistically significant association	Pearson's Chi square test Multivariate regression	p = 0.534 OR: 1.31 [0.86–1.98]

Table 2 continued

Study	Type of adherence reported	Definition of aherence	Percent adherence	Percent disclosure	Association conclusion	Statistical test	Statistical value reported
	Percent of patients adherent based on child survey	Any report of adherence difficulties on survey	Disclosed: 76 % Non-disclosed: 83 %	26 %	Non-adherence associated with disclosure	Pearson's Chi square test	P = 0.027

[a] Horizontally infected adolescents included in this analysis

[b] Medication Event Monitoring System, Aardex, Switzerland

[c] Caregivers report child medication adherence along a line labeled "none given," "half given" and "all given"

[d] Only patients older than 8 years used for this calculation

[e] All disclosed patients were $\geq$6 years old

[f] Disclosure variable not included in multivariate analysis due to inadequate sample size for age-based stratification

determine the relationship between the two factors independent of other demographic factors that were found to have statistically significant impacts on adherence [15, 16, 41, 42, 44–46]. In these analyses, Vreeman et al. (OR = 1.31 [0.86–1.98]) showed no association [42]; Biressaw et al. (aOR = 2.35, [1.09, 5.06]) [16], Dachew et al. (aOR = 0.27, [0.24, 0.32]) [45], and Biadgilign et al. (aOR = 2.53, [1.24, 5.19]) [46] showed disclosure and adherence to be negatively associated; while Arage et al. (aOR = 3.47, [2.10, 6.81]) [44], Haberer et al. (IRR = 0.62, [0.46–0.81]) [15], and Cluver et al. (OR = 2.18, [1.47–3.24]) [41] showed positive associations between disclosure and adherence.

Discussion

Adherence to ART and disclosure of HIV status to HIV-infected children continue to pose a challenge in the management of pediatric HIV in resource-limited countries. It is critical to understand the psychological and treatment effects that disclosure can have on these children and adolescents to inform pediatric HIV management and ensure optimal outcomes. While psychological, medical and social positive impacts of disclosure have been reported mainly in qualitative studies [12, 22, 35, 39], this review was undertaken to synthesize quantitative data showing the effect that disclosure is having on medication adherence.

While we expected to find a clear benefit of disclosure on adherence outcomes in these patient populations, the outcomes reported by the studies reviewed show mixed results in their association between disclosure and adherence. Five studies reported no association [32, 43, 49–51], five showed a positive effect of disclosure on adherence [15, 41, 44, 47, 48], and four reported decreased adherence in children who knew their HIV status [16, 42, 45, 46]. The studies reporting a negative effect provided several explanations for this, including children's fear of social stigma and, therefore, the tendency to hide taking medications from others [42], as well as denial of their status, leading to increased refusal to take medications [16]. Another surmised factor was that disclosure might increase depressive symptoms and lead to decreased desire to develop strong adherence habits [42]. Several reasons were given for the positive association between adherence and disclosure, such as disclosure empowering the child to partner with their caregiver in maintaining adherence, greater willingness to take medications due to knowing why the medications were being taken, and more open discussions about adherence occurring between the caregivers, the healthcare providers, and the children [15, 32, 41].

The quality of the studies evaluated was generally low and may limit the generalizability of results, while reinforcing that longitudinal studies are needed to make definitive conclusions about the associations of disclosure with adherence. Twelve of the fourteen studies were cross-sectional, thus limiting the evaluation of causation between status disclosure and development of adherence habits. The methods of determining adherence were variable, with eight of the studies choosing to exclusively use caregiver or child recall to determine adherence (Table 2). These recall measures are subject to social desirability bias and may thus overestimate adherence [43], further decreasing the quality of evidence. Sample sizes were small and sub-analyses were not conducted, limiting the conclusions that can be drawn from the data. Additionally, it is worth noting that only three of the records reviewed examined the association of disclosure with adherence as their primary endpoint [41, 42, 51]. Of these three, Vreeman, et al. showed no association by caregiver report and negative association by child report [42]; Sirikum et al. showed no association by pharmacy-based pill count [51]; and Cluver, et al. showed a moderate association between the two based on patient report, especially when disclosure occurred before the age of twelve (OR = 2.65, 95 % CI [1.34–5.22]) [41]. The latter study, undertaken with patients 10–19 years old in Eastern Cape, South Africa, was also the most broad-reaching study, with all pediatric HIV patients in the Eastern Cape contacted for possible enrollment [41]. Only the Sirikum et al. study, conducted in Thailand, measured adherence pre- and post-disclosure in a prospective manner. This study showed no statistically significant change in adherence at 6 or 12 months post-disclosure; however, the authors noted that this lack of association may have resulted from unusually high levels of adherence reported at baseline [51]. The lack of prospective data on adherence levels after disclosure and the low quality of evidence in the studies found highlight the need for further longitudinal research to be done.

Due to lack of information on adherence values, there were several studies ultimately omitted from our review that nevertheless showed some degree of quantitative association between disclosure and disease outcomes. One study in Romania reported a decrease in disease progression and an increase in survival for children and teens who knew their HIV-positive status [13]. A study in South Africa reported an increase in viral suppression for those patients who had gone through the process of disclosure [32]. A study conducted in Uganda demonstrated in their sample population (N = 42) some patients who were "non-disclosed" or "partially disclosed" reported "frequently" missing medication doses, while none of the patients who were "fully disclosed" reported missing frequent doses [23]. Moreover, a multinational study conducted in Cote d'Ivoire, Senegal and Mali published a statistically significant association between disclosure and retention in care at pediatric ART clinics [14]. These studies add additional evidence to the benefit of disclosure on health outcomes, though no conclusive link between the two can be drawn from these studies and those included in the review.

Several limitations to this review warrant consideration. Only 14 studies met inclusion criteria, and thus there was a limited amount of evidence from which to draw conclusions. There was lack of geographical diversity in the studies that met the inclusion criteria. Eleven of the studies were conducted in sub-Saharan Africa, which may limit generalizability beyond this setting. Another weakness is the use of caregiver or patient report to determine adherence in many of these publications, which has been shown to overestimate adherence and have a weaker correlation with viral load suppression than pill count or MEMS methods of measuring adherence [16, 43]. A publication bias may be present, as studies that found no association or a negative association of disclosure with adherence may not have published their results. While we sought to be as rigorous as possible in our search, it is possible that there were studies that were missed using our search criteria. Taken together, the review has several strengths; one of the strengths of the study is the utilization of quantitative data in order to examine the relationship of disclosure and adherence independent of other demographic and psychosocial factors that may also influence adherence. In addition, the review reveals an important need for more high quality, longitudinal data to conclude any form of causation between the disclosure process and adherence development.

Recommendation for Practice and Research

A major finding that this study revealed is the paucity of data measuring effects of disclosure on treatment outcomes. Most of the associations reported between disclosure and adherence have come from cross-sectional data, and very few longitudinal studies have quantitatively examined the effects of disclosure on adherence habits and behavioral changes over time. Future research should investigate ways of integrating disclosure counseling with medication adherence counseling, while finding ideal measures for adherence to reduce the incidence of social desirability bias inherent in some of the caregiver and patient recall measures in use.

Pediatric HIV programs should not consider disclosure as a one-time event, but a process where both caregivers and children are equipped with the knowledge and skills to maximize the treatment benefits of disclosure. Disclosure and adherence interventions should be culturally

appropriate, be executed in tandem, and personalized, taking into consideration the cognitive and developmental stage of the child. Several such support interventions are being piloted in some resource-limited settings [30, 35, 52]. A trusting and collaborative relationship between healthcare systems, caregivers, HIV-infected children, and healthcare providers should be established in order to increase adherence through the process of disclosure, thereby achieving better health outcomes for children and adolescents living with HIV.

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Compliance with Ethical Standards

Conflict of Interest Author JN declares that he has no conflict of interest. Author AS declares that he has no conflict of interest. Author EP declares that he has no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the studies used for the review.

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