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Abstract

Objectives: 82% of HIV-positive adolescents live in sub-Saharan Africa (SSA). Despite the availability of antiretroviral therapy (ART), adherence levels are suboptimal, leading to poor outcomes. This systematic review investigated factors impacting ART adherence among adolescents in SSA, including religious beliefs and intimate relationships.

Methods: A systematic review was conducted between June and August 2016 using eight electronic databases, including Cochrane and PubMed. Published, ongoing and unpublished research, conducted in SSA from 2004 to 2016, was identified and thematic analysis was used to summarise findings.

Results: Eleven studies from eight SSA countries, published in English between 2011 and 2016, reported on factors impacting ART adherence among adolescents living with HIV (ALHIV). 44 barriers and 29 facilitators to adherence were identified, representing a complex web of factors. The main barriers were stigma, ART side-effects, lack of assistance and forgetfulness. Facilitators included caregiver support, peer support groups and knowledge of HIV status.

Conclusions: Stigma reflects difficult relations between ALHIV and their HIV-negative peers and adults. Most interventions target only those with HIV, suggesting a policy shift towards the wider community could be beneficial. Recommendations include engaging religious leaders and schools to change negative societal attitudes. Limitations of the review include the urban settings and recruitment of predominantly vertically infected participants in most included studies. Therefore, the findings cannot be extrapolated to ALHIV residing in rural locations or horizontally infected ALHIV, highlighting the need for further research in those areas.

Key words: HIV, adolescents, sub-Saharan Africa, antiretroviral therapy, adherence

Introduction

Acquired immunodeficiency syndrome (AIDS) is the main reason for death in African adolescents aged 10 to 19 years.[1] Out of 2.0 million human immunodeficiency virus (HIV) positive adolescents worldwide, 82% live in sub-Saharan Africa (SSA).[2] Adolescents acquire HIV either vertically from their mother or horizontally through sexual contact or risky behaviour.[3]

Although still incurable, HIV in SSA has changed from a 'killer disease' to a treatable chronic condition since paediatric antiretroviral therapy (ART) was introduced in SSA in 2004,[4] leading to great improvements in survival and life quality among adolescents.[5] But effective treatment outcomes depend on optimal ART adherence,[6] where adherence refers to an individual's capability to take drugs at recommended times.[7] In addition, ART dramatically reduces rates of onward HIV transmission.[8] Public health strategies today are building on this to contain the epidemic. All HIV-positive pregnant women are given ART to prevent infection of babies.[9] Countries are introducing 'Test and Treat' policies where all patients testing HIV-positive immediately start treatment.[9] But low infectivity depends on optimal ART adherence, classified as at least 95% of doses expected to be used.[10] Poor ART adherence can lead to treatment failure, disease progression, increased risk of transmission[11] and health care costs.[12,13]

According to Gulick,[14] adherence varies over time, making frequent adherence assessments crucial. Assessments are performed either subjectively through patient or caregiver reports; or objectively: pharmacologically through pill count or electronic measurement, physiologically through viral load tests. All methods have limitations and can lead to inaccurate estimates.[15] Pill counts can be modified; verbal reports present an easily biased subjective result and frequent viral load tests are often unaffordable in developing countries.[16] Combining methods could improve accuracy.[17]

Today, HIV in SSA is a public health challenge: how to get millions of people in rural areas with poor health infrastructure to take daily medicines.[18] The challenge is greatest for adolescents undergoing the physical, social and psychological changes of sexual maturity. Being HIV-positive adds to the complexity of difficulties faced by this group.[19] While data on ART coverage and adherence is limited, [10] studies suggest less than half of adolescents living with HIV (ALHIV) know their

status and that adherence levels are suboptimal.[10, 20] One study reported only 20.7% of adolescents achieve good adherence.[20] ART adherence levels are poorer in ALHIV compared to adults.[21,22]

The factors impacting ART adherence can be categorised according to the patient, the medication, the caregiver and the health system.[23] Multiple factors are involved which may vary according to age, context, culture, health system, education and caregiver support.[24] Some factors may be temporary, others permanent. Poverty, stigma, lack of social support, family disintegration, drug side-effects, weak health systems, and disclosure of HIV status are cited as impacting adolescent ART adherence.[25-27]

Disclosure is defined as acquiring knowledge about one's HIV status[28] or informing others about one's HIV status.[29] Adolescents who do not know why they are taking medicines are more likely to miss doses and those unable to tell their family and friends of their HIV status may need to hide their treatment, making adherence more difficult.[30] Additionally, religious beliefs,[31] described as "the belief in and worship of a superhuman controlling power",[32] and intimate relationships,[33] may play a role in ALHIV adhering to ART. Often ALHIV hide poor adherence from health-care providers to avoid rejection.[34, 35]

With limited resources available, interventions need to be designed to address different contexts and continuously evaluated for effectiveness.[25] Agwu and Fairlie[36] found that interventions to promote disclosure and counselling facilitate adherence among ALHIV. HIV peer support groups were also mentioned as beneficial.[37] However, strategies can only be improved through increased knowledge of the factors impacting ART adherence. Huge resources are spent on viral load tests to assess adherence clinically, but much less on interventions to address root causes of poor adherence.[38]

Several systematic reviews have been published regarding this topic for different age groups and contexts.[39-45] This study differs from previous reviews by including both quantitative and qualitative data and exclusively within the SSA context, where HIV prevalence is the highest globally.

This systematic review aims to identify factors that enable and impede ART adherence among ALHIV in SSA; to build on the findings of previous reviews it includes religious beliefs and intimate relationships as factors impacting ART adherence among ALHIV. Additionally, it intends to guide decision makers involved

in HIV programmes, service providers, researchers and the general population, making recommendations to improve adolescent adherence to ART in SSA.

Methods

The review was conducted between 3 June and 15 August 2016, as the final research project for an online Master in Public Health at the University of Hertfordshire, UK. A systematic, all-language search including quantitative and qualitative studies that addressed factors impacting ART adherence in SSA ALHIV was performed.

Search strategy

Eight electronic databases providing high quality medical publications (Cochrane, PubMed, CINHAL Plus, Scopus, Web of Knowledge, TRIP, Science Direct, Google Scholar) were searched systematically to identify relevant peer-reviewed articles. All searches were conducted directly without using an intermediate interface such as Ovid. Databases of ongoing research were included and OpenGrey was searched. Relevant publications from reference lists of five articles were retrieved and screened for duplications.[23,25,40,43,46]

The following keywords and MESH terms were used: HIV, adolescents, sub-Saharan Africa, antiretroviral therapy, adherence. Alternative keywords for each concept were utilised (see Supplementary online resource(s)).

Search filters included 'human studies', 'the adolescent age group (10-19 years)' and studies performed in 'SSA countries'. Publications from 2004 (when paediatric ART was introduced in SSA) to June 2016 were examined. All-language studies were included. Children aged less than10 years and adults were excluded.

Study selection and eligibility criteria

After removal of duplicates, all titles, abstracts and full-text articles were reviewed by one investigator, using pre-defined inclusion and exclusion criteria. Articles and abstracts were excluded if they did not address the population, intervention or outcome of interest. Potentially eligible studies met the following criteria: (1) used a qualitative, quantitative or mixed-methods design, (2) were peer-reviewed original studies, (3) were studies conducted after ART induction in SSA in 2004, (4) discussed and evaluated an association between ART adherence among ALHIV in SSA and at least one patient-related, medication-related, caregiver-related or health system-related factor, and (5) displayed good quality, with ethical approval and informed participant consent.

For inclusion, studies needed: adherence to be assessed using pill count, self-report, caregiver report, viral load result or electronic monitoring; good adherence defined as >90%;[10] ≥50% participants aged 10 to 19 years. Studies could include both vertically- and horizontally- infected ALHIV. Studies on ALHIV were excluded if they did not identify factors impacting ART adherence. Before inclusion, cross-sectional studies were appraised for quality of evidence, using the appraisal tool from the National Institutes of Health.[47] For qualitative studies, the Critical Appraisal Skills Programme (CASP)[48] was used. A second reviewer screened and assessed the studies independently. Heterogeneity was assessed by including studies with same outcome measures and consistency of results.

Data extraction and analysis

After identifying final studies, data were extracted using a standard template and summarised in tabular form. The data analysis was designed to develop a list in word of factors reported as impacting ART adherence in ALHIV in SSA, with explanations of how behaviour and attitudes of ALHIV are influenced. Data from qualitative studies was extracted using thematic analysis[49] with results sorted into four main categories: patient-related, medication-related, caregiver-related, and health system-related factors.[50] These categories were further divided into facilitators

and barriers. Quantitative data results were listed under the same headings. Finally, findings were recorded according to frequency of topics occurring across studies. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[51] guided the review protocol.

Study selection process

The literature search yielded 656 potentially relevant studies. After removal of duplicates, 75 articles remained; further review of titles and abstracts excluded 45 articles which did not meet inclusion criteria. The remaining 30 papers were full text screened with a focus on studies including religious belief and intimate relationships as factors influencing ART adherence, leaving 11 studies which were published in English between 2011 and 2016 (research carried out 2007-2014) from eight SSA countries. A flow diagram outlining the study selection process is detailed in Figure 1.

<Figure 1>

Results

Study characteristics

Characteristics of the 11 included studies are summarised in Table 1. Study countries were Congo (Democratic Republic), Ghana, Kenya, Rwanda, South Africa, Uganda, Zambia and Zimbabwe. Seven studies used a qualitative, three a mixed methods approach and one a quantitative cross-sectional design. All qualitative studies used in-depth interviews, five used focus groups, one role play and one participant observation. The quantitative study used a cross-sectional design. Additional to the adolescent study participants, seven studies included caregivers, three healthcare workers, one community members and one stakeholders.

All but one study[52] sampled their population purposively. Quantitative methods used logistic regression to examine associations and produce odds ratios. Eight studies comprised an urban and three both rural and urban clinic setting. Qualitative study samples varied from 19 to 42 participants. Despite the fact that authors rarely acknowledged their own role in influencing the research, included studies were of high methodological quality addressing potential bias. Their results were appraised to be valid using recommended tools[47,48]. Ethical approval was obtained by all studies.

<Table 1>

Characteristics of study participants

Studies included 3,407 participants broken down as follows: 3,199 adolescents (2,999 in quantitative and 200 in qualitative studies); 191 caregivers (parents, non-parental caregiver, biological relative, non-relative, or foster-carer) and 17 healthcare providers. The proportion of female adolescent study participants ranged from 45% to 63%. Three studies examined selectively ALHIV aged 10 to 19 years. Two studies divided the study population into two age-groups, early (10-14 years) and late adolescence (15-19 years). Six studies did not report participant mode of transmission, two involved only vertically infected ALHIV and three included majority (79%-89%) vertically infected participants. Six studies considered only participants who knew their HIV status, two did not specify and in three, the proportion of disclosed participants ranged from 20% to 90%. In three studies most participants belonged to an HIV support group, whilst in the remaining eight this aspect was unreported. Six studies documented adolescents who had lost one (21-45%) or both parents (15-78%).

ART adherence measurements

Documented adherence levels ranged from 64% to 90%. Non-adherence in the past week ranged from 6% to 95%. ART adherence was measured by self-reports in six

studies; pill counts in one study. Thresholds for optimal adherence ranged from >90% to >95%. Study population duration on ART ranged from 6 months to 6 years. One study compared adolescents and caregiver reports, finding only 33% concordant. ALHIV reported missing doses more often than their caregivers. In one study 95% of ALHIV interviewed reported poor ART adherence at some time.[26] Nabukeera-Barungi et al.[37] reported better urban ALHIV adherence levels compared to rural.

Factors impacting ART adherence

Seven studies identified both facilitators and barriers impacting ART adherence: one focused on the barriers only; one examined the association between knowledge of HIV status and adherence; one looked at lived experiences, another the psychosocial challenges of ALHIV. The studies found 73 factors impacting ART adherence among ALHIV in SSA. Results of the factors in qualitative and quantitative studies are presented in order of most emergent reported themes and summarised in Table 2. Overall, 44 barriers to ART adherence were reported, with most (N=23) patient-related. Twenty-nine facilitators to ART adherence were counted; most (N=12) were patient-related. Table 3 summarises the findings, highlighting the most emergent factors in their categories.

Religious beliefs and perceived positive treatment outcomes were described as both facilitator and barrier. Two studies explored reasons for ALHIV not revealing poor adherence to caregivers and healthcare workers, which included protecting and maintaining relations, fear of abuse or being scolded by caregivers and unease with medical staff. One study[52] found travel time to the clinic did not impact adherence, while another[53] encountered the opposite. Only two studies discussed the role of intimate relationships,[37,54] finding that fear of rejection by the partner impacted adherence.

<Table 2>

7

<Table 3>

Discussion

This systematic review identified 11 studies, representing 3,407 participants in eight SSA countries.

The findings evidence a complicated web of factors influencing ALHIV adherence. In total, 44 barriers and 29 facilitators were identified. Most were patient-related, with stigma as the greatest barrier, followed by drug side-effects, forgetfulness, lack of caregiver support, not knowing the reason for taking the drugs, poverty, and depression. Important factors facilitating adherence were caregiver support, peer support groups, knowledge of HIV status, use of reminders, and support from healthcare workers. Results concur with existing reviews examining different age groups.[23,25,43,44] Factors were found to inter-relate and it is important to note that an individual's adherence behaviour is not linear, but changes over time.[14,55]

Stigma appeared universally as a main barrier to ART adherence. Perceived stigma, as a consequence of HIV status disclosure to peers, but also stigma experienced within families and schools was repeatedly mentioned.[54,56] Frequently, ALHIV felt the need to lie that medicines are taken for other conditions, such as asthma, because they feared rejection or discrimination.[54,57] Often only one caregiver was aware of the adolescent's HIV status. Caregivers frequently reinforced the fear of stigma, discouraging disclosure and encouraging taking medicines in secret.[26,34,57,58] ALHIV reported that taking ART produced feelings of shame and anger[26] making them feel different to their peers.[27,54,58] Disrupting social activities for medication intake created fear of unwanted questions and unintended disclosure.[24,34,58] Multiple participants preferred to delay or miss doses rather than being seen by others.[24,54,56] Stigma and applying secrecy as a coping strategy repeatedly led to incomplete adherence.[34,58] Lack of privacy, expressed in the home environment,[27] was especially reported in boarding schools,[37,54] with congested accommodation and lack of psychosocial support.[59] This link between stigma and non-adherence is consistent with the already mentioned narrative review[25] in SSA,

the review of ALHIV in USA[44] as well as the review of adults globally.[60] Only one small study of 30 ALHIV in Thailand found no quantitative association between stigma and ART adherence.[61]

ALHIV unaware of their HIV status and taking daily medicines without a comprehensible reason, showed consistently poorer adherence.[24,26,34,58] ALHIV who were suspected of being HIV-positive before disclosure suffered frustration at being lied to, which resulted in refusal to take ART.[26,27,34] Caregivers often explained late disclosure because of fear of revealing their own HIV status[54,60] or guilt.[28] Understanding the reason for taking medicines daily and the importance of ART convinced ALHIV mostly to adhere.[26,34,63] Disclosure before age 12, following World Health Organization recommendations,[64] was associated with better outcomes.[53] This finding is consistent with multiple SSA studies[50,62,65] and two systematic reviews[30,66] but contrasts with an Indian study in which caregivers expressed no difference.[67] However, disclosure to older ALHIV was associated with mistrust and poorer adherence.[53] A positive experience with disclosure acted as motivator, enabling children to seek information, express feelings and access support groups.[26,54] Furthermore, there is a clear link between how ALHIV discover their HIV status and their ability to disclose it to others.[30]

Depression as barrier to adherence was linked to lack of acceptance of HIV status and weak social support,[27,56] especially for ALHIV orphans.[26,34] Support from caregivers and healthcare workers, but also support groups were crucial to accepting HIV status and facilitating adherence.[27] Reminding ALHIV to take medicine, as forgetfulness was mentioned as a major barrier in several studies[57,68-70] beside emotional support[52] helped in maintaining ART adherence. However, non-parental caregivers and boarding schools provided a less supportive environment.[27] The combination of stigma, secrecy and mental health challenges pushes ALHIV to emotional distress undermining the ability to adhere and seek support.[54]

ART side-effects, mainly nausea and dizziness, were reported as a major barrier. Lack of food discouraged ALHIV taking their ART as required.[26,34,37] Here, nutritional support and change of ART regimen mitigated side-effects. Also, education by healthcare workers to warn of potential side-effects was found important.[37]

After caregiver support, peer support groups ranked highest as a facilitator. These provided an environment for sharing experiences and encouragement that did

not require secrecy[71] and an understanding that ALHIV are not alone.[56,58] Support groups being effective for other chronic conditions such as diabetes[72] helped also in reducing HIV-related stigma among South African adults.[73]

Religious beliefs

Religious beliefs play an important role in SSA.[74] In this review, religious beliefs were found as facilitating but also impeding adherence to ART among ALHIV. Similarly, a study, involving adults in the Democratic Republic of Congo, found that the belief that ART was God-created positively impacted adherence while faith-healing had a negative impact.[75]

Faith in a superhuman power, as reported by studies in this review, helped ALHIV gain self-awareness and self-confidence. Prayers as coping strategy were mentioned as motivators to overcome challenges.[52] Believing brings hope and strength to live positively with HIV.[76] This finding concurs with other studies. Youth aged 14 to 22 in USA[77] were found to have better adherence among those with higher religious practise. In another study of USA adults[78] participants showing good ART adherence had faith, as they felt connected to a higher being and it made their life meaningful. Also regarding other chronic conditions, spirituality was mentioned as a coping strategy for caregivers.[77]

But religious belief can also play a negative role. Faith-healing, as a health-seeking strategy, is mostly practised by Christians and Muslims in SSA; also shamans are consulted.[79] This practice often leads ALHIV to stop taking their ART[27,37,58] in the belief of being cured by prayers, or particularly in Ethiopia, the use of holy water.[80] Braitstein et al.[81] found belief of being healed by prayer accounted for 9% of children failing to return to the clinic in Kenya. Several studies highlighted the disruption of ART after spiritual healing ceremonies in adults in Uganda,[82,83] Tanzania,[76,84] Malawi[85] and the USA.[86]

Additionally, religious fasting was reported as leading to incomplete adherence due to changes in eating times, including ART intake, to comply with their religious duties.[27] An Ethiopian study[80] revealed that fasting during Ramadan and fasting practices of the Ethiopian Orthodox Church affected ART adherence. Similarly, a Nepalese study, which included adults showed that Ramadan and Teej, a

Hindu tradition, both negatively impacted ART adherence.[87] Conversely a Nigerian study of adults found no association between religious fasting and ART adherence,[88] but highlighted the need for dosing time adjustments during fasting periods. Most religions do not oblige children, pregnant women or the sick to follow religious fasting.[85]

Religious belief is a major factor in shaping social attitudes in SSA, including attitudes towards ART. Faith-healing and traditional medicine often coexist with clinic visits.[89] Evidence regarding religious beliefs was largely from the adult population due to data availability, highlighting the need for more research in ALHIV. Religious belief could be included in counselling sessions, but also involvement of religious authorities in HIV programming could improve ART adherence.

Intimate relationships

As intimate relations gain importance in late adolescence, these also impact attitudes to ART.[90] In this review, the obstacles to ART adherence identified included the need to disclose,[54] against the fear that disclosing one's HIV status to partners would create stigma and rejection.[37,54,57] This is consistent with other studies.[29,91-93] A study of Ugandan ALHIV[37] described how non-disclosure to intimate partners led to ART defaulting because of the fear of being recognised as HIV-positive. Additionally, a study of Nepalese adults showed 17 times more non-adherence among participants who have not disclosed their status.[87] While one study reported participants experienced post-disclosure stigma,[27] another[54] revealed that 27% of participants who disclosed their status to their partners had a positive response. Nöstlinger et al.[94] found in Kenya and Uganda an ALHIV disclosure rate of 34.3% to intimate partners with mostly optimistic outcomes. A study of Ugandan adults, where 69% of participants disclosed their HIV status to sexual partners, showed that the reduced need for secrecy in this group improved adherence behaviour and measures to prevent onward transmission.[95] These findings suggest some of the stigma and fear may be self-imposed or imposed by caregivers. First intimate relationships may well not be with other HIV-positive adolescents. Ideally, adolescents need to be given the skills, knowledge and confidence to allow them to disclose their status to potential partners, before relationships become sexual.

Counselling needs to disseminate the link between good adherence and low risk for HIV transmission through reduced infectivity. This could decrease fears of ALHIV infecting intimate partners.[54]

While this link is now at the centre of strategies to treat and contain the epidemic, with countries moving to a "Test and Treat" policy, evidence suggests that most ALHIV and adults on treatment do not know about the link.[96] Indeed, healthcare workers may not tell for fear of promoting intercourse without condoms. More evidence to evaluate the potential benefit and harm of a campaign to inform ALHIV of this link is needed. Furthermore, psychosocial support in case of experienced or perceived stigma is important and should be provided in the home environment and also in clinical care. Disclosure to intimate partners is crucial for preventing onward transmission of HIV.[97] Considering the high number of ALHIV not knowing their status,[98] intimate relationships pose a serious concern for public health.

Limitations

The strengths of this review derive from the extensive search strategy employed, the inclusion of qualitative and quantitative studies which involved adolescents, caregivers and service providers to gain a holistic perspective. Additionally, the inclusion of unpublished research limited publication bias and the all-language consideration minimised language bias. However, limitations also need to be acknowledged. First, the inclusion of cross-sectional study designs limits corroboration of causal relationships. Second, the subjectivity of qualitative research could have caused bias, but the consistent recurrence of factors in the studies supports the inference of external validity for the SSA context. However, internal validity could have been affected as four studies did not acknowledge the researchers' role in analysis and data selection. It also needs to be noted that some reported factors might be culturally specific and therefore the transferability of the findings to a context outside SSA is limited. Third, most studies were conducted in urban settings and recruited predominantly vertically infected participants. Therefore, the findings cannot be extrapolated to ALHIV residing in rural locations or horizontally infected ALHIV, highlighting the need for further research in those areas.

While this study reveals a complex picture of barriers and facilitators for ALHIV adherence, there is a common thread between them, which suggests possible benefits in shifting public health policy. The major barriers to adherence all stem from tensions between ALHIV and their HIV-negative peers and adults. Stigma, the need for secrecy, disclosure challenges, depression, religious beliefs and problematic intimate relationships all relate to wider societal attitudes to HIV.

By contrast, all the facilitators mentioned, and interventions built around them, such as caregiver or peer group support, are directed only at ALHIV. While they may help mitigate the perceived wider societal attitudes, they are not going to fundamentally change the situation. Indeed, many interventions and attitudes of both healthcare workers[99] and caregivers have tended to increase this division between ALHIV and HIV-negative peers.[56]
Previous HIV campaigns[100,101] using fear and morality about sex as prevention messages contributed to the current scenario.

Today, ALHIV and their HIV-negative peers still receive very different health messages. ALHIV often first learn about HIV at schools which push a moralistic fear-based message to frighten adolescents into abstention.[59] They face a crisis when they learn their HIV status which is overcome with a completely different positive message in peer support groups. The evidence of this review strongly suggests that culturally-appropriate, large-scale campaigns, also aimed at schools, including religious authorities, could change attitudes in the wider society and create greater acceptance of ALHIV. A film produced by Picturing Health[102] will highlight the findings of this review and aid in guiding researchers, policy-makers and healthcare workers involved with ALHIV.

Ethical approval

None sought, as using secondary data.

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Tables

Table 1. Study characteristics (*N* = 11)

Reference	Country, Setting	Type of study	Study population	Study aim
Ankrah et al., 2016[57]	Ghana, urban hospital	A qualitative cross-sectional study using semi-structured interviews Time of study not included; over a period of 6 weeks	Age 14-19 years, Mean age 16.3; 2 groups: 12-15 years (*N* = 8) and 16-19 years (*N* = 11), 63% female, *N* = 19	To identify facilitators and barriers to ART adherence among adolescents
Cluver et al., 2015[53]	South Africa, 39 urban and rural health facilities	A cross-sectional study: Quantitative interviews used standardised questionnaires and clinic records. Qualitative approach: 18 months of in-depth interviews, focus group discussions and participant observations. Time of study: 2013	Age 10-19 years (10-14 years (*N* = 465), 15-19 years (*N* = 216)), 52% female *N* = 684 Caregivers and healthcare workers included	To examine associations between adolescents' knowledge of HIV status and ART adherence
Denison et al., 2015[58]	Zambia, 2 urban hospitals	Qualitative: In-depth interviews Time of study: from December 2011 to February 2012	Age 15-18 years, 50% female *N* = 32 and 23 caregivers (19 female, 4 male)	To explore ART adherence from experience of older ALHIV (15-18 years) and adult caregivers in Zambia
Fetzer et al., 2011[26]	Congo (Democratic Republic), urban hospital	Qualitative: In-depth interviews with 20 HIV disclosed and non-disclosed children and their caregivers Time of study: not reported	Age 8-17 years → 8-11years (*N* = 5), 12-15years (*N* = 11), 16-18 (*N* = 4)). > 50% aged 10-19 years, 60% female. *N* = 40 (20 children, 20 caregivers: 25-63 years, 13 females)	To assess barriers and facilitators of ART adherence
Gross et al., 2015[52]	Zimbabwe, 2 urban low-income clinics	Quantitative: Cross-sectional questionnaire Time of study: not reported	Age 10-19 years, Median age: 15.5, 61% female *N* = 262	To identify risk/protective factors for non-adherence in adolescents
Kawuma et al., 2014[34]	Uganda, 4 urban research centres	Qualitative in-depth interviews Time of study: July 2011 to November 2012	Age 11-13 years, 46% female *N* = 26 Caregivers and healthcare workers included	To examine reasons for non-adherence to ART among children and why they may not report non-adherence
Kunap-areddy et al., 2014[24]	Kenya, 1 rural health centre and 1 urban clinic	Qualitative design: 3 focus group discussions and 3 individual semi-structured interviews Time of study: March to November 2007	Age 10-16 years, Mean age: 13.2, 48% female N = 23	To identify key factors contributing to ART adherence
Mavhu et al., 2013[56]	Zimbabwe, urban clinic	Mixed methods: Use of a quantitative questionnaire and qualitative data through in-depth interviews (*N* = 10), 3 focus group discussions and 16 life history narratives; involved youth researchers Time of study: between August and September 2009	Age 15-18 years, Median age: 14, 59% female *N* = 229, all members of support group. Care givers, healthcare workers and community members included	To describe lived experiences of young people with HIV
Mutumba et al., 2015[54]	Uganda, urban hospital	Qualitative in-depth interviews Time of study: between August and November 2011	Age 13-19 years, Mean age: 16.9, 53% female *N* = 38	To identify psychosocial challenges and coping strategies among perinatal HIV infected adolescents
Mutwa et al., 2013[27]	Rwanda, urban clinic	Qualitative: Role-plays, focus group discussions, in-depth interviews Time of study: October to November 2010	Age 12-21 years, Median age: 17, 45% female *N* = 42; a selection caregivers included	To understand barriers to adherence for Rwandan adolescents
Nabukee-ra-Barungi et al., 2015[37]	Uganda, 30 urban and rural health facilities from 10 districts	Mixed methods: Focus group discussions and in-depth interviews with adolescents, key informant interviews with various stakeholders. Retrospective records review to extract the last recorded adherence level. Time of study: December 2013 to February 2014	Age 10-19 years, 63% female *N* = 1824 Caregivers and stakeholders included	To explore barriers and facilitators of adherence to ART among adolescents

Table 2. Factors impacting ART adherence according to themes (Summary qualitative and quantitative studies)

Themes	Barriers	Facilitators
Patient related factors	Stigma, forgetfulness, not knowing the reason why taking the drugs/late disclosure, poverty (lack of food, lack of money for transport to health facility), secrecy (covert storage, fear of being seen by others when taking the medicine), treatment fatigue, depression/frustration/isolation, delaying doses (due to travelling, school or work), lack of disclosure to other family members, religious belief (myths and misconceptions), faith healing, religious fasting, refusal to take drugs, substance use (alcohol, marijuana), older age (>15 or 16 years), interpersonal conflicts, non-acceptance of HIV status, non-disclosure to peers or partners, male gender, self-image/identity/peer-pressure, perceived positive outcome (patient feels healthy/cured), duration on ART (<1 year and <3 years)	Adolescents' knowledge of HIV status (best before age 12), use of reminders (watches, clocks and phone alarms), integration of ART into daily routine, religious belief/faith, knowledge about disease, desire to be physically healthy/normal, belief that medication helps, self-motivation, perceived positive outcomes, keeping medicine at same spot, positive experiences with disclosure, log keeping
Medication related factors	ART side-effects (especially on empty stomach), pill burden/quantity, pill size, palatability, smell, colour, mistrust of medication	Tablets are easier to carry than syrups
Caregiver related factors	Lack of caregiver assistance (adult supervision), late disclosure, Institutional barriers (boarding schools – lack of privacy), lack of privacy at home, lack of caregiver accompanying to clinic, domestic discrimination, strategies to induce fear (social censure, illness or death) during disclosure process	Caregiver support (reminding to take medicine, accompanying to the clinic), early disclosure to adolescent (prior to age 12) and disclosure to other family members, having other family members on ART, caregiver understanding importance of adherence, assistance of 2 or more caregivers, psychosocial support for caregivers, interventions that involve caregivers
Health system related factors	Inconvenient clinic appointment times, longer travel time to clinic, long waiting time at clinic, repeated missed clinic appointments, rural health facilities, private health facilities, health centres	Peer support groups, (psychosocial) support from healthcare providers, counseling, scheduling clinic visits during school holidays, short waiting time, telephone calls or text messages from health facilities, hospital care (vs health centre), short travel time to clinic, provision of food and transport

Table 3. Most emergent facilitators and barriers associated with ART adherence among ALHIV in SSA

Patient-related factors		Medication-related factors		Caregiver-related factors		Health-system related factors	
Facilitators (N=12)	**Barriers (N=23)**	**Facilitators (N=1)**	**Barriers (N=8)**	**Facilitators (N=8)**	**Barriers (N=6)**	**Facilitators (N=7)**	**Barriers (N=7)**
Knowledge of HIV status (N=5) Use of reminders (N=4) Integration of ART into the daily routine (N=3) Knowledge about the disease (N=2) Belief that the medication helps (N=2) Desire to be healthy/normal (N=2) Religious beliefs (N=1)	Stigma (N=9) Forgetful-ness (N=7) Secrecy (N=5) Not knowing the reason for taking the drugs (N=5) Treatment fatigue (N=5) Poverty (N=5) Depression (N=4) Delaying doses (N=4) Non-disclosure to other family members (N=3) Religious beliefs (N=3) Intimate relation-ships (N=2)	Tablets (N=1)	Drug side effects (N=8) Pill burden (N=5) Pill size (N=4) Palatability (N=3)	Caregiver support (N=6) Early disclosure (N=1) Disclosure to other family members (N=1) Having two or more caregivers (N=1) Other family members on ART (N=1)	Lack of assistan-ce (N=7) Late disclosure (N=2) Lack of privacy at home and at boarding schools (N=2)	Peer support groups (N=6) Support from healthcare workers (N=4) Counselling (N=2)	Inconve-nient clinic appoint-ment time (N=1) Distance to the health facility (N=1) Long waiting times (N=1) Repeated missed appoint-ments (N=1)

Supplementary online resource: Identification of the main concepts

Concept	Alternative keywords
Population	(Adolescent) OR (Adolescents) OR (Adolescence) OR (Adolescen*) OR (Youth) OR (Youths) OR (Teen*) OR (Teenager) OR (Teenagers) OR (Juvenile) OR (Juveniles) OR (Minor) OR (Minors) OR (Young person) OR (Young persons) OR (Child*) OR (Child) OR (Children) OR (Paediatric) OR (Pediatric)
	(HIV) OR (HIV 1) OR (HIV-1) OR (HIV 2) OR (HIV-2) OR (HIV infection) OR (HIV infected) OR (HIV positive) OR (HIV-positive) OR (Human Immunodeficiency Virus) OR (Human Immunodeficiency Viruses) OR (Human Immuno-Deficiency Virus) OR (Human Immuno-Deficiency Viruses) OR (AIDS Virus) OR (AIDS Viruses) OR (Acquired Immune Deficiency Syndrome Virus) OR (Acquired Immune Deficiency Syndrome Viruses) OR (Acquired Immunodeficiency Syndrome Virus) OR (Acquired Immunodeficiency Syndrome Viruses)
	(Sub Saharan Africa) OR (Sub-Saharan Africa) OR (SSA) OR (Africa South of the Sahara)
Intervention	(ART) OR (Anti-retroviral treatment) OR (HAART) OR (Highly active antiretroviral therapy) OR (cART) OR (Combination antiretroviral therapy)
Outcome	(Adherence) OR (Compliance) OR (Retention) OR (Viral load) OR (VL)