Title of review article

Interventions to improve treatment, retention and survival outcomes for adolescents with perinatal HIV-1 transitioning to adult care: Moving on up

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Abstract (195 words; limit 200)

Purpose of review: There are an increasing number of deaths among adult survivors of perinatal HIV. Multiple and complex factors drive this mortality, including problems with retention in care and adherence during adolescence, coupled with the critical period of transition from paediatric to adult care, increasing their risk of treatment failure and severe immunosuppression. We reviewed studies which evaluated the impact of service delivery interventions to improve the health of perinatally infected adolescents living with HIV (P-ALHIV), to gain insight into what might help them survive the vulnerable period of adolescence.
Recent findings: Youth-focused health services and individual-level interventions may improve P-ALHIV adherence and retention in care. However, there have been few studies, many with small sample sizes and with short durations of follow-up that end before the transition period. Studies from other childhood-onset chronic diseases are similarly limited.
Summary: Further studies are urgently needed to identify optimal intervention strategies to reduce mortality and poor outcomes as the adolescent population expands and ages into adult care. Until we have a more robust evidence base, programs can develop transition plans based on best practice recommendations, in order to optimise the health and longevity of ALHIV in adulthood.

Keywords:
Intervention, survival, adolescent, HIV, high-income, middle-income

Abbreviations:

PMTCT, prevention of mother-to-child transmission
ART, antiretroviral therapy
ALHIV, adolescents living with HIV
P-ALHIV, perinatally infected adolescents living with HIV

Introduction

Prevention of mother-to-child transmission (PMTCT) interventions and expansion of antiretroviral therapy (ART) coverage have led to a 58% decline in new HIV infections in children since 2000.[1] However, there is broadening awareness of the increasing numbers of deaths among the generation of children who have survived to adolescence and adulthood with perinatal HIV. This, together with failures to prevent new infections among young adults and link them successfully into care,[2, 3] has resulted in a serious youth-centred threat to our achievements in controlling the HIV epidemic globally. There are multiple and complex factors that drive HIV mortality in adolescents and young adults, but most paths eventually lead to poor adherence, causing treatment failure and severe immunosuppression.

Interventions to promote adherence and retention which have been developed from experiences with HIV and other chronic diseases have the potential to push back against this wave of adolescent deaths. In this paper we review studies which have evaluated the impact of service delivery interventions to improve the health of perinatally infected adolescents living with HIV (P-ALHIV). While we focus primarily on studies targeting P-ALHIV who have had lifelong infection and as a result are likely to have more complex health needs, the interventions highlighted would potentially benefit the broader ALHIV population including behaviourally infected youth. We also consider evidence from the wider literature among patients with other childhood-onset chronic illnesses on factors which could lead to improved outcomes in the period of paediatric to adult care transition for ALHIV.

The global adolescent epidemic

When characterizing adolescent HIV infections, treatment coverage, and associated mortality, there are varying ways that data for this age group have been analysed. Global HIV surveillance estimates variably categorize adolescents (10-19 years) with children (<15 years), youth (15-24 years), and young adults (<25 years). At the end of 2013, there were 2.1 million adolescents living with HIV (ALHIV), 220,000 of whom had been newly infected that year.[4] In 2014, there were 3.9 million youth with HIV, of whom 2.8 million were in sub-Saharan Africa.[5] While the sex distribution is balanced among children aged <15 years living with HIV, almost two-thirds of all adolescents and youth with HIV are females, reflecting the highly inflated risk of HIV infection among adolescent girls. Within current surveillance systems, we are unable to distinguish and estimate the proportion of the adolescent HIV population who are perinatally infected survivors.

The World Health Organization reported that HIV had become the second leading cause of death for adolescents worldwide by 2012, and the fourth leading cause of disability-adjusted life-years lost, with broadly equal impact across males and females, [6] most likely driven by increased morbidity and mortality among P-ALHIV. These findings were consistent with the Global Burden of Disease (GBD) Study which showed that HIV rose from the 101st cause of adolescent disability-adjusted life-years lost in 1990 to the 6th highest cause in 2013.[7] These trends are primarily being driven by mortality within low- to middle-income countries in Africa, but initial signals of these mortality trends are also emerging from high-income countries.[8, 9]

Problems with adherence and poor clinic retention directly increase the risk of death from treatment failure and consequent opportunistic infections. There are indications from high-income countries that perinatally infected and behaviorally infected adolescents who are transitioning to adult HIV care are being lost to follow-up (LTFU) during this age period and defaulting from treatment. Analyses of US national and international cohort data have described poorer outcomes among adolescents and young adults compared to older adults at every step of the treatment cascade, leading to viral suppression rates as low as 6-13%, and higher rates of death.[2, 3, 8, 10-12] The US HIV Research Network reported that 20% of youth receiving HIV care at the age of 21 years were LTFU within one year.[13] Similarly, young adults aged 15-24 years in the UK, particular those with perinatal HIV, had much higher risk of LTFU compared to older adults and those infected through sex between men.[14] Poorer adherence to treatment and mental health issues such as depression, addiction, and reactions to stigma have been identified as critical factors for higher LTFU and death, that have their roots in social marginalization as much as due to the virus itself.[15-18] These reversals in treatment success of perinatally nfected ALHIV are coming after a lifetime of effort to secure their survival across childhood.[19] Thus more effective program-level strategies and youth-focused interventions are urgently needed to support vulnerable adolescents during the transition into independent adult life and self-care.

Interventions for young people with perinatal HIV

We identified 12 studies which evaluated interventions to improve the adherence/ viral suppression[20-29] and retention of P-ALHIV (Table).[30, 31] Four studies had randomised components,[20-22, 25], of which two were fully powered randomised controlled trials[20, 21] and two were pilots,[22, 25] four were prospective cohort studies,[23, 24, 26, 29] and four analysed routinely collected programme data collected at health facilities.[27, 28, 30, 31] Two studies were multi-country; the remainder were conducted in the USA, Europe, Thailand and Kenya. The number of patients included in studies ranged from 9[28] to 730[30], and inclusion criteria varied by age. Most studies included participants aged between 10 and 24 years,[20, 21, 23-26, 29-31] and four studies including younger patients.[21, 22, 27, 28] For ten studies, the majority of the participants had perinatal HIV, and in one study the proportion with perinatally acquired HIV was not stated.[30]

Adherence interventions

The two randomised controlled trials were individual-level interventions to improve adherence and viral suppression. The first, the “BREATHER” trial, evaluated the effect of weekends off therapy,[20] and the second, the “KONCERT” trial, compared outcomes of twice-daily versus once-daily lopinavir-containing regimens to reduce pill burden.[21] The BREATHER trial randomised patients aged 8 to 24 years, who had good adherence (virological suppression for at least 12 months) on an efavirenz-containing regimen, to five days on and two days off ART, versus continuing on daily ART.[20] At 48 weeks, there was no difference in the proportions which were virologically suppressed, demonstrating non-inferiority. A qualitative sub-study and pre- and post-trial questionnaires showed that young people expressed preference for the weekends off ART, particularly as it enabled weekend time with friends without thinking about treatments. In the KONCERT trial, children aged <18 years were randomised to continue lopinavir/ritonavir twice-daily or change to once-daily.[21] However, the once-daily arm failed to demonstrate non-inferiority in suppression of viral load.

A further four studies applied individual level psycho-social interventions to ultimately improve adherence; there were a variety interventions, all involving sessions to explore knowledge about HIV and potential barriers to adherence,[22] health knowledge and coping skills, sexual risk reduction, and life goals,[23] and health empowerment.[24] An additional study evaluated multi-systemic therapy which involved interventions to improve adherence at the individual, family and community levels.[25] This therapy included, for example, cognitive behavioural therapy to reduce individual depressive symptoms, develop family routines such as set times to take medication , and working with families and healthcare providers to build positive working relationships. All studies reported improvement in some outcomes in intervention groups compared to control groups. For example, the largest of the four studies found that among Thai adolescents, knowledge and attitude scores about ART management, reproductive health, sexually transmitted infections, and risk behaviours, increased in the intervention group but not the control group, although the effect of increased knowledge on viral suppression was not evaluated.[23] Similarly, adolescents in an outpatient unit in the USA who participated in multiple systemic therapy sessions had decreased viral load, although there was no difference in CD4 or self-reported adherence compared to a control group.[25]

Three studies, two from the USA and one from the UK, implemented individual-level interventions among adolescents with suspected or documented adherence problems, but had no control groups.[26-28] One study of 11 adolescents with very low CD4 counts (≤200c/mm^3), who were off-ART despite multiple prior attempts to restart treatment, offered motivational interviewing combined with financial incentives. The level of financial incentives was dependent on the extent of viral load decrease or sustained suppression over 12 months.[26] Twenty-four months after enrolment, half of the participants had a viral load <50c/mL, and the mean CD4 gain was 122c/mm^3, showing sustained longer-term impact. The other two studies implemented inpatient directly observed therapy for patients with non-adherence.[27, 28] The duration of inpatient stay for one study was seven days and reported no change in the subsequent viral load results of the nine patients.[28] In the second study, the mean duration of admission was 40 days, the 19 patients had improved CD4 and viral load at discharge and at six months post-discharge.[27]

In terms of health service interventions, a French study implemented 90-minute peer support group sessions, once every six weeks for 26 months, in a paediatric outpatient department in Paris, to improve adherence.[29] The sessions were led by two therapists trained in psychodynamic and family therapy and invited participants to determine their own themes for discussion. After two years, worries about illness had decreased, with less negative perception about treatment among the intervention group receiving peer support. However these outcomes increased or stayed the same among patients who declined the intervention or lived too far away to participate (p=0.026, p=0.030 respectively). Additionally, the proportion with a viral load ≤200c/ml increased in the intervention group from 30% to 80% (p=0.063) but did not change in the other two groups (33% to 56% in the declined group and 50% to 50% in those living too far away). Overall, the decrease in viral load was correlated with increased positive perceptions about ART treatment.

Retention interventions

There is growing recognition that barriers to the availability, accessibility and acceptability - of health services may affect the way that adolescents access health services, and that strategies are needed to develop HIV care services which are responsive to their needs.[32] In Kenya, adolescent-friendly services were implemented at six health facilities, and were designed to improve retention in HIV care for both perinatally and behaviourally HIV-infected young people newly presenting to care.[30] The adolescent-friendly services comprised: training and mentorship for healthcare providers on care for adolescents; a dedicated adolescent clinic day at least once a month, providing integrated sexual and reproductive health services; and peer support groups and education programs. Among newly enrolled patients yet to start ART, loss-to-follow-up over 12 months was 33% pre-implementation, falling to 22% post- implementation of adolescent friendly services. Although this improvement was not statistically significant (p=0.15), and the follow-up time post-intervention was shorter than for the French study.[29] For young people starting ART, loss to follow-up over six months pre-implementation was 12%, and 17% after (p=0.19). In clinics without adolescent-friendly days, similar rates of loss-to-follow up were reported among young people yet to start ART (p=0.28), and significantly higher rates of losses among those starting ART in the post-implementation period (p=0.04). The limited improvement in retention despite adolescent-friendly services may have been due to a number of factors such as high rates of migration and self-referrals to other clinics in this age group/region.[30]

Another study examined whether the following components of care were adolescent-friendly across 12 sites in the US: location of the clinic; waiting area; patient-provider communication modalities; appointment availability and scheduling; and types of providers caring for youth. The investigators then analysed whether the availability of adolescent-friendly structures was associated with improved retention in care, defined as having two or more HIV care visits at least 90 days apart in a 12-month period.[31] Among young people aged 15 to 24 years, of whom a third were P-ALHIV, retention in care was better in youth attending clinics with an adolescent-friendly waiting area (adjusted odds ratio [aOR] 2.5, 95% confidence interval [CI] 1.1, 5.5), evening clinic hours (aOR 1.9, 95% CI 1.1, 3.3) and providers with training in adolescent health (aOR 2.0, 95% CI 1.0, 3.9). These findings are in contrast to the Kenyan study; importantly, the two studies were conducted in settings with different social, cultural and resource contexts. The observed variations in outcomes highlight the importance of conducting locally-appropriate research to evaluate and optimise interventions.

Interventions in other childhood-onset chronic illnesses – what can we learn?

We did not identify any studies which evaluated the effect of interventions on retention and outcomes in P-ALHIV patients during the transition period from separate paediatric to adult HIV care settings. This is a common model in middle- and high-income countries, and where we might expect the risk of loss to follow-up to increase.[2, 33] Recent systematic reviews on the impact of interventions in the transition period for adolescents with other childhood-onset chronic illnesses [34-37] have described poor outcomes after transition, including dramatic drops in attendance rates, and increased disease-related hospitalisations and complications.[38-40]

Three systematic reviews[34, 35, 41] assessed the impact of transition interventions in adolescents across multiple chronic illnesses. An additional three reviews were disease-specific and related to interventions in adolescents with type-1 diabetes[37, 40] and congenital heart disease[38]. All studies included in the reviews were in high-income country settings and with participants ranging from 16 to 25 years. The reviews focused on studies with discrete interventions around the time of transfer, with either a control group or a pre/post intervention study design, and included outcomes in adult care. Across the six reviews, only four randomised studies were identified, all evaluating different educational interventions, with or without other features, to improve knowledge and self-management skills of adolescents in preparation for transition to adult care.[41] The interventions were: a pilot comprehensive transition package, including a transition coordinator, for adolescents with type 1 diabetes,[42] a two-day workshop-based transition preparedness training for adolescents with spina bifida;[43] a nurse-led one on one teaching session for adolescents with heart disease;[44] and a web- and SMS-based education intervention for adolescents with a range of conditions.[45] Findings suggested that three of the interventions may have slightly improved transitional readiness in young people.[43-45]

The remaining studies reviewed largely included cohort data with historical controls or single cohorts with pre/post intervention outcomes. One review highlighted how three of four studies which involved implementing dedicated adolescent-friendly young adult clinics, held on separate days from the general adult clinics, resulted in improved clinical outcomes.[34] The same review showed that three of eight studies involving joint clinics across the transition period (attendance of staff from both services at one or more clinics, within either paediatric or adult services) had improved outcomes.[34] One of these studies included over 1,500 youth with childhood-onset diabetes in multiple clinics across one province of Canada. Patients were categorised according to the diverse range of transition models that already existed across the various clinics. After adjusting for all other factors, patients who had no change in their physician following transfer to adult care had a 77% reduced risk of diabetes-related hospital admissions in the two years post-transfer compared to those with a change in physician.[46]

Such models of joint staffing during the critical period of transition need to be assessed in the adolescent HIV population, and may be particularly appealing in settings where dedicated young adult clinics are not feasible. Indeed, a descriptive account of the transition experience of perinatal ALHIV in a hospital in northern Thailand suggests factors that may be key to their success. These include an integrated approach involving paediatric and adult healthcare providers, respecting the individual patient's readiness to transfer, and transitioning youth in groups so that there is a support system for the process.[47]

Few studies have focused on the effect of age at transfer. One study in patients with chronic kidney failure/transplant reported significantly increased mortality among those transferred to adult care at a younger age of <21 years versus those aged ≥21 years, after adjusting for various demographic and clinical history factors.[48] Although the study was not randomised, it nonetheless highlights the potential importance of age, maturity and readiness for transition to more independent, self-managed care. This is an emerging area of research, with a number of studies assessing and validating tools to assess transition readiness.[49] To date these studies have been limited to the North American setting and need to be tested and validated in other settings, age groups and chronic diseases. If they are to be assessed in the ALHIV population, they would ideally be embedded in studies with long-term follow-up post-transfer, as this would allow evaluation of the effect of transition readiness with retention and treatment outcomes in adult care. In addition, a number of the reviews highlighted concerns about lack of involvement of parents in a supportive capacity during transition, despite adolescents still being highly dependent on parents in most home life settings.[37, 38] This may be particularly salient for P-ALHIV given the higher risk of orphanhood in this population compared to youth with other chronic diseases.[50] Indeed, findings from a recent observational study in P-ALHIV reported a three-fold increased risk of viremia among adolescents when their parents were absent at the previous clinic visit, compared to adolescents whose parents were present.[51]

The way forward

Findings from these studies suggest that while youth-focused health services and individual-level interventions may improve ALHIV adherence and retention in HIV care, it is difficult to generalise their results due to the limited numbers of studies, sample sizes and short follow-up.[41] Results from the BREATHER trial are encouraging and suggest that weekends off therapy are a viable option for adherent youth. Psycho-social interventions and peer support may help to improve adherence, and there may be a role for financial incentives and directly-observed therapy in those with known or suspected adherence problems. Although the KONCERT trial did not support routine use of once-daily lopinavir/ritonavir, long-acting ART drugs are currently under development and may improve adherence to therapy and transform the way ART is delivered to patients struggling with daily adherence, including ALHIV.[52]

Systematic reviews from other chronic disease areas similarly highlighted the need for more data and better quality studies, in particular randomised trials. These would help us understand what intervention or combination of interventions around the time of transfer could have the greatest impact on improving short- and long-term retention and clinical outcomes in adult care, and, ultimately, survival. Harmonisation of common outcomes of interest, such as retention, gaps in care, and adherence, would improve the ability to compare findings across models and settings. Within the HIV field, such definitions could be shared in common resource areas, such as HICDEP (http://hicdep.org), an online platform for standardising data formats for collaborative analyses. Also, most studies to date have been based in tertiary or specialist clinics, and there are limited data on those receiving care in primary care settings. For primary care clinics there may be no change in location or the service provider team during transition to adult care, but rather a shift in focus from a child- to adult-focused health system.[35] This is highly relevant for the majority of ALHIV residing in low- and middle-income country settings who may require alternative integrative models of transition preparation and support.

There are emerging efforts to apply what has been learned in social protection research for youth prevention to the treatment arena. A recent review summarises the evidence for the impact of cash transfers, parenting support and educational support on program outcomes for ALHIV.[53] These offer a way in which individual and community level interventions can be supported or enhanced by interventions addressing wider socio-economic, structural and environmental constraints, to improve HIV treatment outcomes. The use of novel technologies such as eHealth and social media may help improve how traditional healthcare systems reach and retain youth.[54] Also, interventions which have been tested in adults living with HIV, and behaviourally infected adolescents, may have relevance to P-ALHIV, but were beyond the scope of this review.

Whilst awaiting further studies on the determinants of successful transfer of care of ALHIV, what should programs do to help their own patients who have problems with adherence and retention, and may be at greater risk of dying? Existing guidelines suggest the importance of early engagement and participation of youth and their families with both paediatric and adult healthcare teams, and individualised transition plans that prioritise youth-specific needs. These approaches need to be situated within the context of health systems which themselves recognise the importance of transition pathways.[55-57] Evaluation of individual programs would substantially strengthen the evidence base for what might work to retain ALHIV in care; it is likely there will be no “one size fits all” approach for ALHIV, and that interventions will need to take into account the specific needs of the clinic population to prevent morbidity and mortality over this vulnerable period of development.

Key points

- There are an increasing number of deaths in ALHIV, and those with perinatally acquired HIV may be at particular risk, especially during the period of transition to adult care
- Problems with adherence and poor clinic retention are likely to be associated with higher mortality
- Youth-focused interventions may improve P-ALHIV retention and adherence, but there are few studies and sample sizes tend to be relatively small; evidence from other chronic diseases is limited

- In the absence of better evidence for how to successfully transition P-ALHIV, programs should follow transition guidelines to ensure individualised transition planning within current health system approaches

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Conflicts of interest
None declared

Table: Summary of studies describing the impact of interventions to improve P-ALHIV health outcomes

Lead author, country, year	Intervention	Main outcome(s)	Inclusion criteria	Number receiving intervention	Comparison	Number receiving comparison	Impact of intervention
Individual level intervention, adherence outcome							
Butler, Europe, Thailand, Uganda, Argentina, USA, 2011-2014[20]	Randomisation to 5 days on, 2 days off ART vs. continuous ART ("BREATHER" trial)	Confirmed viral load (VL)>50c/ml by 48 weeks	Patients aged 8-24 years on efavirenz + 2 NRTIs and VL <50c/ml for >12 months	99	Standard of care (continued daily ART)	100	At 48 weeks: - 6 in the intervention arm v. 7 in control arm had confirmed VL>50c/ml (difference (90% CI) -1.2% (-7.3, 4.9)
PENTA, Europe, Thailand, South America, 2010-2013[21]	Randomisation to once daily vs. twice daily lopinavir/ritonavir ("KONCERT" trial)	Confirmed VL ≥50c/ml by 48 weeks	Patients aged <18 years with weight ≥15kg, and VL <50c/ml for at least 24 weeks on lopinavir/ritonavir-containing ART	86	Standard of care (twice daily lopinavir/ritonavir)	87	At 48 weeks: - 12 in the intervention arm v. 7 in control arm had confirmed VL≥50c/ml (difference (90% CI) 6% (-2, 14))
Berrien, USA, 2000-2001[22]	Randomisation to 8 structured home visits over 3 months by a nurse, to improve knowledge of HIV, and identify real and potential barriers to adherence	Knowledge and understanding about HIV and ART; self-reported and pharmacy refill ART adherence	All patients receiving care at a children's hospital, age range 1.5 to 20 years (presumed all P-ALHIV)	20	Standard of care medication adherence education, including a single home visit if ART adherence was poor	17	At baseline there were no differences between groups in terms of HIV knowledge or adherence. Post-intervention: - the intervention group improved their knowledge score compared to the control group(p=0.02), but not their adherence score (p=0.07) - pharmacy adherence was better in

							intervention than control (p=0.002) - there were no differences in CD4 or VL
Chokephaibulkit, Thailand, 2010-2011[23]	Two group and two individual sessions focusing on health knowledge, coping skills, sexual risk reduction, life goals	Knowledge, attitudes and practices (KAP) scores between baseline and 2 months post-intervention	P-ALHIV aged ≥12 years	107	Standard of care	32	At baseline there were no differences between groups in terms of KAP scores Post-intervention v. pre-intervention: - knowledge scores increased for the intervention (p<0.01) but not control (p=0.15) groups -attitude scores increased for the intervention (p=0.03) but not control (p=1.0) groups - practice scores (% with desirable answers) did not increase in either group
Individual level intervention, adherence outcomes, patients with known poor adherence							
Kaihin, Thailand, 2011[24]	Health empowerment intervention over 5 sessions, within an 8 session intervention	% with ART adherence ≥95% of prescribed doses before and after the intervention	Patients aged 15-24 years (2/3 P-ALHIV) with <95% adherence (based on pharmacy records)	23	Standard of care	23	Baseline: - no one in either group had ART adherence ≥95%. Post-intervention: - 82.6% of the intervention group and 21.7% of the control group had adherence

							≥95%
Letourneau, USA, (no year given)[25]	Randomisation to multiple multisystemic therapy (MST) sessions over 6 months for ART adherence problems	Rate of change in VL, CD4 and medication adherence over 9 months	Patients in 2 paediatric clinics aged 9-17 years with adherence problems (33/34 P-ALHIV)	20	Standard of care (3 monthly clinic visits) plus one session of motivational interviewing	14	Rate of change over 9 months was: - VL: decreased in intervention but not control (p=0.008) CD4: no difference between groups (p=0.107) - adherence: no difference between groups (p=0.693).
Individual level intervention, adherence outcome, patients with documented problems with adherence, no comparison group							
Foster, UK, 2010-2011[26]	ART restart, motivational interviewing, plus financial incentives dependent on VL reduction for 12 months	Median CD4 and % VL<50c/mL at baseline and 12 months, and 12 months after cessation of financial incentives and motivational interviewing (end of study)	P-ALHIV aged 16-25 years, CD4≤200c/mm3, off ART despite multiple attempts	11	None	N/A*	Median CD4 was: - 30 cells/mm3 at baseline - 140 cells/mm3 at 12 months - 75 cells/mm3 at end of study VL was: - median 12,870c/mL at baseline - 5/11 had VL<50c/mL at 12 months - 6/11 had VL<50c/ml at end of study
Parsons, USA, 2000-2003[27]	Inpatient directly observed therapy (DOT) for ~40 days	Mean CD4 and VL at admission, discharge, and 6 months post-	P-ALHIV aged <18 years who were hospitalised for adherence problems	19	None	N/A*	Mean CD4 count (log viral load): - 262 (5.7) at admission - 492 (4.7) at discharge (p<0.001 and p<0.001 respectively, v.

		discharge					admission) - 429 (5) 6 months post-discharge (p=0.01 and p<0.004 respectively, v. admission))
Glikman, USA, 2004-2006[28]	Inpatient directly observed therapy (DOT) for 7 days	Change in VL between day 1 and end of DOT, day 1 of DOT and 1st clinic visit post-DOT, and day 1 of DOT and 6 month post-DOT follow-up	P-ALHIV aged 7 to 17 years who were hospitalised for non-adherence	9 patients with 13 admissions	None	N/A*	VL at end of DOT was lower than 1st day of DOT in 8 patients (mean decrease 0.8 (SD 0.55) log10 copies per mL), but there was no change in VL at post-DOT clinic appointments compared to 1st day of DOT.
Health service intervention, adherence outcome							
Funck-Brentano, France[29]	Peer support group sessions, 90 minutes long, once every 6 weeks, for 26 months	Emotional wellbeing; change in proportion with VL ≤200c/ml between baseline and 24 months	P-ALHIV aged 12-18 years	10	a) Those declining to participate in the intervention b) Those living too far away from the clinic, so not invited to participate	a) 10 b) 10	At 24 months: - worries about illness decreased in the intervention group, and stayed the same or increased for a) and b) - perceptions about treatment were less negative in the intervention group than a) or b) - the proportion with VL≤200c/ml increased in the intervention group from 30% to 80% (p=0.063), but did not change in a) or b)

Health service intervention, retention outcome							
Teasdale, Kenya, 2011-2013[30]	Adolescent friendly services, including: training of healthcare providers; dedicated adolescent days with integrated services; peer support groups	Incidence of pre-ART loss-to-follow-up (LTFU) (not attending any visits within 12 months) and post-ART LTFU (not attending any visits within 6 months) pre-intervention and post-intervention	Newly enrolled patients aged 10-24 years, perinatal and behavioural HIV (proportion with perinatal HIV not stated)	304 in pre-ART comparison 102 in post-ART comparison	The pre-intervention period	426 in pre-ART comparison 172 in post-ART comparison	Pre-ART LTFU was: - 33.2% at 12 months pre-intervention and 25.2% post-intervention (p=0.15) Post-ART LTFU was: - 11.9% at 6 months pre-intervention and 17.0% post-intervention (p=0.19)
Lee, USA, 2011[31]	Components of clinics which were adolescent-friendly, including waiting areas, evening clinic hours, and adolescent health-trained providers	Completing ≥2 primary HIV care visits ≥90 days apart in a 12-month period	15-24 year olds attending at least one clinic visit in 12 sites (7 adult, 5 paediatric) in 2011 (35% P-ALHIV)	680	None	N/A*	ALHIV were more likely to be retained in clinics with a youth-friendly waiting area (adjusted odds ratio (aOR) 2.5, 95% confidence interval (CI) 1.1,5.5), evening clinic hours (aOR 1.9, 95% CI 1.1, 3.3), and providers with adolescent health training (aOR 2.0, 95% CI 1.0, 3.9)

Notes:
* N/A, not applicable
VL, viral load

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Papers of particular interest, published within the annual period of review, (18 months/ 2012-2013) have been highlighted as:
• of special interest
•• of outstanding interest

Of the papers published since 2014:

Papers of special interest which provide key context and background data on the adolescent HIV epidemic, as well as present suggestions for research and intervention:
#19 Bernays (Viewpoint describing the clinical, social and structural complexities associated with management of adolescents with perinatal HIV, as well as the moral imperative of addressing gaps in their care)
#33 Ryscavage (Study describing health outcomes following transition in one institution, where CD4 and VL suppression levels pre- and post-transfer were similar, but retention in adult care following transition was low)
#47 Hansudewechakul (Descriptive account of one transition model in Chiang Rai, Thailand, where a strong collaboration between paediatric and adult providers led to high rates of post-transition retention and virologic suppression)
#51 Lowenthal (Analysis of factors associated with HIV treatment failure in adolescents, suggesting the important role of psychosocial support, including supportive caregivers)
#53 Cluver (Review paper of social protection interventions which have the potential to improve HIV, health and development outcomes in adolescents)
#54 Anand (Evaluation of a web-based and social media communications strategy, which engaged over 1.5 million viewers in 3.5 years, as well as linking several thousand to HIV testing and care)

Outstanding interest (reason in parentheses):
#2 Zanoni (literature review describing the adolescent HIV cascade of care in the USA, suggesting that less than 6% of HIV-infected youth in the United States remain virally suppressed)
#7 Kyu (analysis of routine datasets globally to estimate the levels and trends in fatal and non-fatal diseases and injuries in children and adolescents, highlighting the importance of HIV in adolescents)
#20 Butler (novel randomised controlled trial of weekends off therapy in P-ALHIV, suggesting that this is a viable strategy to reduce toxicity and improve quality of life in adherent young people)
#26 Foster (innovative pilot study suggesting that financial incentives and motivational interviewing can have a sustained beneficial effect on virological and immunological outcomes)
#30 Teasdale (study evaluating the effect of "adolescent-friendly" services on retention in care among youth with HIV, suggesting some improvement in outcomes, albeit not statistically significant)
#31 Lee (novel cross-sectional study attempting to ascertain whether retention in care is improved if different components of service delivery are offered in an adolescent-friendly way)
#41 Campbell (new Cochrane review to evaluate the effectiveness of interventions designed to improve the transition of care for adolescents from paediatric to adult health services)

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