DOI: 10.1111/hiv.12091
HIV Medicine (2014), **15**, 239–244

SHORT COMMUNICATION

Mortality in perinatally HIV-infected young people in England following transition to adult care: an HIV Young Persons Network (HYPNet) audit

R Fish,[1] A Judd,[2] E Jungmann,[1] C O'Leary[2] and C Foster[3] on behalf of the HIV Young Persons Network (HYPNet)
[1]TEAM Clinic, Mortimer Market Centre, Central Northwest London NHS Foundation Trust, London, UK, [2]Medical Research Council Clinical Trials Unit, London, UK and [3]The 900 Clinic, Imperial College Healthcare NHS Trust, London, UK

Objectives
Mortality in young people with perinatally acquired HIV infection (PHIV) following transfer to adult care has not been characterized in the UK. We conducted a multicentre audit to establish the number of deaths and associated factors.

Methods
Fourteen adult clinics caring for infected young people reported deaths to 30 September 2011 on a proforma. Deaths were matched to the Collaborative HIV Paediatric Study, a clinical database of HIV-infected children in the UK/Ireland, to describe clinical characteristics in paediatric care of those who died post-transition.

Results
Eleven deaths were reported from 14 clinics which cared for 248 adults with PHIV. For the 11 deaths, the median age at transfer to adult care was 17 years (range 15–21 years), and at death was 21 years (range 17–24 years). Causes of death were suicide (two patients), advanced HIV disease (seven patients) and bronchiectasis (one patient), with one cause missing. At death, the median CD4 count was 27 cells/μL (range 0–630 cells/μL); five patients were on antiretroviral therapy (ART) but only two had a viral load < 50 HIV-1 RNA copies/mL. Nine had poor adherence when in paediatric care, continuing into adult care despite multidisciplinary support. Eight had ART resistance, although all had potentially suppressive regimens available. Nine had mental health diagnoses.

Conclusions
Our findings highlight the complex medical and psychosocial issues faced by some adults with PHIV, with nine of the 11 deaths in our study being associated with poor adherence and advanced HIV disease. Novel adherence interventions and mental health support are required for this vulnerable cohort.

Keywords: audit, HIV, mortality, transition, young people

Accepted 21 August 2013

Introduction

Mortality in children with perinatally acquired HIV infection (PHIV) has declined following the introduction of antiretroviral therapy (ART), and this group is now surviving into adulthood and transitioning from paediatric to adult care [1,2]. However, adherence to medication in adolescence is often poor, and complicated by issues involving family, home and school circumstances. Some young people with PHIV have lost one or both parents, and may be a young carer for a relative with HIV infection. HIV diagnoses are often surrounded by secrecy and stigma, limiting support from family and friends [3,4]. Over half of

Correspondence: Dr Ruth Fish, Mortimer Market Centre, Off Capper Street, London WC1E 6JB, UK. Tel: +44 020 3317 5245; fax: +44 020 3317 5190; e-mail: ruth.fish@nhs.net

*The copyright line for this article was changed on September 18, 2014 after original online publication.

UK children with HIV infection were born abroad [5] and may struggle with immigration and cultural adjustment. Higher rates of mental health problems and neurocognitive impairment are reported in adolescents with PHIV, and these factors may impact on adherence, although data are conflicting [6–10]. Adolescents with PHIV who have transitioned to adult care have a lower prevalence of virological suppression compared with horizontally HIV-infected young people [11], increasing the risk of disease progression, mortality and onward transmission to partners and offspring.

While newly infected adults look forward to a near-normal life expectancy [12], little is known about mortality rates and predicted life expectancy for adults who acquired HIV infection in early childhood. While deaths in paediatric care are reported to the Collaborative HIV Paediatric Study (CHIPS), a prospective cohort of > 95% of HIV-infected children receiving care in the UK or Ireland, until recently follow-up ceased on transfer to adult care. There was thus no mechanism for routinely reporting deaths in adults with PHIV in adult care, and thus it was unclear whether the low mortality observed in paediatric care was being maintained on transfer to adult care. We therefore conducted a multicentre audit of a sample of adult HIV services caring for young people with PHIV to establish the number of deaths and factors associated with mortality, including adherence to antiretroviral therapy (ART), mental health issues and comorbidity.

Methods

A structured audit questionnaire was disseminated to 21 adult clinics during 2011 via the HIV Young Persons Network (HYPNet), a multidisciplinary group of health professionals and voluntary sector representatives working with HIV-infected young people aged 13–24 years, largely in the south-east of England. Clinics provided individual patient data on each young person who had been in paediatric care for at least 1 year and who had subsequently transitioned to adult care and died by 30 September 2011. Data collected included demographics, cause of death, virological and immunological parameters at transition and death, ART history, adherence, resistance, hospital admissions, physical and mental health diagnoses, and social history. A London voluntary sector organization also reported deaths known to them and details were matched to clinic returns. All reported deaths were subsequently matched to CHIPS, to elucidate clinical characteristics at the time of last paediatric report pre-transfer to adult care.

Questionnaire data were entered into an Excel database. Mutations associated with resistance to ART were identified from the Stanford University HIV Database (Stanford University, Stanford, California, USA). Potentially suppressive ART regimens were defined as two or more fully active drugs with two or more partially active agents available in the year of death.

Crude mortality rates per 100 person-years and rate ratios by age and type of HIV care (13–15 years old; 16–20 years old in paediatric care; 16–20 years old in adult care; and ≥ 21 years old in adult care) for the UK and Ireland for the most recent 5-year period (2006–2011) were generated from CHIPS data using Poisson regression, in STATA (Stata Corp, College Station, TX). Denominator person-years for the whole CHIPS cohort were calculated from the date a child was 13 years old or 1 January 2006, whichever was later, to 30 September 2011. Young people in adult care and no longer in CHIPS follow-up were assumed to be alive until 30 September 2011 unless they were known to have died. Adolescents with less than 1 year of follow-up between presentation and the date of the last clinic visit or death were excluded.

The audit was registered with Imperial College Healthcare NHS Trust. The CHIPS cohort has ethical approval from the London Multicentre Research Ethics Committee.

Results

Fourteen (67%) of the 21 adult clinics returned audit data and together reported 11 deaths in young people with PHIV following transfer to adult care. These deaths occurred between September 2003 and March 2011. Six of those who died were female, 10 had acquired HIV perinatally, and one had parenteral HIV exposure during infancy. Nine were Black African (eight born in Africa and one born in the UK), one was White British and one was White other European. The median age at transfer from paediatric to adult services was 17 years (range 15–21 years), while the median age at death was 21 years (range 17–24 years).

Cause of death

Table 1 presents clinical characteristics of the 11 patients who died, at transition to adult services and also at death, as well as cause of death, opportunistic infections and comorbidities in adult care. Seven deaths were related to advanced HIV disease (patients 2–6, 9 and 10), two to suicide (patients 7 and 8) and one to complications of bronchiectasis (patient 1), and for one the cause of death was missing. Two deaths occurred in the hospital of the reporting clinic, three in other hospitals, one in a hospice and four in the community.

Antiretroviral therapy

The median CD4 count at transfer to adult services was 120 cells/μL (range 0–651 cells/μL), and at death was

Table 1 Characteristics at transition and death, and key clinical indicators, of perinatally HIV-infected young people who died

	Transition			Death							
No.	Age (years)	CD4 count (cells/μL)	Viral load (copies/mL)	Age (years)	CD4 count (cells/μL)	Viral load (copies/mL)	Cause of death	Other opportunistic infections/ comorbidites in adult care	Mental health diagnoses	Adherence support in adult care	Cumulative resistance to ART
1	17	290	< 50	18	270	< 50	Infective exacerbation of bronchiectasis	Scoliosis; delayed puberty	Depression	Not applicable	None
2	17	120	16 300	19	50	160	Progressive multifocal leucoencephalopathy	PCP	Depression	CNS, HA, PEG, psychology	None
3	17	0	145 299	20	0	136 258	End-stage AIDS	Multisystem inflammatory disorder; hip fracture secondary to HIV/steroid-associated osteoporosis	Depression	CNS, DOT, PEG, psychology	NRTI, NNRTI, PI, T20
4	19	2	111 874	20	14	4 123	Pulmonary RSV infection	Herpes zoster infection; oral candidiasis	None	CNS	NNRTI
5	17	50	41 456	20	10	39 583	Sepsis	End-stage renal failure caused by HIVAN (declined dialysis); HIV-associated thrombocytopaenia; bronchiectasis; PCP	Depression	CNS, DOT, PEG, psychology	NRTI, NNRTI
6	18	30	24 300	21	3	Missing	Cerebral bleed following cerebral toxoplasmosis	End-stage renal failure (on dialysis) caused by bilateral renal dysplasia; CMV colitis; sterile pelvic collections; oesophageal candida; bacterial pneumonia	Eating disorder	Missing	NRTI, NNRTI
7	16	348	125 800	22	40	72 689	Suicide	Herpes zoster infection; PCP; oesophageal candida; cryptosporidiosis; weight loss (requiring TPN); CMV viraemia	Suicidal ideation	CNS, DOT	NRTI, NNRTI, PI, T20
8	18	651	< 50	22	630	< 50	Suicide	None	Psychosis, low mood	Not applicable	none
9	17	90	78 100	23	10	110 000	Sepsis; end-stage AIDS	Oesophageal candida; nontyphoid salmonella; norovirus gastroenteritis; respiratory infections	Psychosis, depression	CNS, HA, PEG, psychology	NRTI, NNRTI, PI
10	21	120	8 970	24	110	97 933	Cerebral lymphoma	Memory problems; seizure	Depression	CNS, DOT	NRTI, NNRTI
11	16	480	500	Missing	Missing	Missing	Missing	Bacterial pneumonia; herpes zoster infection	None	CNS, psychology	NRTI, PI

PCP, *Pneumocystis carinii* pneumonia; CMV, cytomegalovirus; RSV, respiratory syncitial virus; HIVAN, HIV-associated nephropathy; ART, antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; T20, enfuvirtide; CNS, clinical nurse specialist; HA, health advisor; PEG, percutaneous endoscopic gastrostomy; DOT, directly observed therapy; TPN, total parenteral nutrition.

27 cells/μL (range 0–630 cells/μL). Of nine patients prescribed ART at the time of transfer (the other two having declined ART), only two had a viral load < 50 HIV-1 RNA copies/mL at transfer. These two patients were also the only two to have a viral load < 50 copies/mL at death, and neither had any reported ART resistance. The remaining nine patients had a history of poor adherence in paediatrics (documented in clinical notes), which continued following transition, with only two of the nine ever achieving a viral load < 50 copies/mL in adult care. Reported reasons for poor adherence included limited motivation (nine patients), limited acceptance of diagnosis (three patients), side effects (three patients) and limited adherence skills (e.g. ability to plan) (two patients). All those with poor adherence were offered multimodal support, including support from clinical nurse specialists, community nurses and health advisors, psychology and directly observed therapy. Three patients had gastrostomies inserted to aid adherence.

At the time of death, five patients were on ART, although only two had a viral load < 50 copies/mL. Patients not on ART at death had all declined previous offers of treatment. Eight of the nine patients with a viral load > 50 copies/mL at the time of death had ART resistance (two had single-class, three dual-class, one triple-class and two four-class resistance) (Table 1). However, all patients had potentially suppressive treatment regimens available in the year of their death.

Comorbidity

All but one of the patients had additional health problems, many of which were HIV-related (Table 1), although no patients had hepatitis coinfection. Three patients had *Pneumocystis carinii* pneumonia in adult care. Mental health problems were documented in nine of the 11 patients: two had required in-patient mental health services for a psychotic episode (with one going on to commit suicide), while a further seven had a history of depression, and one an eating disorder.

Social circumstances

At the time of death, three of the 11 young people were living with one or both parents, four were living with adoptive/foster parents, two were living alone and two were alternating between family and friends. Ten had at least one infected family member, and for three at least one parent had died from an HIV-related illness. Six were in education, one was employed and four were not in education, employment or training. Two had been involved with youth offending services. Six had previous involvement with social services, most commonly in relation to adoption/foster care.

Six were known to be sexually active (median age of coitarche 16 years; range 15–20 years) with no reported pregnancies. Three young people were known to smoke and one was an ex-smoker. Six reported alcohol use, with five not having this documented. Drug use was reported in four cases, including cannabis alone (one patient), cannabis and ecstasy (one patient), cocaine (one patient) and unspecified (one patient). Nine had attended peer support services outside the hospital setting.

Mortality rates

Mortality rates for children and young people with PHIV in CHIPS who were in paediatric care or who transferred to adult care in the UK and Ireland are presented in Table 2. A total of 996 patients aged 13 years and over between 1 January 2006 and 30 September 2011 were included in the analysis. The crude mortality rate rose from 0.2 per 100 person-years [95% confidence interval (CI) 0.1–0.6] in those aged 13–15 years in paediatric care to 0.9 (95% CI 0.3–2.3) for those aged ≥ 21 years in adult care, although CIs were wide because of the low number of events. Similarly, the mortality rate ratio was 4.9 (95% CI 1.1–22.0) and 2.7 (95% CI 0.6–12.2) for those aged ≥ 21 years and those aged 16–20 years in adult care, respectively, compared with those aged 13–15 years in paediatric care ($P = 0.18$).

Table 2 Estimated minimum* mortality rates by age and type of HIV care in perinatally HIV-infected young people, 2006–2011

Age group and type of care	No. of deaths	Person-years	Rate/100 person-years (95% CI)	Rate ratio (95% CI)
13–15 years, paediatric	3	1689	0.2 (0.1–0.6)	1.0
16–20 years, paediatric	2	786	0.3 (0.1–1.0)	1.4 (0.2–8.6)
16–20 years, adult†	4	825	0.5 (0.2–1.3)	2.7 (0.6–12.2)
≥ 21 years, adult†	4	458	0.9 (0.3–2.3)	4.9 (1.1–22.0)

CI, confidence interval.
*Mortality rates are considered 'minimum estimates' as not all adult clinics treating young people with perinatal HIV infection were included in the audit and so additional deaths may have been missed.
†Three deaths were excluded from this analysis as they occurred prior to 2006.

CHIPS data suggest that a total of 404 children had transferred to 70 adult clinics in the UK and Ireland by 30 September 2011, of whom 248 transferred to the 14 clinics providing data for this audit.

Discussion

This audit identified 11 young people with PHIV who had died following transfer to one of 14 adult HIV clinics. Of the 404 young people across the UK and Ireland who had transferred to adult care in a similar time period, 248 transferred to one of these adult clinics and 156 transferred elsewhere, for whom the mortality status is presently unknown. Thus, the mortality rates presented here can be considered minimum estimates of the size of the problem. Although the mortality rate in the general population rises in early adulthood, rates in our study remain much higher than in the general population (2010 mortality rates for male and female individuals in England and Wales were 0.03 and 0.02 per 100 population for 15–19-year-olds and 0.06 and 0.02 for 20–24-year-olds, respectively) [13].

Details of the 11 deaths reported in our audit highlight the complex medical and psychosocial issues faced by some young adults growing up with HIV infection. Seven of the 11 deaths were considered to be directly related to HIV progression, one was attributable to an exacerbation of HIV-related bronchiectasis that had been present from early childhood, and two were from suicide. The prevalence of comorbidity was high and *Pneumocystis carinii* pneumonia was the commonest opportunistic infection reported. Mental health problems were very common, home circumstances often unstable, and drug and alcohol use prevalent, highlighting the multidisciplinary needs of this diverse group.

Comparable mortality data for horizontally infected UK adults suggest that deaths directly related to HIV infection are decreasing and that nearly a third of deaths are not HIV related [14]. For horizontally infected adults, multidrug resistance, poor adherence to ART and not taking ART contributed to only 14% of all the reported deaths [15]. However, in our study nine of 11 deaths were associated with poor adherence and advanced HIV disease, with poor adherence patterns in paediatrics continuing in adult care, highlighting the importance of combating barriers to adherence soon after ART initiation. Other studies have similarly shown that early patterns of adherence may predict long-term adherence [16,17]. Our persistent low levels of adherence despite multimodal support highlight the need for novel interventions for this particular group. A recent pilot intervention of motivational interviewing and financial incentives linked to virological response in a comparable cohort of poor adherers showed sustained virological response in half of participants [18]. Such interventions require assessment in much larger studies which may be complex in nature as a consequence of the study population having issues of attendance, adherence, mental health and social instability. Although rates of mother to child transmission of HIV in the UK have been falling over the last decade, there continue to be new diagnoses of PHIV, often in children originating from Africa. As of March 2013 there were 1131 children with HIV infection in paediatric care in the UK and Ireland (A. Judd, Medical Research Council Clinical Trials Unit, London, UK, personal communication). Novel interventions need to be developed to address the health needs of young people in this group.

The main limitation of this study is that reporting of deaths in adult care is likely to be incomplete. Only 248 of the 404 young people with PHIV who have transferred to adult care to 30 September 2011 were seen at one of the 14 clinics included in our study, and it is therefore likely that the number of deaths in this group in adult care is underreported. Notwithstanding, mortality rates post-transition to adult care were still higher than comparable rates for paediatric care.

Findings from this audit clearly highlight the need for continued comprehensive surveillance of health outcomes in young people with PHIV following transfer to adult care. Several initiatives are now underway to tackle this issue. Firstly, from 2012 onwards, young people transitioning to adult care (as well as those who have already transitioned) are being invited to join the UK Register of HIV Seroconverters, a prospective cohort study of HIV-infected individuals whose date of seroconversion can be estimated. Characteristics of study participants are routinely matched to the national register of deaths to estimate mortality. Secondly, a growing proportion are being 'flagged' with the national register of deaths to provide ongoing mortality estimates that are not conditional on participating in a study. Thirdly, those leaving CHIPS are now being linked to the Survey of Prevalent HIV infections Diagnosed (SOPHID) database as well as the UK Collaborative HIV Cohort Study (CHIC), in order to maintain anonymous surveillance in adult care. Fourthly, the Adolescents and Adults Living with Perinatal HIV (AALPHI) cohort will give further insight into long-term treatment and psychosocial outcomes [19]. These new studies, which involve linking and harmonizing paediatric and adult data sets, will enable more accurate estimates of mortality rates in this group as a whole, as well as clarifying the characteristics of young HIV-positive patients transitioning into adult clinics. Finally, within the EuroCoord network of excellence, a working group has been formed to prioritize and ensure a coordinated approach to this issue across Europe.

Acknowledgements

We thank the following adult clinics (in alphabetical order) for participation in this audit: Brighton and Sussex University Hospitals, Brighton; Chelsea and Westminster Hospital, London; Ealing Hospital, London; Ipswich Hospital, Ipswich; King's College Hospital, London; Luton and Dunstable Hospital, Luton; Manchester Royal Infirmary, Manchester; Mortimer Market Centre, London; Newham Hospital, London; North Staffordshire Hospital, Stoke; Royal Free Hospital, London; St George's Hospital, London; St Mary's Hospital, London; St Thomas' Hospital, London.

Author contributions: RF, EJ and CF designed the audit. RF contacted clinics and entered the data. AJ and CO'L analysed the data. All authors contributed to the drafting and revision of the article, and approved the final version prior to submission.

References

1 Gibb DM, Duong T, Tookey PA *et al.* Decline in mortality, AIDS, and hospital admissions in perinatally HIV-1 infected children in the United Kingdom and Ireland. *Br Med J* 2003; **327**: 1019.

2 Foster C, Judd A, Tookey P *et al.* Young people in the United Kingdom and Ireland with perinatally acquired HIV: the pediatric legacy for adult services. *AIDS Patient Care STDS* 2009; **23**: 159–166.

3 Fielden SJ, Sheckter L, Chapman GE *et al.* Growing up: perspectives of children, families and service providers regarding the needs of older children with perinatally-acquired HIV. *AIDS Care* 2006; **18**: 1050–1053.

4 Martinez J, Harper G, Carleton RA *et al.* The impact of stigma on medication adherence among HIV-positive adolescent and young adult females and the moderating effects of coping and satisfaction with health care. *AIDS Patient Care STDS* 2012; **26**: 108–115.

5 Judd A, Doerholt K, Tookey PA *et al.* Morbidity, mortality, and response to treatment by children in the United Kingdom and Ireland with perinatally acquired HIV infection during 1996–2006: planning for teenage and adult care. *Clin Infect Dis* 2007; **45**: 918–924.

6 Chernoff M, Nachman S, Williams P *et al.* Mental health treatment patterns in perinatally HIV-infected youth and controls. *Pediatrics* 2009; **124**: 627–636.

7 Mellins CA, Elkington KS, Leu CS *et al.* Prevalence and change in psychiatric disorders among perinatally HIV-infected and HIV-exposed youth. *AIDS Care* 2012; **24**: 953–962.

8 Paramesparan Y, Garvey LJ, Ashby J, Foster CJ, Fidler S, Winston A. High rates of asymptomatic neurocognitive impairment in vertically acquired HIV-1-infected adolescents surviving to adulthood. *J Acquir Immune Defic Syndr Hum Retrovirol* 2010; **55**: 134–136.

9 Rudy BJ, Murphy DA, Harris DR, Muenz L, Ellen J. Prevalence and interactions of patient-related risks for nonadherence to antiretroviral therapy among perinatally infected youth in the United States. *AIDS Patient Care STDS* 2010; **24**: 97–104.

10 Malee KM, Tassiopoulos K, Huo Y *et al.* Mental health functioning among children and adolescents with perinatal HIV infection and perinatal HIV exposure. *AIDS Care* 2011; **23**: 1533–1544.

11 Ryscavage P, Anderson EJ, Sutton SH, Reddy S, Taiwo B. Clinical outcomes of adolescents and young adults in adult HIV care. *J Acquir Immune Defic Syndr* 2011; **58**: 193–197.

12 Nakagawa F, Lodwick RK, Smith CJ *et al.* Projected life expectancy of people with HIV according to timing of diagnosis. *AIDS* 2012; **26**: 335–343.

13 Office for National Statistics. *Death Registration Summary Statistics, England and Wales*. Newport, Office for National Statistics, 2010.

14 Crum NF, Riffenburgh RH, Wegner S *et al.* Comparisons of causes of death and mortality rates among HIV-infected persons: analysis of the pre-, early, and late HAART (highly active antiretroviral therapy) eras. *J Acquir Immune Defic Syndr* 2006; **41**: 194–200.

15 Lucas SB, Curtis H, Johnson MA. National review of deaths among HIV-infected adults. *Clin Med* 2008; **8**: 250–252.

16 Lindsey JC, Bosch RJ, Rudy BJ, Flynn PM. Early patterns of adherence in adolescents initiating highly active antiretroviral therapy predict long-term adherence, virologic, and immunologic control. *AIDS Patient Care STDS* 2009; **23**: 799–801.

17 Kent A, Foster C, Fidler S. How do patterns of antiretroviral adherence in childhood impact on adherence in adult life? *17th Annual Conference of the British HIV Association*. Bournemouth, April 2011 [P59].

18 Foster C, McDonald S, Frize G, Walsh J, Fidler S. Financial incentives and motivational interviewing for adolescents with advanced HIV disease; a pilot service. *18th Annual Conference of the British HIV Association*. Birmingham, April 2012 [P85].

19 Judd A, O'Leary C, Le Prevost M *et al.* Characteristics and risk behaviours of perinatally HIV-infected and HIV-uninfected young pepple recruited into a new adolescent cohort, UK. In: *5th International Workshop on HIV Pediatrics*. Kuala Lumpur, Malaysia; 2013.