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Clinical outcomes post transition to adult services in young adults with perinatally acquired HIV infection: mortality, retention in care, and viral suppression.

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Abstract

Objective: Adolescence is the only age group globally where HIV associated mortality is rising, with poorer outcomes at all stages of the care cascade compared to adults. We examined post-transition outcomes for young adults living with perinatal HIV (YAPaHIV).
Design: Retrospective cohort analysis.

Setting: A tertiary Youth Friendly Service (YFS) London, UK.

Participants: 180 YAPaHIV registered between 01.01.06 and 31.12.17 contributed 921 person-years of follow up post-transition to adult services.

Intervention: YFS with multidisciplinary care and walk-in access.

Main outcome measures: mortality, morbidity, retention in care, antiretroviral (ART) uptake and HIV-viral load (HIV-VL) suppression. Crude incidence rates (CIR) are reported per 1000 person-years.

Results: Of 180 youth registered; 4 (2.2%) died, 14 (7.8%) transferred care and 4 (2.2%) were lost to follow up. For the 158 retained in care the median age was 22.9 years (IQR 20.3-25.4), 56% were female, 85% Black African, with a median length of follow up in adult care of 5.5 years (IQR 2.9-7.3). 157 (99.4%) ever received an ART prescription, 127/157 (81%) with a latest HIV-VL < 200 copies RNA/ml, median CD4 count of 626 cells/ul (IQR 441-820). The all-cause mortality was 4.3/1000 person-years (95% CI 1.2 – 11.1), ten fold the aged-matched UK HIV-negative population (0.43/1000 person-years (95% CI 0.41 – 0.44). Post-transition, 17/180 (9.4%) developed a new AIDS diagnosis; CIR 18.5/1000 person-years (95% CI 10.8 – 29.6).

Conclusion: Whilst this youth-friendly multi-disciplinary service achieved high engagement and coverage of suppressive ART, mortality remains markedly increased compared to the general UK population.

Introduction

Globally an estimated five million youth aged 15-25 years live with HIV, an increasing proportion infected perinatally [1]. For this group transition from paediatric to adult services is a highly vulnerable period linked to significant loss-to follow-up [2]. Adolescence is the only age group where HIV associated mortality continues to rise, driven predominantly by survivors of the perinatal epidemic [3]. In order to drive better clinical outcomes and reduce HIV transmission, UNAIDS in 2014 developed the 90-90-90 targets; 90% of the population were aware of their HIV status, of those living with HIV 90% should have access to antiretroviral therapy (ART) and of those receiving ART 90% should have suppressed HIV viral load (VL) [4]. Leading to 73% of all people living with HIV having access to suppressive ART. This has become a key metric to access coverage of care.

There remains a paucity of data on outcomes post transition to adult services, although available data reveals poorer outcomes for adolescents at all stages of the care cascade when compared to adults or children [2,5]. A meta-analysis of 850,000 South African youth (15-24 years), both behaviourally and perinatally infected, reported that less than 10% were retained in care on suppressive ART compared with 60% amongst adults and younger children in the same setting and time period [6].

Resourced settings do not necessarily fare better; in the US pre-2013, only a quarter of diagnosed young adults with perinatally acquired HIV (YAPaHIV) were retained in care, with only half on suppressive ART [7]. Subsequently specialist youth clinics with integrated mental health and substance use services have shown promise with evidence of improved retention on suppressive ART [8]. European data suggests higher rates of loss to follow up and mortality in perinatal cohorts compared with behaviourally infected adults [9,10]. Whilst adults living with HIV in London achieved UNAIDS 90-90-90 targets in 2016, ART uptake

was significantly lower in those aged 15-24 years compared with > 50 years (89% v 98%) with rates lower in YAPaHIV compared to youth with behavioural acquisition [11,12].

We assessed clinical outcomes including mortality, retention in care, ART uptake, VL suppression, AIDS and mental health diagnoses in the largest UK perinatal cohort following transition to adult care, comparing outcomes to aged matched UK HIV-negative population data and to 90-90-90 goals.

Methods

Setting: The "900 Clinic" a specialist HIV service for YAPaHIV in London, with care provided by a multidisciplinary team; adult HIV physicians, adult nurse practitioners, a psychologist, and peer support workers from the third sector group "Positively UK". A physician specialising in adolescent medicine, provides care in both paediatric and 900 Clinic services, supporting transition that occurs between 15-20 years of age, determined by individual need. Services are constructed around a "one stop appointment or drop-in model" including; medical care, sexual and reproductive health: contraception, vaccination, partner, conception and pregnancy care, psychological health and peer support. Referral is through paediatric services, self and peer led. Youth with behavioural HIV acquisition access the service but are excluded from this analysis.

Study design: Retrospective database and electronic record review of all YAPaHIV who ever attended the service between January 2006 and December 2017. Outcomes included mortality, transfer of care, loss to follow up (defined as failure to attend within the last 12 months of the study period), AIDS diagnoses, malignancy, neurocognitive/sensorimotor disability and mental health diagnoses. A severe learning disability was defined as intellectual impairment preventing independent living. For those currently accessing the

service, demographics, most recent CD4 count, HIV-VL, current ART and cumulative HIV-1 associated drug resistance mutations are described.

Statistical analysis: Data was anonymised with median and interquartile ranges (IQR) summarising non-normally distributed continuous variables and numbers and percentages summarising categorical variables. Crude Incidence rates (CIR) per 1000 person-years at risk with 95% confidence intervals (CI) were calculated for all-cause mortality, AIDS diagnoses and malignancies assuming a Poisson distribution for all outcomes. Statistical analysis was performed using MedCalc Statistical Software version 18 (MedCalc Software bvba, Ostend, Belgium; 2018).

Results

180 YAPaHIV contributed 921 person-years of follow-up; with a median transition age of 17.5 years (range 15.2-20.4). At the end of the study 158/180 (86%) remained in care of whom, 157 (99%) had ever received ART, 127/157 (81%) with an HIV-VL < 200 c/ml. 14 (7.8%) had transferred care to other HIV services, 4 (2.2%) were lost to follow up (LTFU) and 4 (2.2%) died (table 1).

Retention: The four patients LTFU were last seen in 2013 (2), 2015 (1), and 2016 (1) with median CD4 count 459 cells/ul (range 214-680), three with HIV-VL <20 c/ml. One was ART naïve with a CD4 count 683 cells/ul, and HIV-VL 12,444 c/ml.

Mortality: Four patients (2.2%) died, at a median age of 20 years (range 19-27). Three due to advanced HIV; wasting syndrome and noma (1), gram negative sepsis/acute renal failure (1) and gastrointestinal Mycobacterium genovense (1), all with long term poor ART adherence; CD4 count <200 cells/ul for 18, 4 and 8 years respectively. A fourth patient developed a rapidly progressive hepatocellular carcinoma (HCC) despite a decade of HIV/HBV

suppression and has been previously reported [13]. The all-cause mortality in adult services was CIR 4.3/1000 person-years (95% CI 1.2 – 11.1).

AIDS defining diagnoses: 17/180 (9.4%) experienced one or more new AIDS diagnoses post transition including; HIV wasting (6), recurrent sepsis (5), lymphoma (3), Mycobacterium avium intracellulare (3), oesophageal candidiasis (3), Cryptococcus [meningitis (1), disseminated (1)], pneumocystis pneumonia (2), pulmonary tuberculosis (2) and multidrug resistant lymph node tuberculosis (1). The CIR of a new AIDS diagnosis in adult care was 18.5/1000 person-years (95% CI 10.8 – 29.6).

Malignancies: 7/180 (3.9%) patients, six male, ever had a malignancy diagnosis; three in paediatric care (lymphoma (2) and Kaposi's sarcoma (1)) and four in adult care; lymphoma (3) and HCC (1). The CIR of a new malignancy following transition was 4.3/1000 person-years (95% CI 1.2 – 11.1).

Current Cohort: Of the 158 in follow-up at the end of the study period, the median age was 22.9 years (IQR 20.3-25.4; range 18.1-33.6), 88 (55.7%) were female, with ethnicity self assigned as Black African (84.8%), mixed (7.6%), Caucasian (7%) and Asian (0.6%). Median length of follow up in adult care was 5.5 years (IQR 2.9-7.3) (table 1).

ART coverage: 157/158 (99.4%) had received ART; one patient with capacity to make healthcare decisions continued to decline treatment; nadir CD4 count 336 cells/ul, HIV-VL 2348 c/ml. 126/157 (80.3%) are on standard ART regimens of two nucleoside reverse transcriptase inhibitors (NRTI) and; a boosted protease inhibitor 65 (41%), integrase strand transfer inhibitor 43 (27%), or a non-nucleoside reverse transcriptase inhibitor 26 (17%) detailed in table 1. 56/157 (36%) are on single tablet regimens. 66/158 (42%) have documented HIV-1 associated resistance mutations, 10 (6%) with triple-class resistance (table 1).

22 (14%), median age 24.5 years (IQR 22.3-27.9) are on complex regimens consisting of three or more classes due to acquired HIV-1 drug resistance mutations.14/22 (64%) have a history of mono/dual NRTI exposure prior to 1998. At study end 11/22 (50%) have a HIV-VL <200 c/ml, median CD4 count 268 (IQR 54-670) cells/ul.

Viral suppression: At study end 127/158 (80.4%) had an HIV-VL <200 c/ml. All 31 patients with a detectable viral load had documented adherence issues and had potentially suppressive ART regimens available. Including the four patients lost to follow up, viral suppression rates were 78.4% (127/162).

Immune function: At study end (n=158) the median CD4 count of 626 cells/ul (IQR 441-820). 18 (11.4%) young people, median age 23.7 years (IQR 21.7-24.6) had CD4 counts <200 cell/ul, four with HIV-VL <200 c/ml.

Neurocognitive and sensorimotor disability: 13/158 (8.2%) were registered with one or more disability impacting on daily living; severe learning disability (4), motor: a sequelea infantile HIV encephalopathy (4); two of whom are wheel chair using, hearing deficits requiring augmentation (5) and visual impairment (4).

Mental Health: 33/158 (21%) have been diagnosed in adult care with anxiety and/or depression; 3 young people have attempted suicide and a further 4 self-harmed. 6 (4%) YA have a diagnosis of alcohol/drug dependency. 11/158 (7.0%), 6 (55%) male, have experienced at least one psychotic episode. The median age at first psychotic episode was 21 years (range 16-26). Their median CD4 count at first presentation was 701 cells/µl (IQR 51-923) with 7/11 (66%) having a suppressed plasma HIV-VL. The CIR of experiencing a first psychotic episode in adult care was 9.8/1000 person-years (95% CI 4.5 – 18.6).

Discussion

Within a specialised service for perinatally infected young adults overall UNAIDS 90-90-90 targets have been achieved; ie more than 73% of the cohort are retained in care and on suppressive ART [4]. However when considering individual targets, although retention rates more than 5 years following transition to adult services, and uptake of ART are high, 97% and 99% respectively, viral suppression rates still fall below 90%.

Our data suggests that tailored multidisciplinary youth friendly service with open drop-in access may facilitate retention in care, although further interventions are required to improve ART adherence. Globally, there remains a paucity of data on outcomes of youth friendly differentiated care models, with studies limited by small sample sizes, short-term follow up and insufficient operational details [14]. The importance of longer term follow up is highlighted in an American cohort (n=72) with post transition retention in care falling from 89% at 12 months to 56% in year two [15]. Whilst high retention rates have been reported in small perinatal European cohorts from Holland (n=59) and Sweden (n=23) a recent review of 43 global studies estimated 75% retention four years post transition [16-18].

Reassuringly, mortality in this cohort remained low (2.2%). However, concerningly, the all-cause mortality of 4.3/1000 person-years is 10-fold the UK population aged 19-29 (0.43/1000 person-years (95% CI 0.41 – 0.44) [19]. By contrast, UK adults living with HIV, excluding those diagnosed late, have mortality rates comparable to the general population, highlighting the inequality in health outcomes for youth when compared to older adults [12]. UK national data suggests mortality rises steeply post transition to adult care with 10% mortality at 5 years; a four-fold increase from our experience [20]. A US YAPaHIV cohort, reported mortality of 55.8/1000 in the year following transition, compared to 2.3/1000 in the year prior and 0.5/1000 in the general 15-24 year old population [21].

HIV care and ART is free in the UK, yet despite excellent ART uptake, overall viral suppression rates were only 78%, with one in ten having severe immunosuppression. Rates of new AIDS diagnoses of 18.5/1000 person-years were 3 times that of a younger Thai paediatric and adolescent cohort [22]. The incidence of a malignancy of 4.3/1000 person-years was ten-fold the general UK population aged 20-24 years (0.35/1000 person years (95% CI 0.33 – 0.36), consistent with findings in other perinatal cohorts [23]. Whether the increased malignancy risk will be mitigated by guideline shifts to earlier ART initiation from infancy is unknown [24,25].

Mental health outcomes are poor in this cohort. Studies from the US and UK with aged matched HIV exposed uninfected controls show higher rates of mental health diagnoses in both groups when compared to the general population [26,27]. In a comparable US PaHIV cohort (mean age 22 years, n=151), 16% had received psychotropic medication within the past year, compared with 6% of controls [27]. In the UK sociodemographic risk factors for psychosis include; black ethnicity, migration and socio-economic deprivation [28]. However even when compared to UK adults of Afro-Caribbean ethnicity, the incidence of psychosis was markedly raised (9.8/1000 person-years vs 0.19/1000 person-years (95% CI 0.17 – 0.23) [29]. Half of our cohort were born abroad, almost all were first/second generation migrants, and may in part explain the excess risk [29].

This analysis has several limitations, being a retrospective single centre study with a small sample size, although larger than other reported European cohorts, and lacking in more detailed socioeconomic data [15,16]. The small number of events may over estimate risk when compared to general population rates, but highlights the need for monitoring perinatal cohorts well beyond transition. Importantly, open access multidisciplinary transition services can successfully support young people towards achieving overall 90-90-90 goals.

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SA and SM provided clinical data and reviewed the manuscript

GF provided mental health and neurocognitive data and reviewed the manuscript

SC and TP provided statistical analyses and reviewed the manuscript

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Table 1 Characteristics of cohort currently in care at latest follow up (n=158)

	N	[%]
Age median (IQR)	22.9 (20.3-25.4)	
Sex (female %)	88	[55.7]
Ethnicity		
Black African	133	[84.8]
Mixed	12	[7.6]
Caucasian	11	[7]
Asian	1	[0.6]
Hepatitis co-infection	6	[3.8]
Hepatitis B (HBV)	4	
HBV and delta virus	1	
Hepatitis C	1*	
Antiretroviral therapy	157	[99]
NNRTI + 2NRTI	26	[17]
EFV	14 [9]	
NVP	9 [6]	
RPV	4 [2]	
bPI + 2NRTI	65	[41]
DRV/r	52 [33]	
ATZ/r	11 [7]	
LPV/r	2 [1]	
INSTI + 2NRTI	43	[27]
DTG	37 [24]	
ELV	5 [3]	
RAL	1 [1]	
Complex – 3+ class	22	[14]
Other (bPI monotherapy, unboosted ATZ + 2NRTI)	2	[1]
HIV-1 associated resistance mutations		
Nil	92	[58]
Single class	23	[15]
Dual class	33	[21]
Three+ class	10	[6]
INSTI major	1 [0.6]	
Immunology CD4 cells/ul		
0-199	18	[11]
200-349	9	[6]
350-499	23	[15]
>500	108	[68]
Virology HIV VL copies/ml		
<200	127	[80]
200-999	6	[4]
1000-10,000	9	[6]
>10,000	16	[10]

* Genotype 3, recent sustained remission following 12 weeks of sofosbuvir and velpatasvir.

Non-nucleoside reverse transcriptase inhibitor (NNRTI), nucleoside reverse transcriptase inhibitors (NRTI), efavirenz (EFV), nevirapine (NVP), rilpivirine (RPV), boosted protease inhibitor (bPI), darunavir (DRV), ritonavir (r), atazanavir (ATZ), lopinavir (LPV), integrase strand transfer inhibitor (INSTI), dolutagravir (DTG), elvitegravir (ELV), raltegravir (RAL).

Table 2. Crude Incidence rates (CIR) of adverse events post transition to adult care

	Patients post transition to adult care (n=180 [%])	Crude Incidence rate per 1000 person-years (CIR 95% CI)
Loss to follow up	4 2.2%	4.3 (1.2-11.1)
Mortality	4 2.2%	4.3 (1.2-11.1)
New AIDS diagnoses	17 8.4%	18.5 (10.8-29.6)
New malignancy	4 2.2%	4.3 (1.2-11.1)
New onset psychosis	9 5%	9.8 (4.5-18.6)