Title

Clinical status of adolescents with perinatal HIV at transfer to adult care in the UK/Ireland

Authors:

Intira Jeannie Collins[1], Caroline Foster[2], Anna Tostevin[3], Pat Tookey[4], Andrew Riordan[5], David Dunn[3], DM Gibb[1] Ali Judd[1] on behalf of the Collaborative HIV Paediatric Study (CHIPS) Steering Committee

Affiliations:

1 MRC Clinical Trials Unit at UCL, Institute of Clinical Trials & Methodology, University College London, UK

2 Imperial College Healthcare NHS Trust, London, UK

3 Research Department of Infection and Population Health, University College London, UK

4 Institute of Child Health, University College London, UK

5 Alder Hey Children's NHS Foundation Trust, Liverpool, UK

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Corresponding author: I. Jeannie Collins, MRC Clinical Trials Unit at UCL, University College London, Aviation House, 125 Kingsway, London WC2B 6NH

Email: jeannie.collins@ucl.ac.uk, Telephone: +44 20 7670 4767

Alternate contact: Ali Judd, MRC Clinical Trials Unit at UCL, University College London.

Email: a.judd@ucl.ac.uk Telephone: +44 20 7670 4830

40 word summary: One-third of the UK/Ireland national paediatric HIV cohort has transferred to adult care. Three-quarters of adolescents were on ART at transfer, of whom 74% were virologically suppressed <400cps/mL. The prevalence of triple class resistance was 12%.

Abstract

Background: Increasing numbers of perinatally HIV-infected children are surviving to adolescence and transitioning to adult care, yet there are scarce data on their clinical status at transfer.

Methods: We analysed prospective cohort data from the UK/Ireland national Collaborative HIV Paediatric Study (CHIPS). Clinical status at last paediatric clinic visit prior to transfer was described. Factors associated with higher CD4 cell count and viral load (VL) suppression<400c/mL among patients on ART at transfer were assessed using linear and logistic regression, respectively. Data were matched with the UK HIV Drug Resistance Database (UKHIVDRB) to assess cumulative resistance profiles at transfer.

Results: Of 1,907 children followed in CHIPS from 1996 to November 2014, 644 (34%) transferred to adult care: 53% were female, 62% born outside the UK/Ireland, 75% black African. At last paediatric follow-up, median age was 17.4 years [interquartile range 16.5,18.1], 27% had previous AIDS diagnosis, CD4 was 444 cells/mm^3 [280,643], 76% were on ART, 13% off-ART and 11% ART-naive. Among patients on ART, 74% had VL<400c/mL. In multivariable analysis, higher CD4 at transfer was associated with younger age, higher CD4 at ART initiation and lower VL at transfer ($p \leq 0.001$). Predictors of viral suppression include no AIDS diagnosis and later year of transfer ($p \leq 0.05$). Of 291 patients with resistance data, 82% had resistance to ≥1 drug class, 56% to ≥2 classes and 12% had triple-class resistance.

Conclusion: Three-quarters of adolescents were on stable ART at transfer, of whom 74% were virologically suppressed. The prevalence of triple-class resistance was relatively low at 12%.

Introduction

In 2015, there were an estimated 1.8 million children aged <15 years were living with HIV, with an estimated 48% coverage of antiretroviral therapy (ART) globally [1]. As treatment programmes continue to expand and mature, a growing proportion of perinatally HIV-infected children are surviving to adolescence and transitioning from paediatric to adult HIV care[2-4]. However, there are scarce data on their clinical status during and beyond the transition period. Such data will be critical in informing long-term clinical care of adolescents and young adults with perinatal HIV across the globe.

Such data are particularly needed in light of recent reports which highlighted HIV/AIDS as a top ten leading cause of deaths among adolescents globally [5] [6]. As these data are not disaggregate by mode of infection, it is unclear if this trend is partly driven by increased morbidity and mortality among perinatally-infected adolescent survivors who have been reported to have poor access to and retention in care, and poorer adherence on ART as compared to adults and children in both resource-rich and resource-poor settings [7-9]

High-income countries have some most mature perinatal HIV cohorts with early access to ART, and recent surveillance reports in the UK suggest that significantly lower proportions of adolescents in HIV care are on ART, and achieving viral suppression, as compared to adults [10], with similar trends observed in the US [11, 12]. However, these studies also combine adolescents of all modes of infection, raising questions of whether perinatally-infected adolescents are particularly at risk of viremia and disease progression, particularly around the time of transition to adult care, when they may require additional support[13].

In this study, we investigate the clinical profile of HIV-infected adolescents at transfer to adult care in the national paediatric cohort, which has almost complete coverage of all HIV-infected children diagnosed and followed in UK

and Ireland. We describe clinical, treatment status and resistance profiles at transfer to adult care by calendar year of transfer, and explore factors associated with improved immunological and virological status at transfer.

Methods

Our national cohort has been described elsewhere[14]. In brief, the National Study of HIV in Pregnancy and Childhood (NSHPC) collects reports of all infants born to HIV-infected women in the UK and Ireland and all children aged <16 years diagnosed with HIV-infection (regardless of country of birth or mode of infection). Subsequent follow-up information on HIV-infected children were reported from 2000 onwards is collected annually through the Collaborative HIV Paediatric Study (CHIPS). The follow up ceases when a patient transfers from paediatric to adult care. Both studies have NHS Research Ethics approval.

This analysis included data on HIV infected children followed in NSHPC/CHIPS from 2000 to November 2014, with clinical data dating back to 1996.

Statistical methods

Among patients reported to have transferred to adult care, the clinical and treatment status at last paediatric clinic visit prior to transfer (henceforth referred to as 'at transfer') were described overall and compared by country of birth (UK/Ireland or abroad/unknown) using chi-square and Mann-Whitney Wilcoxon tests. Being born abroad was considered a potential confounder as it is strongly associated with older age at first presentation for HIV care in the UK/Ireland and subsequently older age at start of ART.

The outcomes of interest were CD4 cell count and HIV-1 RNA viral load (VL) suppression <400 copies/mL among patients on ART at transfer, excluding ART-naive patients and those off-ART (defined as stopped all antiretroviral drugs for ≥14 days) as lack of treatment is known to strongly affect these outcomes[2]. Factors associated with

higher CD4 cell count and VL suppression on ART at transfer were assessed using linear and logistic regression, respectively. The VL<400 copies threshold was used due to varying detection levels over calendar years.

Potential predictors were: sex, ethnicity, born abroad; characteristics at ART start (age, CD4 percentage and initiation on combination ART (cART) (defined as ≥3 drugs across 2 classes or 3 Nucleoside Reverse Transcriptase Inhibitors (NRTIs) including abacavir); and characteristics at transfer to adult care (age, CDC stage, CD4 count, VL, current ART status, exposure to triple class ART, duration since starting ART and calendar year at time of transfer). Current ART status was defined as: (i) on initial cART regimen, (ii) subsequent ART regimen (defined as change of ≥2 drugs or addition of a new drug class) or (iii) mono/dual ART. Triple class ART exposure was defined as ever received NRTIs, Non-NRTIs (NNRTI) and Protease Inhibitor (PI) drugs. Calendar years at transfer were grouped in three year intervals and groups were collapsed in analyses where there were no differences in estimates. As ethnicity and born abroad are strongly correlated; only the latter was included in multivariable models. As some patients initiated ART in older ages and may have had insufficient follow-up time to observe immune recovery before transfer, sensitivity analyses of CD4 outcome was conducted restricted to patients with ≥2 years follow-up after ART start. Variables with $p<0.2$ in univariable analyses were included in multivariable models, and backwards selection (exit probability $p=0{\cdot}1$) identified those with the strongest association.

To explore resistance profiles, data on patients from CHIPS who had transferred to adult care were matched to the UK HIV Drug Resistance Database (UKHDRD) [15] , with resistance data up to end of December 2015 using an algorithm of unique patient identifiers. Resistance data (excluding tropism) on all tests conducted prior to transfer, or if unavailable, the closest test up to 1 year after transfer or while ≤18 years of age were analysed. Where multiple resistance tests were available per patient the cumulative resistance was described, including all current and archived resistance mutations. Among patients who were treatment experienced at time of latest test, resistance was defined as the detection of ≥1 major mutation using the 2015 International Antiviral Society guidelines[16]. For

patients who were reported with no previous treatment at time of test, resistance was defined as ≥1 mutation from the WHO 2009 surveillance list [17].

All children followed in CHIPS were included in the above analyses, irrespective of their mode of HIV infection, the large majority (>90%) were documented as perinatally-infected with small proportions of children with reported blood transfusion, other or unknown modes of infection, many of the latter were born abroad and unable to verify the source of transmission. To assess any potential effect of mode of infection, we conducted sensitivity analyses restricted to children with documented perinatal infection and those with 'Unknown' mode of infection and aged≤10 years at time of first HIV diagnosis in the UK/Ireland as a proxy for vertical transmission. All analyses were conducted using Stata 14, College Station, TX.

Results

Of 1,907 children enrolled in CHIPS from 1996-2014, 93% (n=1,777) were perinatally infected. Overall, 644 (34%) had transferred to adult care by November 2014, 109 (6%) had died in paediatric care, 103 (6%) had left the country, 106 (6%) were loss to follow-up, and 945 (50%) remained in paediatric follow-up. Among the 106 children lost to follow up, the median age at last visit in paediatric care was 12.5 years (IQR, 8.8-14.7), 11 patients were aged≥16 years.

Of the 644 transferred to adult care, 53% were female, 62% were born outside the UK/Ireland, and 75% were black African (Table 1). The large majority (91%) were documented as perinatally infected (91%), 21 (3.3%) through blood transfusion, 8 (1.2%) other and 31 (4.8%) with an unknown mode of infection. The majority (95%) of children with other and unknown mode of infection were born abroad.

The majority of children initiated ART in paediatric care, 26% on mono or dual NRTIs, 4% on triple NRTIs, 48% on NNRTI-based regimens (66% efavirenz and 34% nevirapine-based), and 22% PI-based regimens (most nelfinavir (55%)), reflecting the historical context of this cohort. A higher proportion of children born in the UK/Ireland presented for HIV care in earlier calendar years (before 2000), with lower median age at HIV diagnosis and at ART initiation, and had a higher proportion with triple class exposure at transfer as compared to those born abroad (all $p<0.001$).

Overall, the median age at transfer to adult care was 17.4 years [interquartile range (IQR) 16.5, 18.1], with a median duration of follow-up in paediatric care of 10.9 years [6.4, 15.6]. At transfer, the median CD4 was 444 [280, 643] cells/mm^3, with no difference by country of birth ($p=0.15$). Twenty-seven percent of patients had a previous AIDS diagnosis and 16% of patients were severely immunocompromised at transfer with CD4≤200cells/mm^3. Eleven percent of patients (n=69) were ART naïve at transfer, 26% were on their initial cART regimen, 44% were on subsequent ART regimens, 6% were on mono or dual ART (approximately half were on mono-PI regimens) and 13% were off-ART having previously taken it. The median duration since ART start was 7.8 years [4.3, 12.0] at transfer, with shorter duration among patients on their initial cART regimen (3.6 years [2.3-6.7], $p<0.0001$). Among those on cART at transfer, the majority were on efavirenz (32%), lopinavir (19%) and atazanavir (15%) based regimens.

Immunological and virological status by calendar year of transfer

Overall, 21 (3%) patients transferred to adult care in 2000-2002, 68 (11%) in 2003-2005, 126 (20%) in 2006-2008, 226 (35%) in 2009-2011 and 203 (32%) in 2012-2014. The proportion of patients with CD4≤350 cells/mm^3 at transfer declined over time, from 67% in 2000-2002 to 32% in 2012-2014, while the proportion with CD4>500 cells/mm^3 increased from 24% to 49% respectively (χ^2 $p=0.002$, Figure 1a). The overall proportion of patients (irrespective of ART status) with VL<400 copies at transfer was 58%, this proportion increased over time from 14% to 65% respectively (χ^2 $p<0.001$). When restricted to patients on ART at transfer, the proportion suppressed <400 c/mL increased from 15% in 2000-2002 to ≥75% from 2003 onwards and remained stable thereafter ($p<0.0.001$ Figure 1b).

When using the VL<50cps/mL threshold, the proportion of patients on ART with undetectable VL was 60% overall, with increasing suppression rates over time, peaking at 68% among those transferred in 2012-2014.

Patients ART naïve and off-ART at transfer

Sixty-nine (11%) patients were antiretroviral naïve at transfer: 67% were female, 70% were born abroad, and 81% were black African. Eighty-seven percent were documented as perinatally infected, 6% infected through blood products and 7% (n=5) with unknown mode of infection, of whom all were diagnosed aged 10-15 years. The median age at first presentation to HIV care was 10.6 [2.6-13.3] years and age at transfer to adult care was 17.3 [16.0-17.9] years. Seventy-two per cent were CDC stage N/A, 20% stage B and 7% (n=5) ever had a stage C event by time of transfer. Median CD4 at transfer was comparable to ART-experienced patients (465 cells/mm^3 [340, 560] vs 434 cells/mm^3 [267, 651] respectively, p=0.44). At transfer, median viral load was 3.8 $\log_{10}$ copies/mL [3.4, 4.3], and ten patients (15%) had VL<1000 copies/mL. Eighteen (26%) of the naive patients had a CD4<350 cells/mm^3 at transfer, of whom twelve transferred in earlier calendar years (2000-2008). The naïve patients transferred in most recent calendar years (2012-2014) all had CD4>350 cells/mm^3 at last paediatric visit.

Eighty-five patients (13%) were treatment experienced but were off-ART at transfer. The proportion of patients off-ART at transfer declined over time from 24% in 2000-2002 to 9% in 2012-2014 (χ^2 p<0.0001). The median duration off-ART was 16 months [6.2-29]. The median CD4 at transfer was 279 cells/mm^3 [186,443], one third of patients off-ART (27/85) were severely immunocompromised with CD4<200 cells/mm^3 at transfer.

Predictors of immunological and virological status among patients on ART at transfer

In multivariable analyses, predictors of improved immunological status at transfer among patients on ART were: higher CD4% and younger age at ART start, lower viral load at transfer, (all p≤0.001) (Table 2). Patients initiating ART aged ≥15 years had 235 cells/mm^3 (95%CI -333, -137) lower CD4 at transfer compared to patients initiating aged <5

years. In sensitivity analyses restricted to patients with ≥2 years follow-up after ART start, the age effect persisted but was less significant (p=0.044, data not shown).

Predictors of viral suppression <400 c/mL at transfer were CDC stage N/A/B (vs. C ,p=0.003), higher CD4 cell count at transfer (p<0.001) and being on an initial cART regimen (vs. subsequent regimen, p<0.04)). Patients who transferred in the earliest calendar years (2000-2002) had lower odds of viral suppression at transfer as compared to those transferred from 2003 onwards (p=0.021).

Resistance profile

A total of 841 drug resistance tests were available for analysis from 381 (59%) of the 644 transitioned patients. Ninety patients were ART naïve at time of their last resistance test, conducted either at first presentation to HIV care or prior to initiation of ART (median age 14 years at test [IQR 11.4, 15.6]). Among the naïve children, five (6%) had ≥1 surveillance drug resistance mutation detected (two with resistance to NRTI and NNRTI, three with NNRTI resistance), the age ranged from 11-18 years at time of test, none had prior ART reported, four patients were born abroad and presented for HIV care aged >10 years.

Among 291 patients who were ART-experienced at time of their last resistance test, median age at test was 15.9 years [13.7, 17.3]. Eighty-two per cent of patients had cumulative IAS major resistance mutations (all resistance tests ever reported) to one or more drug class while 18% had no resistance mutations detected. One-quarter (26%) of patients had resistance mutations to a single drug class (16.2% NNRTI, 9.3% NRTI and 0.7% PI). Forty four percent had resistance mutations to two drug classes, most common being NRTI+NNRTI resistance (38.1%), followed by NRTI+PI (4.1%) and NNRTI+PI (1.7%). Twelve percent of patients (n=34) had triple class resistance. Overall, the most frequently detected mutations were to the NRTI drug class (M184V, 44% and thymidine analogue mutations, 37%) and NNRTI drug class (K103N, 37%) with much lower prevalence of resistance mutations to the PI drug class (L90M, 6%) (Supplement Table S1).

No major integrase mutations were detected among five patients tested for integrase resistance.

Of the 34 patients with triple class resistance, 62% were male, 71% were born in the UK/Ireland and 47% initiated on mono/dual NRTIs, 35% on nelfinavir-based regimens and 18% on NNRTI-based regimens. At transfer, the median CD4 was 310 cells [170, 472], 85% were on ART, of whom 52% had VL<400 c/mL.

Sensitivity analyses

In sensitivity analyses (n=589), restricted to children with documented perinatal infection (n=584) and those with unknown mode of infection and aged≤10 years at first HIV diagnosis in the UK (n= 5), their characteristics were very similar to that of the overall cohort, with 10% of children ART naïve at transfer (n=59). The CD4 and VL distributions at transfer, associated factors and resistance profile were also comparable. Among the 280 patients with linked resistance data, 26% had resistance mutations to a single drug class, 45% to two drug classes and 12% (n=33) had triple class resistance (data not shown).

Discussion

To our knowledge, this is the first national cohort study reporting characteristics of perinatally HIV adolescents at the time of transfer to adult care. Our study benefits from high coverage of children attending paediatric HIV clinics across the UK and Ireland, the inclusion of all children diagnosed with HIV, irrespective of country of birth and low rates of loss to follow-up. One-third of our national cohort had already transitioned to adult care by the end of 2014, at a median age of 17 years; three-quarters of patients were on ART at transfer of whom 74% were virologically suppressed. However, when we include all patients, irrespective of their ART status, the proportion with VL<400c/mL reduces to 57%.

To date, only three comparable studies have reported clinical status of perinatally infected patients at transfer to adult care. These were small (each <120 patients) single clinic cohorts from high-income countries of Canada, Spain

and Argentina [18-20]. At the point of transfer, at a median age of 17-19 years, a comparable 42-56% of all patients, irrespective of ART status, had suppressed viral load <500 c/mL at transfer[18-20]. These studies did not report the proportion suppressed among those on ART at transfer, which was shown to have improved over calendar years in our cohort, which may be due to improved regimens available.

In terms of immune status at transfer, the largest comparable cohort is the Spanish cohort with 112 perinatally infected adolescents, with a mean CD4 of 627 cells/mm3 and 55% with CD4≥500 cells at transfer [18]. The CHIPS cohort had a lower median CD4 and a lower proportion of patients (42%) with CD4≥500 cells. This likely to be due to key differences in patient characteristics: over 85% of patients in the Madrid cohort were of European origin and were diagnosed at an earlier age (median 2 years as compared to 6.4 years in our cohort) and initiated ART earlier (median age 5.6 vs 9.6 years, respectively). Indeed the strongest predictor of high CD4 among patients on ART at transfer in our cohort was younger age and higher CD4 at initiation of ART. Numerous studies have shown that children initiating ART at older ages are less likely to or will take substantially longer to achieve immune reconstitution as compared to younger children[21, 22]. These findings supports updated WHO guidelines recommending universal ART in all HIV-infected children and adolescents, irrespective of age or CD4 [23].

In terms of drug resistance, a small number of children who were ART naïve at time of test had resistance mutations detected, most (n=4/5) were born abroad and some presented at older ages and are likely to be due to unreported ART exposure. Among ART experienced patients with matched resistance data, 82% had ≥1 class and 12% had triple class resistance. This proportion with triple class resistance was lower than other cohorts at transfer to adult care: 17.3% in Spain[18], 31.6% in Canada [19] 41% in Argentina and 18%-24% in US paediatric and adolescent HIV cohorts [24, 25]. However the large majority of children in those cohorts were exposed to mono or dual therapy prior to availability of combination ART, as compared to one-quarter of patients in the CHIPS cohort. Furthermore, our resistance data were only matched in half of the patients transferred and may represent an over-estimation of prevalence as those more at risk of developing resistance were more likely to have been tested. Nonetheless, this

raises important questions over risk of onward transmission of resistant viruses to partners and future offspring, particularly among patients with dual or triple-class resistance who are not suppressed on treatment, as an increasing proportion of this adolescent population are sexually active[26]. Further monitoring of resistance through adulthood is needed.

Interestingly, in our study 69 patients (11% of the cohort) were antiretroviral naïve at transfer to adult care, with a similar proportion observed in the sensitivity analysis restricted to children with perinatal infection (10% naïve). This is markedly higher than the proportions reported in other European paediatric HIV cohorts (1-3%)[2, 18]. Approximately one-third of the naïve adolescents had CD4<350 cells/mm^3 at transfer, the majority of whom were transferred in earlier calendar years prior to PENTA 2009 revised guidelines recommending immediate ART in all children aged>5 years with CD4<350 cells/mm^3[27]. The remainder were asymptomatic (72% CDC stage N/A) and 15% had low viral load (<1000 c/mL) despite never having received treatment. Some of these adolescents may be elite controllers, a unique and rare population of interest to the HIV cure agenda [28] and is an area of ongoing study.

There are some important limitations to this study. First, analyses were based on the last paediatric care visit and findings may not accurately reflect clinical status at entry to adult care, especially if there is a gap between paediatric and adult care. Second, there were no data on broader clinical status at transfer, related to comorbidities, neurological development or mental health. Nor are there data on the socio-economic or orphan status to assess if these factors affect the clinical status at or after transition. Such data are being collected as part of the ongoing AALPHI study, an in-depth quantitative and qualitative study of a sub-group of adolescents with perinatal HIV followed in CHIPS (n=~300) [29] which will explore the effect of these factors on various clinical outcomes.

Lastly, data on clinical outcomes after transfer to adult care are not yet available, although we are planning follow-up into adulthood of perinatally infected patients in the UK through the “CHIPS+” cohort and linkages with existing

adult cohorts and the national HIV surveillance to assess long-term clinical outcomes. This process will also allow us to assess the survival and HIV care status of patients lost to follow up in paediatric care.

In summary, the majority of perinatally-infected adolescents in the CHIPS national cohort were on stable ART at transfer to adult care with relatively high CD4 counts and good virological disease control; although 12% have triple-class resistance, this is one of the lowest prevalence reported for a perinatally infected adolescent population a high-income country setting. However one-quarter of patients were naïve or off-ART at transfer, the latter were more likely to be severely immunosuppressed at transfer and at risk of disease progression and will require particularly careful management. Previous study in the UK highlighted the increased rate of mortality and hospitalisation among a group of perinatally-infected young people in adult care as compared to younger children. [30] This along with worrying trends of poor retention among HIV infected youth in adult care[12] highlight the importance of continued follow-up of this unique population through adulthood, to assess long-term morbidity, mortality and retention. Such data will be critical in informing future care in the UK/Ireland and across resource-limited settings where the first waves of adolescent survivors of perinatal HIV are emerging[4].

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Table 1. Characteristics at last paediatric care visit of patients transferred to adult care

Characteristic	Total (N=644)	Born in UK/Ireland (N=245)	Born abroad* (N=399)	P
	n (%) or median [IQR]			
Female sex	343 (53)	131 (53)	212 (53)	0.93
Ethnicity				
Black African	480 (75)	140 (57)	340 (85)	<0.0001
White	86 (13)	64 (26)	22 (6)	
Other	78 (12)	41 (17)	37(9)	
Age at first presentation in UK (years)	6.4 [1.8, 11.1]	1.4 [0.1,4.3]	9.3 [5.7,12.3]	<0.0001
Calendar year of first presentation in UK				
<2000	364 (57)	210 (86)	154 (39)	<0.0001
≥2000	280 (43)	35 (14)	245 (61)	
Ever received ART	575 (89)	224 (91)	351 (88)	
Characteristics at ART start (n=575)				
Age (years)	9.6 [5.4,12.8]	6.5 [3.0,10.7]	10.7 [7.7,13.8]	<0.0001
<5 years	116 (24)	81 (45)	35 (11)	
CDC C stage	127 (22)	58 (26)	69 (20)	0.079
CD4% for age<5 yrs (n=91, 71, 20)	15 [8,24]	15 [8,24]	15 [8,22]	0.80
CD4 cell count for age ≥5 yrs (n=365, 116, 249)	210 [91,350]	205 [100,386]	214 [80,330]	0.51
Viral load (log_{10}) (n=364, 133, 231)	4.9 [4.3,5.3]	5.0 [4.4,5.5]	4.8 [4.3,5.2]	0.021
Initial ART regimen				
Mono/dual NRTI	149 (26)	85 (36)	64 (18)	<0.0001
Triple NRTI	22 (4)	8 (4)	14 (4)	
NNRTI+NRTI	276 (48)	72 (32)	204 (58)	
PI+NRTI	128 (22)	59 (26)	69 (20)	
Characteristics at transfer to adult care				
Age (years)	17.4 [16.5,18.1]	17.4 [16.4,18.3]	17.3 [16.5,18.1]	0.62
CDC C stage	171 (27)	75 (31)	96 (24)	0.68
CD4 cell count, cells/mm^3	444 [280,643]	412 [250,640]	456 [289,648]	0.15
≤200	101 (16)	50 (20)	51 (13)	
201-350	122 (21)	47 (19)	86 (22)	
351-500	142 (22)	56 (23)	86 (21)	
>500	268 (42)	92 (38)	176 (44)	
Viral load (log_{10}) (n=643)	2.0 [1.7,3.8]	2.0 [1.7,4.0]	2.0 [1.7,3.7]	0.19
VL <400 copies if on ART at transfer (n=481)	357/481 (74)	131/178 (74)	226/303 (75)	
ART status				<0.0001
Naïve	69 (11)	21 (9)	48 (12)	
On initial cART	167 (26)	43 (18)	124 (31)	
On subsequent cART	284 (44)	114 (47)	170 (43)	
On mono/dual ART	39 (6)	23 (9)	16 (4)	
Off-ART after previous exposure	85 (13)	44 (18)	41 (10)	
Duration since start of ART (years) (n=575)	7.8 [4.3,12.0]	10.8 [6.9,14.5]	6.2 [3.4,9.8]	<0.0001
Triple class exposure (n=575)	312 (54)	143 (64)	169 (48)	<0.0001
Calendar year of transfer				0.52
2000-2002	21 (3)	5 (2)	16 (4)	
2003-2005	68 (11)	22 (9)	46 (12)	
2006-2008	126 (20)	49 (20)	77 (19)	
2009-2011	226 (35)	91 (37)	135 (34)	
2012-2014	203 (32)	78 (32)	125 (31)	

Notes: * Includes 11 patients with unknown country of birth.

Table 2. Factors associated with immunological and virological status at transfer to adult care in ART-exposed patients

	CD4 cell count increase				VL<400 copies/mL			
	Univariable Coef (95% CI)	P	Multivariable Coef. (95% CI)	P	OR (95% CI)	P	aOR (95% CI)	P
Constant	505 (479, 532)		774 (682,867)					
Sex - female vs male	-23.3 (-76, 29)	0.39			0.87 (0.6, 1.2)	0.41		
Born abroad vs UK/Ireland	25.4 (-80, 29)	0.36	33 (-23, 89)	0.25	1.25 (0.9, 1.8)	0.2	0.9 (0.5, 1.5)	0.60
Ethnicity: Black African/Other vs Caucasian	-76 (-153, 1.4)	**0.054**			0.85 (0.5, 1.4)	0.522		
Characteristics at ART start								
Age: <5 years	1	**0.033**	1	**<0.001**	1	**0.04**	1	0.62
5 - 9 years	-46 (-118, 27)		-38 (-112,36)		0.6 (0.4,0.9)		0.8 (0.5,2.3)	
10 – 14 years	-36 (-106, 33)		-79 (-156,-2)		0.9 (0.6, 1.4)		1.1 (0.5, 2.3)	
≥15 years	-178 (-274, -83)		-268 (-371, -165)		1.2 (0.6, 2.4)		1.6 (0.6, 4.8)	
CD4 percentage, per 1% increase	7 (4, 10)	**<0.001**	5.1 (2.4, 7.8)	**<0.001**	1.03 (1.0, 1.05)	**0.04**	0.98 (0.94, 1.01)	0.211
Initiation on non cART vs cART	-5.8 (-68, 56)	0.86			0.7 (0.4,1.0)	**0.079**	0.8 (0.4,1.5)	0.43
Characteristics at transfer								
Age, per year increase	-9 (-27, 9)	0.307			0.92 (0.8, 1.0)	0.19	1.09 (0.9, 1.3)	0.87
CDC stage: C vs N/A/B	19.2 (-38, 77)	0.514			0.7 (0.5, 1.0)	**0.066**	0.43 (0.2, 0.75)	**0.003**
CD4 per 100c/mm^3 increase	-		-		1.94 (1.7, 2.2)	**<0.001**	2.1 (1.8, 2.4)	**<0.001**
VL per log increase	-146 (-166, -124)	**<0.001**	-139 (-162, -115)	**<0.001**	-		-	
ART status: Initial cART	76 (18,132)	**0.033**	67 (7,127)	0.09	2.8 (1.7, 4.5)	**<0.001**	2.2 (1.2, 4.1)	**0.04**
Subsequent cART	1		1		1		1	
Mono/dual ART	35 (-64,135)		14 (-77,104)		0.9 (0.4, 1.8)		0.86 (0.3, 2.2)	
Exposure to triple class ART	-77 (-130, -24)	**0.004**	-5 (-74,64)	0.90	0.6 (0.4, 0.9)	**0.006**	0.6 (0.3, 1.3)	0.20
Duration since start ART, per year increase	6.7 (1.1, 12)	**0.019**	11 (-2, 24)	0.104	0.98 (0.94, 1.0)	**0.176**	0.97 (0.9, 1.03)	0.35
Calendar year: 2000-2002	-179 (-348, -9)	**0.019**	-29 (-198,139)	0.94	0.06 (0.01,0.3)	**0.002**	0.06 (0.01,0.5)	**0.021**
2003-2008	1		1		1		1	
2009-2014	40 (-20, 101)		-1 (-58,57)		0.9 (0.6,1.2)		0.6 (0.3, 1.2)	

Notes: OR; odds ratio, aOR; adjusted odds ratio. P values <0.2 are shown in bold. Shaded variables were included in the final multivariable models.

Figure 1(a) CD4 distribution at transfer to adult care by calendar year of transfer[1] (n=644) (top); (b) Viral load at transfer among patients on ART at transfer to adult care (n=481) (bottom)

Notes: 1 includes all patients irrespective of ART status at transfer (includes ART naïve (n=69) and those off-ART (n=85))

Figure 1a(.tif and .eps files only)

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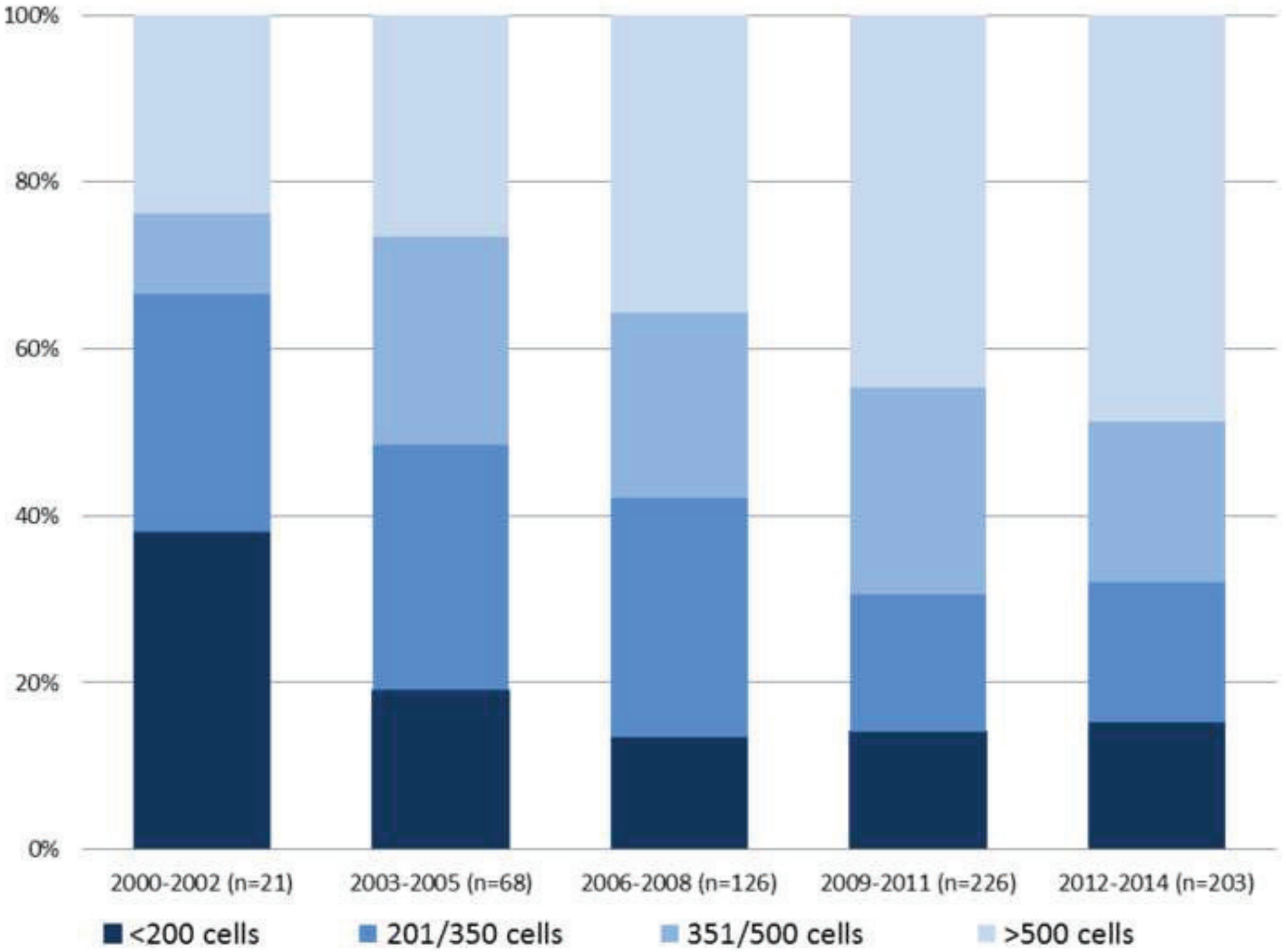

Figure 1b(.tif and .eps files only)

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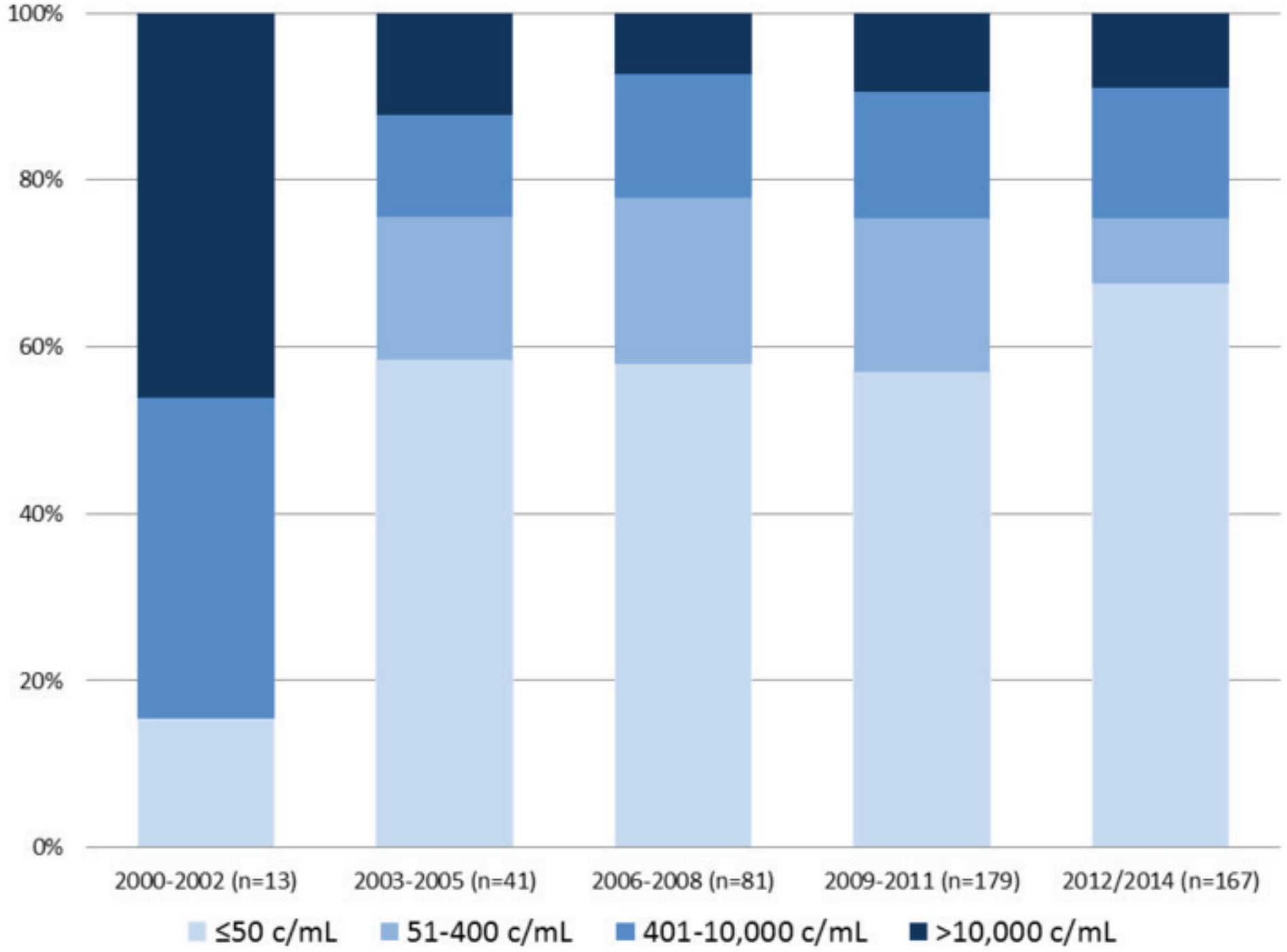

Supplementary Table

Table S1: Most common resistance mutations within each drug class among ART experienced patients (n=291).

Drug class	Mutation	n	Frequency
NRTI	M184V	128	44
NRTI	D67N	71	24.4
NRTI	M41L	60	20.6
NRTI	T215Y	48	16.5
NRTI	K70R	43	14.8
NNRTI	K103N	107	36.8
NNRTI	Y181C	55	18.9
NNRTI	G190A	37	12.7
NNRTI	H221Y	32	11
NNRTI	V106M	28	9.6
PI	L90M	17	5.8
PI	M46I	17	5.8
PI	D30N	14	4.8
PI	N88S	10	3.4
PI	Q58E	9	3.1

Notes: IAS 2015 major mutation, based on cumulative resistance (archived and current mutations).