AIDS, Publish Ahead of Print

DOI: 10.1097/QAD.0000000000003825

Rapid antiretroviral therapy in primary HIV-1 infection enhances immune recovery

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Funding statement: The HEATHER study was funded by an MRC senior fellowship grant to Prof John Frater and Imperial College NIHR BRC

Abstract

Objective. We present findings from a large cohort of individuals treated during Primary HIV Infection (PHI) and examine the impact of time from HIV-1 acquisition to antiretroviral therapy (ART) initiation on clinical outcomes. We also examine the temporal changes in the demographics of individuals presenting with PHI to inform HIV-1 prevention strategies.

Methods: Individuals who fulfilled the criteria of PHI and started ART within three months of confirmed HIV-1 diagnosis were enrolled between 2009 and 2020. Baseline demographics of those diagnosed between 2009-2015 (before pre-exposure prophylaxis (PrEP) and universal ART availability) and 2015-2020 (post-PrEP and universal ART availability) were compared. We examined the factors associated with immune recovery and time to viral suppression.

Results: 204 individuals enrolled, 144 from 2009-2015 and 90 from 2015-2020; median follow-up was 33 months. At PHI, the median age was 33 years; 4% were women, 39% were UK-born, and 84% were MSM. The proportion of UK-born individuals was 47% in 2009-2015, compared with 29% in

2015-2020. There was an association between earlier ART initiation after PHI diagnosis and increased immune recovery; each day that ART was delayed was associated with a lower likelihood of achieving a CD4>900 cells/mm^3 [HR 0.99 (95%CI 0.98, 0.99), P=0.02) and CD4/CD8>1.0 (HR 0.98 (95%CI 0.97, 0.99).

Conclusion: Early initiation of ART at PHI diagnosis is associated with enhanced immune recovery, providing further evidence to support immediate ART in the context of PHI. Non-UK-born MSM accounts for an increasing proportion of those with primary infection; UK HIV-1 prevention strategies should better target this group.

Key Words: primary HIV-1 infection, viral suppression, immune recovery, immediate ART, rapid ART

Introduction

Antiretroviral therapy (ART) rapidly controls HIV-1 replication and enables immune recovery. Following the START and TEMPRANO trials, international HIV-1 treatment guidelines recommend ART initiation irrespective of CD4 T-cell count[1, 2]. These trials were not sufficiently powered to determine survival by stage of HIV-1 disease at ART start; however, evidence supports enhanced immune recovery if ART is started close to HIV-1 acquisition[3, 4].

Individuals presenting with primary HIV infection (PHI) often have very high levels of HIV-1 viraemia and transiently low CD4 T-cell counts, which recover rapidly with ART initiation[4, 5]. Persistent immune dysfunction with an inverted CD4/CD8 ratio in chronic HIV-1 infection confers an increased risk of development of malignancy and non-AIDS mortality and morbidity[6-8]. ART initiated in PHI compared to chronic HIV-1 infection markedly increases the likelihood of normalisation of the CD4 T-cell count and the CD4/CD8 ratio compared with later initiation of therapy, irrespective of baseline CD4 T-cell count[3, 4].

At a public health level, there has been a dramatic reduction in HIV-1 incidence in the UK with the introduction of potent, well-tolerated ART irrespective of CD4 T-cell count (universal ART), which prevents onward viral transmission[9]. The addition of pre-exposure prophylaxis (PrEP) into the community of men at high risk of HIV-1 acquisition has further contributed to reduced HIV-1 incidence, which was first observed in London sexual health clinics in early 2015 [10-12]. Those who acquire HIV-1 despite a lower community HIV-1 viral load and increased availability of PrEP represent an important at-risk group to target HIV-1 prevention strategies.

The time taken from ART initiation to achieving viral suppression is related to the class of antiretroviral agents used and the level of pre-ART viraemia[13],[14]. More recently, initiation of rapid or immediate ART (often within seven days of HIV-1 diagnosis) is recommended and has been shown to reduce time to viral suppression and reduce loss to follow-up in low- and middle-income settings[15,

[16]. However, the benefits of immediate ART in the context of primary HIV-1 infection in a high-resource setting are less clear. Long-term non-AIDS morbidity associated with HIV has been shown to reflect persistent inflammation and immune dysfunction. For this analysis, we defined the normalisation of immune function as CD4 T-cell count >900 cells/mm^3 and CD8 T-cell count > 1,000 cells/mm^3. This CD4 T-cell count threshold was chosen following work by Le et al., who sought to define normal CD4 T-cell counts based on reported values in the literature for people without HIV of European Americans or African American ancestry [4].

Long-term clinical outcomes for individuals treated during PHI with highly potent modern ART agents, including integrase inhibitors, are less well described. To address this, we present an analysis of the HEATHER (HIV-1 Reservoir Targeting with Early Antiretroviral Therapy) study, a large multi-centre observational cohort of individuals identified with PHI, all of whom initiated modern ART regimens within three months of PHI diagnosis. We also evaluated temporal shifts in the demographics of individuals identified with PHI in the UK participating centres choosing to enrol into an observational study over time in the context of universal ART and PrEP rollout before and after 2015.

Methods

Study Design

The HEATHER study was an observational cohort of individuals with documented PHI who commenced ART within three months of HIV-1 diagnosis. HEATHER recruited across four clinical sites in London, UK: Imperial College NHS Trust, Guys and St Thomas's NHS Trust, The Royal Free Hospital NHS Trust and 56 Dean St, Chelsea and Westminster Hospital in London. All participants gave informed consent before screening. The West Midlands — South Birmingham Research Ethics Committee approved recruitment to the HEATHER cohort (reference 14/WM/1104).

Definition of Primary HIV Infection

PHI was confirmed according to one of the following criteria: (a) HIV-1 positive antibody test within six months of an HIV-1 negative antibody test, (b) evidence of viral protein or nucleic acid (p24, RNA or DNA) in the absence of detectable HIV-1 antibodies or (c) a recent infection test algorithm (RITA) assay result consistent with recent infection[17]. RITA testing uses the AxSYM assay HIV 1/2 gO (Abbott, United States) modified to determine antibody avidity. This assay indirectly measures the HIV antibody–antigen bond strength or 'avidity', which is typically weaker during the initial stages of the infection[17]. It has a recent HIV window of approximately 142 (95% CI, 101 to 183) days when employing a threshold avidity index of 80%[18]]. All individuals with confirmed PHI commenced three or four-drug ART within a maximum of three months from the date of HIV-1 diagnosis. Individuals with active hepatitis B or C, defined by the presence of hepatitis B surface antigen or DNA detected or by hepatitis C RNA or antigen detected, were not eligible. Lymphocyte subsets, HIV-1 viral load quantification and HIV-1 genotyping for clade and drug resistance were carried out by NHS-accredited laboratories.

Statistical Analysis

Individuals eligible for this analysis included those with at least two HIV-1 viral load measurements, one within at least 150 days of starting ART, and at least six months of follow-up data. Demographic and clinical characteristics were described using frequencies, percentages, medians, and interquartile ranges (IQRs). Non-parametric tests were used to compare the gender, age at diagnosis, ethnicity, country of HIV-1 acquisition, risk group, viral clade and viral drug resistance mutations of individuals diagnosed with PHI in the earlier pre-2015 and the later 2015-2020 periods. The periods pre- and post-2015 to characterise the changing demographics of PHI between before and after ART guidelines shifted to universal treatment in 2015. In addition, a decrease in new HIV diagnoses potentially related to more widespread PrEP use was described in London in early 2015[12]. Immune recovery is defined as the proportion of individuals achieving CD4/CD8 >1.0 and/or the proportion achieving CD4 T-cell counts >900 cells/mm^3.

Cox Proportional Hazards models examined the factors associated with the time to CD4/CD8 ratio >1.0 and time to CD4 T-cell count >900 cells/mm^3. Data were censored at the time of the last viral load measurement. HIV-1 viral suppression was defined as <200 copies per ml (cpm)[19]. The factors associated with time to undetectable HIV-1 viral <200 copies HIV-1 RNA per ml (VL <200 cpm) were evaluated using time to and Cox regression models. All multivariable modes were adjusted for age and gender; other variables were included if P<0.25 in respective univariable models. CD4/CD8 ratio was not included in the adjusted models due to the potential for collinearity with CD4 T-cell count. Statistical analysis was performed using IBM SPSS statistics V24.0.0 and GraphPad Prism.

Results

Baseline Characteristics of Study Participants

Three hundred fifty-seven individuals were enrolled into the HEATHER cohort, supplemental table 1, http://links.lww.com/QAD/D96, of whom 204 were eligible for inclusion in this analysis. The clinical characteristics of those included in this analysis are shown in Table 1. The one hundred and fifty-three participants not included in the longitudinal dataset presented were excluded because they did not meet the inclusion criteria of having at least two HIV viral load measurements, one within at least 150 days of starting ART, and at least six months of follow-up data, supplemental figure 1, http://links.lww.com/QAD/D95. Almost all participants were male (95.6%), and the median (IQR) duration of follow-up was 33 (18, 48) months. The median (IQR) age at primary HIV-1 infection was 33 (28,40) years, while the main risk factor for HIV-1 infection was sex between men (84%). The majority of individuals (76%) were of white ethnicity. UK-born individuals accounted for 39% of the HEATHER cohort, with Brazil (5.9%) and Poland (3.9%) accounting for the highest proportion of individuals born outside the UK.

Early PHI (consistent with Fiebig stage I or II) based on the presence of HIV-1 RNA or p24 antigen positivity without HIV-1 antibodies was diagnosed in 61 individuals (30%), while the remainder were defined as primary infection due to either having a positive HIV-1 antibody test within six months of a negative test (41%) or an incident RITA test (27%). The median baseline pre-ART HIV-1 RNA

measurement was 5.3 (4.4, 6.3) $\log_{10}$ cpm, the median baseline CD4/CD8 ratio was 0.35 (0.54, 0.79), and the median nadir CD4 T-cell count was 507 (405, 656) cells/mm^3.

All individuals commenced ART within three months of confirmed PHI diagnosis: median (IQR) time 23 (18, 38) days. Two hundred and two individuals (99%) achieved an HIV-1 viral load of less than 200 cpm; of these, one hundred and ninety-eight (97%) achieved an HIV-1 load of less than 50 copies per ml during a median (IQR) follow-up period of 33 (18, 48) months. The median time to HIV-1 viral load <200 copies per ml was 115 (62, 200) days and for HIV-1 viral load <50 copies per ml was 162 (94, 258) days. Forty-eight individuals initiated an ART regimen that included an integrase inhibitor (24%), while twelve (6%) were started on a four-drug regimen that included a boosted protease inhibitor in combination with an integrase inhibitor. Of the 162 individuals with baseline resistance data available, twenty-nine (18%) had >/=1 mutation. Resistance-associated mutations in protease (M46I/L, V82A, L90M & L33F) were detected in nine individuals (6%), NNRTI resistance-associated mutation (A98G, E138A, F227L, G190A, H221HY, K101E, V106AIV, V108IV, V179EIT) were present in twenty-eight individuals (17%), while thymidine analogue mutations (TAMs; A62V, D67G, K70R, T215DS, T69TN) were noted in six (4%), see supplemental table 2, http://links.lww.com/QAD/D95. No resistance data for integrase-associated mutations was available. Clade B virus was the predominant clade (69%) and was more prevalent in individuals of white ethnicity (74%) compared to those from other ethnic groups (52%), (P=0.02); similar frequencies of clade B were observed in UK-born and those born outside the UK, 69% for both. There was no difference in time to HIV-1 viral load <200 cpm in those with baseline transmitted drug resistance (TDR) compared to those without TDR (P=0.14). Similarly, there was no significant difference in the frequency of TDR between UK and non-UK born participants, (P=0.86), B clade compared to non-B clade virus (P=0.38), those diagnosed during Fiebig stage compared to later I/II (P=0.63), MSM compared to non-MSM (P=0.37) or by ethnicity (P=0.45) or year of HIV-1 diagnosis (P=0.30).

Clinical characteristics of PHI in the periods pre-2015 and 2015-2020

To better explore the demographics of those at risk of PHI in London during the study period, we compared the characteristics of those presenting with PHI in the pre-2015 (n=114) and 2015-2020 (n=90) periods. As most participants were men, we saw no significant difference by sex (P=0.99) or age (P=0.16) between the two periods. MSM was the largest risk group in both periods, but this likely reflects the diagnosis of PHI, which results from the frequent HIV-1 testing strategies acceptable within this group of individuals. The proportion of UK-born MSM with PHI decreased significantly from 47% pre-2015 to 29% in 2015-2020 (P=0.01). In the pre-2015 period, individuals from Brazil (8%) and Poland (7%) accounted for the largest proportion of non-UK MSM. In contrast, in 2015-2020, individuals from France (4%) and Australia (4%) were the most common countries of origin other than the UK. A higher proportion of individuals were identified with acute infection (Fiebig I or II) in the later period, 2015-2020 (37%), compared to pre-2015 (25%). No significant differences were noted for baseline HIV-1 viral load (P=0.34) or nadir CD4 T-cell count (P=0.32); however, mean maximum CD8 counts were lower in the later period (P=0.02), which may be consistent with more acute infection. Baseline rates of genotypic resistance were similar between groups (P=0.99). The median time to ART initiation was significantly shorter (P<0.001) in the later 2015-2020 period [16 days (IQR 9, 27)] compared to pre-2015 [28 days (17, 44)], which reflects UK guidelines change.

While the proportion achieving a CD4/CD8 ratio greater than 1.0 was similar between groups (P=0.89), a smaller proportion achieved a CD4 T-cell count >900 cell/mm^3 in the 2015-2020 group (41%) compared to the pre-2015 group (51%) during the follow-up period. However, the survival analysis did not demonstrate any difference in time to CD4 T-cell count >900 cells/mm^3 between groups (Log Rank test P=0.76), suggesting any overall difference is due to the shorter duration of follow-up in the latter group. In keeping with changing guidelines, integrase inhibitor use was more common in the later period, 2015-2020 (43%) compared to pre-2015 (8%), as was using a four-drug regimen, which included an integrase inhibitor. However, the median time to HIV-1 VL <200cpm was not significantly different (P=0.34) in the pre-2015 period [126 days (IQR 71, 209)] compared to 2015-2020 [111 days (IQR 41, 181)].

Immune recovery

During the study follow-up period (median 33 months), the proportion of individuals achieving CD4/CD8 >1.0 was 64%, while the proportion achieving a CD4 T-cell count >900 cells/mm^3 was 47%. Firstly, we examined the factors associated with time to CD4 T-cell count >900 cells/mm^3 using Cox proportional hazard models. In the unadjusted model, those of white ethnicity [HR 1.80 (95%CI 1.04, 3.13), P=0.04] and with clade B virus [HR 1.71 (1.03, 2.85), P=0.038] had a shorter time to CD4 T-cell count >900mm^3. Lower baseline CD4 T-cell counts (P<0.001), lower CD4/CD8 ratio (P=0.01), and lower CD8 T-cell count (P<0.01) were associated with a longer time to CD4 T-cell count >900 cells/mm^3, see Table 2. For each day after PHI diagnosis that ART was delayed, there was a lower likelihood of achieving a CD4 T-cell count >900 cells/mm^3 [HR 0.99 (95% CI 0.98, 0.99), P=0.02). Unadjusted variables with a significance level of P <0.25 were included in the adjusted model, as were age and gender. After adjusting, the variables white ethnicity (P<0.01)), Non-MSM transmission (P<0.001), higher CD4 T-cell counts (P<0.001) and the clinically modifiable variable of a shorter time to ART initiation [HR 0.98 (95%CI 0.97, 0.99), P<0.01], were all associated with faster time to CD4 T-cell count >900 cells/mm^3 in this model.

When immune recovery was defined as time to CD4/CD8 >1.0, the factors significantly associated with a shorter time to immune recovery in both the unadjusted and adjusted model included a shorter time between HIV-1 diagnosis to ART initiation (HR 0.98 (95%CI 0.97, 0.99), P<0.01), lower baseline CD8 count (HR 2.21 (95%CI 1.54, 3.17), P<0.001) and higher CD4 T-cell count (P=0.02), Table 3. In addition, there was a trend towards a shorter time for CD4/CD8 recovery with integrase inhibitor use (P=0.08). Those diagnosed between 2009 and 2015 were less likely to achieve CD4/CD8 >1.0 compared to those diagnosed in 2015-2020; however, this was not significant in the multivariable model.

Factors associated with time to viral load suppression

201/204 individuals (99%) achieved an HIV-1 viral load <200 copies per ml during follow-up, and the factors associated with time to viral load <200 copies/ml are shown in Table 4. The median time from ART start to VL <200 copies was 115 (62, 200) days. Unadjusted Cox regression analysis demonstrated that integrase inhibitor use as part of the initial ART regimen was associated with a shorter time to viral load <200 copies/ml [HR 0.69 (95%CI 0.5, 0.96), P=0.03], figure 1, but this was

not observed for four-drug ART as initial therapy [HR 1.28 (95%CI 0.71, 2.30) P=0.41] which included an integrase inhibitor. This may be a consequence of the small number of individuals initiated on four-drug initial ART. In addition, male gender was associated with a longer time to viral suppression in the unadjusted analysis [HR 2.12 (95%CI 1.08, 4.17), P=0.03]. Age, ethnicity, transmission risk, year of HIV-1 infection, HIV-1 clade, HIV-1 viral load, nadir CD4 T-cell count, maximum CD8 T-cell count and time to ART start were not associated with time to viral load suppression. After adjusting for age, baseline HIV-1 viral load and CD8 count, male gender remained significantly associated with longer time to viral load <200 copies/ml (HR 2.09 (95%CI 1.04, 4.18), P=0.04) while there was a trend towards shorter time to viral load <200 copies/ml with integrase inhibitor use [HR 0.70 (95%CI 0.52, 1.01), P=0.06). Longer time to viral suppression was noted in those with maximum CD8 counts less than 1000 cells/mm^3 compared to those with maximum CD8 counts greater than or equal to 1000 cells/mm^3 [HR 1.25 (95%CI 0.93, 1.67), P=0.13].

Discussion

We describe the clinical outcomes of the largest UK prospectively recruited cohort of individuals identified with PHI initiated on rapid ART to date. Immune dysfunction, as measured by CD4/CD8 <1.0, was evident in most individuals at the time of diagnosis of PHI. We demonstrate that rapid initiation of ART (within a maximum of 3 months after confirmed HIV diagnosis) in this cohort of treated PHI is associated with significant improvement in immune recovery and that the sooner ART is started after PHI diagnosis, the greater the chance of immune recovery; each day that ART is delayed in PHI confers a reduced chance of normalisation of markers of immune function. This is a key message to support rapid or immediate ART start amongst all new HIV-1 diagnoses, but especially in PHI[20]. These findings add to previously published results by our group and others, which demonstrated that ART started in PHI compared to chronic infection conferred greater immune recovery; this current work also demonstrates a benefit for earlier ART even within the context of PHI where all individuals had started within three months of HIV-1 diagnosis[3, 21]. The proportion of those achieving CD4 T-cell count >900 cells/mm^3 was lower in our group than reported by Le et al. and likely reflects the shorter duration of follow-up in the HEATHER cohort (33 versus 48 months)[4]. White ethnicity was also a factor in achieving immune recovery; this has been explored in other cohorts. However, the consensus is that any differences related to ethnicity are unlikely determinants of immunological or virological response after therapy initiation but reflect socioeconomic, environmental, and cultural factors[22-24].

In the HEATHER cohort, we observed very low rates of virological failure. However, we observed a higher frequency of TDR in the HEATHER cohort relative to other UK cohorts, which have estimated the frequency of TDR at between 8% and 19.4%[25, 26]. While the frequency of PI and TAM mutations in the HEATHER cohort was similar to other cohorts, NNRTI mutations were over-represented and accounted for the overall higher frequency of TDR observed. This may, in part, reflect differences in the definition of significant resistance between cohorts, but more importantly, it may relate to sampling very early in infection with less time for reversion of resistance mutations in those with PHI. This possibility of archived NNRTI resistance may become relevant for those initiated on injectable cabotegravir and rilpivirine. Work by the CASCADE group has reported a reduction in TDR in seroconverters in more recent years[25]. We did not see such a temporal reduction that may relate to

our cohort's more contemporary nature. However, the CASCADE group also observed that sampling during acute infection was associated with higher odds of resistance; this is more consistent with the HEATHER cohort, which had a large proportion of individuals with Fiebig stage I or II infections. Hence, same-day ART start during PHI diagnosis, avoiding NNRTI agents, can be safely recommended. In addition, the HEATHER study focused on PHI in MSM who frequently tested for HIV-1; most were recruited before PrEP was freely available on the NHS, so we cannot comment on TDR of those who seroconvert in the PrEP era.

The time to achieving an undetectable HIV viral load was based on a cut-off of < 200 copies RNA/mL for three reasons. Firstly, as a cohort study, there was wide variability in the frequency of HIV viral load samples, approximately every 4-5 months, based on the mean (SD) number of viral load tests per person being 7.8 (+/-3.7) over a median duration of follow up of 33 months. Therefore, a 200 copies/mL cut-off was considered more sensitive to qualify an undetectable viral load. Secondly, given the relatively low frequency of HIV viral load monitoring, a cut-off of 200 copies/mL was considered more likely to effectively exclude viral load blips that are not deemed clinically relevant. Thirdly, many studies have validated HIV VL <200 copies/mL as a valid clinical outcome marker; for example, the definition of undetectable in the PARTNER studies, in which the paradigm of U=U was defined, was plasma HIV-1 RNA <200 copies per mL at the most recent visit (within the past year)[19].

Consistent with published randomised control trials, using an integrase inhibitor in the initial ART regimen was associated with faster time to viral suppression in people with PHI. However, in agreement with a recent meta-analysis, no additional benefit was observed with four drug regimens[13, 27, 28]. In the era of integrase inhibitors, some guidelines still recommend using a boosted protease inhibitor in PHI if baseline genotypic resistance data is unavailable[29]. However, this may not be necessary with newer second-generation integrase inhibitors with a higher barrier to resistance[30]. The high rate of INSTI use in our later cohort was also associated with excellent virological outcomes. While achieving an undetectable viral load as quickly as possible is critical for preventing onward transmission, the time taken to achieve suppression of plasma viraemia was not associated with the speed and completeness of CD4 T-cell count recovery in this study. This may reflect the broadly rapid and relatively narrow range of time to an undetectable viral load in this cohort. While integrase resistance data was not routinely assessed in our cohort, as per clinical guidelines, national data suggests baseline integrase inhibitor resistance is rare[31, 32]. It will be important to monitor rates of transmitted integrase resistance with widespread and longer use of this ART class in ART naïve individuals, especially in the context of two drug therapies.

The observational nature of this cohort is a limitation of this analysis, particularly as viral load testing was not done uniformly at a predefined time point from PHI diagnosis. To address this, we excluded those without a first viral load measured within 150 days after starting ART or those without at least two viral load measurements. Furthermore, we used an accepted but less conservative definition of viral suppression. We acknowledge that this cohort may be confounded by selection bias as the presented cohort is a selected group, all of whom wanted to start ART at PHI diagnosis even when this was not routinely recommended.

Whilst immediate or rapid ART is controversial in some settings, there is compelling evidence that rapid ART initiation, even on the same day as confirmed HIV-1 diagnosis, is associated with reduced loss to follow-up in low-middle income settings and more rapid viral suppression[15, 16, 33-36]. Our findings further the rationale for same-day or earlier ART, even during PHI, to support more rapid immune recovery.

The modern era of ART has transformed individual clinical outcomes for people with HIV-1, but challenges in achieving zero HIV-1 transmission persist. The incidence of HIV-1 among MSM in the UK is decreasing, and identifying those MSM still at risk of PHI is critical to continue this trend[37]. UK Health Security Agency data from 2020 suggests that 24% of all new HIV-1 diagnoses were made abroad. However, given that our dataset includes only those with recent HIV-1 infections, it is likely that these individuals acquired HIV-1 in the UK. The recruitment timeframe for the HEATHER study allows us to characterise the changing demographics of PHI between the two periods of analysis, before and after ART guidelines shifted to universal treatment in 2015. This novel data highlights potential gaps and opportunities for HIV-1 prevention in the UK. Therefore, our data highlight that MSM born outside of the UK are at high risk for acquiring HIV-1 while living in the UK. Furthermore, this group accounts for a larger proportion of MSM presenting with PHI in recent years. This supports the data that suggest that migrants may be more vulnerable to HIV-1 acquisition, and novel HIV-1 prevention strategies such as PrEP should be available to and should be targeted at this vulnerable and often difficult-to-reach group.[38, 39]

Acknowledgements

We thank the participants of HEATHER. The HEATHER study is conducted as part of the CHERUB (Collaborative HIV-1 Eradication of Reservoirs: UK BRC) collaboration. (CHERUB Steering Committee: Andrew Lever (University of Cambridge), Mark Wills (University of Cambridge), Jonathan Weber (Imperial College, London), Sarah Fidler (Imperial College, London), John Frater (University of Oxford), Lucy Dorrell (University of Oxford), Mike Malim (King's College, London), Julie Fox (King's College London), Ravi Gupta (University College London), Clare Jolly (University College London).

Author contributions

The HEATHER study was conceived and designed by SF, JFr, JT and JF. Data collection was performed by JT, GM, JL, HL, HB, NR, KK, SK, NN, and GW. JT performed data analysis. JT wrote the paper with input from all authors.

Conflicts of interest

None declared.

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Figure 1. Kaplan-Meier of time to VL <200 copies/ml by integrase inhibitor or other ART use in initial ART regimen.

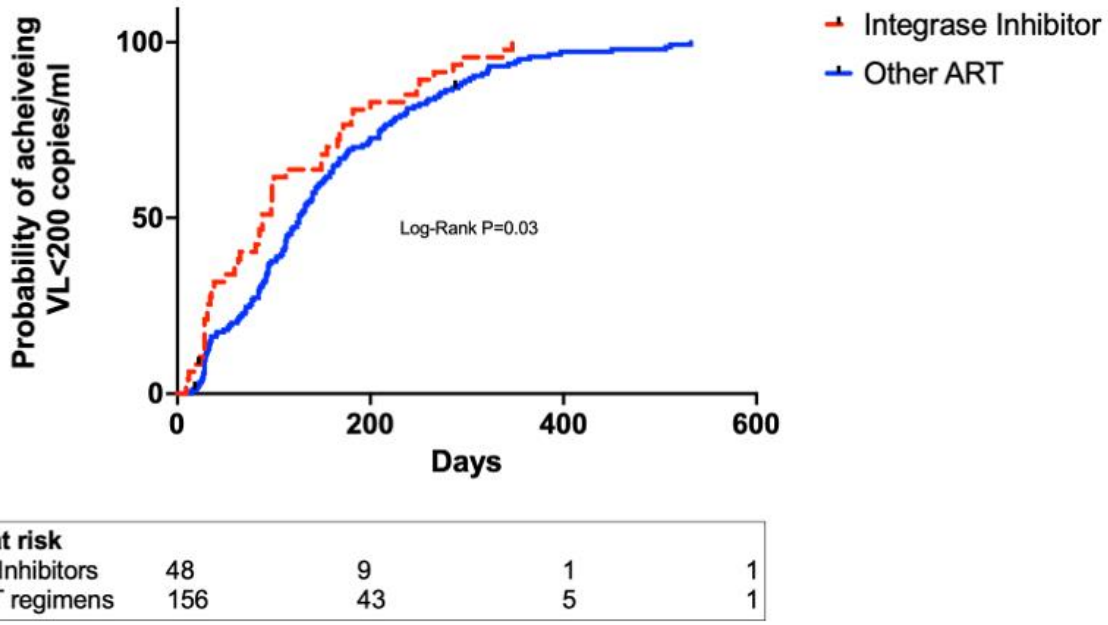

Table 1. Baseline Characteristics of the HEATHER Cohort

	Overall	***Pre-2015***	***2015-2020***	***P-value***
	Median (IQR) or n (%)	*Median (IQR) or n (%)*	*Median (IQR) or n (%)*	
Number of individuals, n	***n=204***	***n=114***	***n=90***	
Age, median years (IQR)	33 (28, 40)	33 (27,39)	34 (29, 41)	0.16
Male, *n* (%)	195/204 (96)	109/114 (96)	86/90 (96)	0.99
Transmission risk, *n (%)*				0.70
MSM	173/204 (85)	98/114 (86)	75/90 (83)	
Heterosexual or unknown	31/204 (15)	16/114 (14)	15/90 (17)	
Ethnicity, n (%)				0.87
White	155/204 (76)	86/113 (75)	69/90 (77)	
Other ethnic groups	49/204 (24)	28/114 (25)	21/90 (23)	
UK-born, n (%)	79/204 (39)	53/114 (47)	26/90 (29)	0.01
Non-UK born, n (%)				
Western Europe	38/204 (18)	16/114 (14)	21/90 (23)	

Central & Eastern Europe Central & South America Australasia North America Africa	35/204 (17) 21/204 (10) 21/204 (10) 4/204 (2) 6/204 (3)	18/114 (16) 14/114 (12) 8/114 (7) 3/114 (3) 2/114 (2)	15/90 (17) 8/90 (9) 14/90 (15) 1/90 (1) 5/90 (5)	
Fiebig stage I or II, n (%)	61/204 (30)	28/114 (25)	33/90 (37)	0.07
Median (IQR) baseline HIV viral load, log_{10} cpm	5.3 (4.4, 6.3)	5.3 (4.6, 6.3)	5.3 (4.2, 6.5)	0.34
Median (IQR) nadir CD4 count, cells/mm^3	507 (405, 656)	514 (408, 514)	483 (391, 634)	0.32
Median (IQR) maximum CD8 count, cells/mm^3 (IQR)	1055 (796, 1698)	1187 (867, 1908)	982 (762, 1459)	0.02
Median (IQR) time to HIV viral load <200cpm, days	115 (62, 200)	126 (71, 209)	111 (41, 181)	0.34
Median (IQR) time to HIV viral load <50cpm, days	162 (94, 258)	162 (106, 245)	162 (84, 275)	0.96
Median (IQR) time to ART start, days	23 (13, 38)	28 (17, 44)	16 (9,27)	<0.001
Median (IQR) duration of follow-up, months	33 (18, 48)	45 (11,55)	28 (17, 37)	<0.001
Proportion of individuals achieving CD4/CD8 >1.0, n (%)	125/204 (61)	69/114 (61)	56/90 (62)	0.89
Proportion of individuals achieving CD4>900 cells/mm^3, n (%)	109/204 (53)	56/114 (49)	53/90 (59)	0.20
Proportion initiated on an INSTI regimen, n (%)	48/204 (24)	9/113 (8)	39/90 (43)	<0.001
Proportion initiated on a four-drug regimen, n (%) Missing data, n	12/204 (6) 10/204	2/114 (2) 3/114	10/90 (11) 7/90	0.005
Proportion with Clade B virus, n (%) Missing data, n	109/158 (69) 46/204	57/86 (66) 28/114	52/72 (72) 18/90	0.49
Proportion with transmitted drug resistance, n (%) Missing data, n	39/162 (24) 42/204	21/89 (24) 25/114	18/73 (25) 17/90	0.99

Abbreviations: IQR, interquartile range; MSM, men who have sex with men; cpm, copies per million.

Table 2. Unadjusted and adjusted Cox regression model of factors associated with time to CD4 count >900 cells/mm^3

	unadjusted		adjusted	
Variable	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Age, years	0.99 (0.97, 1.02)	0.77	0.99 (0.97, 1.03)	0.86
Gender				
Male	1.24 (0.50, 3.05)	0.65	0.21 (0.06, 0.80)	0.01
Female	1		1	
Ethnicity				
White	1.80 (1.04, 3.13)	0.04	2.79 (1.30, 5.98)	<0.01
Other ethnic groups	1		1	
Transmission Risk				
MSM	0.55 (0.33, 0.92)	0.02	0.10 (0.05, 0.23)	<0.001
Non-MSM	1		1	
Year of HIV infection			*Not included*	
2009-2014	1.07 (0.70, 1.62)	0.76		
2015-2018	1			
HIV Clade				
B	1.71 (1.03, 2.85)	0.04	0.74 (0.42,1.30)	0.30
Non-B	1		1	
Initial ART Regimen			*Not included*	
Integrase inhibitor	1			
Non-INSTI	0.84 (0.52, 1.34)	0.47		
Four drug therapy	1.07 (0.47, 2.46)	0.87		
Time to ART, days	0.99 (0.98, 0.99)	0.02	0.98 (0.97, 0.99)	<0.01
Baseline HIV viral load, Log copies/ml	1.01 (0.86, 1.18)	0.92	*Not included*	
Nadir CD4 count, cells per ml		<0.001		<0.001
0-350	0.16 (0.07, 0.37)	<0.001	0.10 (0.04, 0.29)	<0.001
351-500	0.23 (0.13, 0.38)	<0.001	0.20 (0.11, 0.37)	<0.001
>500	1		1	

Maximum CD8 count, cells per ml < 1000 ≥ 1000	 0.52 (0.34, 0.80) 1	 <0.01	 0.64 (0.38, 1.08) 1	 0.09
CD4/CD8 ratio	3.26 (1.28, 8.30)	0.01	*Not included*	

Multivariable model adjusted for age and gender, other variables with P<0.25 were included in the adjusted model (ethnicity, transmission risk, time to ART, CD4 & CD8 T cell counts and Clade B. Adjusted model -2 Log-Likelihood = 628, Chi-Square = 81.532, df=9. HR, Hazard ratio; 95%CI, 95% confidence interval; MSM, men who have sex with men; ART, antiretroviral therapy; INSTI, integrase strand transfer inhibitor.

Table 3. Unadjusted and adjusted Cox regression model of factors associated with time to CD4/CD8>1.0

	unadjusted		**adjusted**	
Variable	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Age, years	0.99 (0.98, 1.01)	0.77	0.99 (0.98, 1.01)	0.42
Gender Female Male	 1.58 (0.69, 3.62) 1	 0.28	 1.63 (0.71, 3.77) 1	 0.25
Ethnicity White Other ethnic groups	 0.98 (0.64, 1.50) 1	 0.91	*Not included*	
Transmission Risk MSM	 0.88 (0.53, 1.47)	 0.88	*Not included*	

Non-MSM	1			
Year of HIV infection				
2009-2014	0.68 (0.47, 0.98)	0.04	0.92 (0.59, 1.43)	0.70
2015-2018	1		1	
HIV Clade			*Not included*	
B	0.83 (0.53, 1.28)	0.40		
Non-B	1			
Initial ART Regimen				
Integrase inhibitor	1		1	
Non-INSTI	0.71 (0.47, 1.08)	0.11	0.65 (0.40, 1.05)	0.08
Four drug therapy	0.70 (0.36, 1.39)	0.31	*Not included*	
Time to ART, days	0.98 (0.97, 0.99)	<0.01	0.98 (0.97, 0.99)	<0.01
Baseline HIV viral load, Log copies/ml	0.95 (0.83, 1.09)	0.45	*Not included*	
Nadir CD4 count,		0.02		<0.001
cells per ml				
0-350	0.54 (0.31, 0.94)	0.03	0.41 (0.23, 0.73)	0.03
351-500	0.52 (0.41, 0.94)	0.02	0.48 (0.32, 0.74)	<0.01
>500	1	1		

Maximum CD8 count, cells per ml < 1000 ≥ 1000	 2.21 (1.54, 3.17) 1	 <0.001	 2.82 (1.92, 4.14) 1	 <0.001
CD4/CD8 ratio	95 (30, 303)	<0.001	*Not included*	

Multivariable model adjusted for age and gender, other variables were included if P<0.25(year of infection, INSTI use, time to ART, CD4 & CD8 T cell counts). Adjusted model -2 Log-Likelihood = 1048, Chi-Square = 48.32, df=8. HR, Hazard ratio; 95%CI, 95% confidence interval; MSM, men who have sex with men; ART, antiretroviral therapy; INSTI, integrase strand transfer inhibitor.

Table 4. Unadjusted and adjusted Cox regression model of factors associated with time to HIV viral load less than 200 copies/ml

	unadjusted		**adjusted**	
Variable	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Age, years	0.99 (0.98, 1.01)	0.60	0.99 (0.98, 1.01))	0.61
Gender Male Female	 2.12 (1.08, 4.17) 1	 0.03	 2.09 (1.04, 4.18) 1	 0.04
Ethnicity White Other ethnic groups	 1 0.90 (0.65, 1.3)	 0.55	*Not included*	
Transmission Risk MSM Non-MSM	 0.99 (0.68, 1.46) 1	 0.98	*Not Included*	
Year of HIV infection 2009-2014 2015-2018	 0.90 (0.68, 1.19) 1	 0.47	*Not included*	

HIV Clade B Non-B	 0.82 (0.59, 1.16) 1	 0.27	*Not included*	
Initial ART Regimen Integrase inhibitor Non-INSTI Four drug therapy	 1 0.69 (0.5, 0.96) 1.28 (0.71, 2.30)	 0.03 0.41	 1 0.70 (0.52, 1.01) *Not Included*	 0.06
Time to ART, days	1.00 (0.99- 1.01)	0.38	*Not Included*	
Baseline HIV viral load, Log copies/ml	0.94 (0.84, 1.04)	0.23	0.95 (0.85, 1.06)	0.34
Nadir CD4 count, cells per ml 0-350 351-500 >500	 0.91 (0.60, 1.36) 1.20 (0.88.1.64) 1	0.36 0.63 0.25	*Not Included*	
Maximum CD8 count, cells per ml < 1000 ≥ 1000	 1.23 (0.93, 1.63) 1	 0.15	 1.25 (0.93, 1.67) 1	 0.13
CD4/CD8 ratio	1.11 (0.57, 2.15)	0.76	*Not Included*	