 Associations between baseline characteristics, CD4 cell count response and virological failure on first-line efavirenz + tenofovir + emtricitabine for HIV

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Abstract

Objectives: The aim of this study was to investigate associations between baseline characteristics and CD4 cell count response on first-line antiretroviral therapy and risk of virological failure (VF) with or without drug resistance. Methods: We conducted an analysis of UK Collaborative HIV Cohort data linked to the UK HIV Drug Resistance Database. Inclusion criteria were viral sequence showing no resistance prior to initiation of first-line efavirenz + tenofovir disoproxil fumarate + emtricitabine and virological suppression within 6 months. Outcomes of VF (>200 copies/mL) with or without drug resistance were assessed using a competing risks approach fitted jointly with a model for CD4 cell count recovery. Hazard ratios for each VF outcome were estimated for baseline CD4 cell count and viral load and characteristics of CD4 cell count response using latent variables on a standard normal scale. Results: A total of 3640 people were included with 338 VF events; corresponding viral sequences were available in 134 with ≥1 resistance mutation in 36. VF with resistance was associated with lower baseline CD4 cell count (0.30, 0.09–0.62), lower CD4 cell count recovery (0.04, 0.00–0.17) and higher CD4 variability (4.40, 1.22–12.68). A different pattern of associations was observed for VF without resistance, but the strength of these results was less consistent across sensitivity analyses. Cumulative incidence of VF with resistance was estimated to be <2% at 3 years for baseline CD4 ≥350 cells/μL. Conclusion: Lower baseline CD4 cell count and suboptimal CD4 cell count recovery are associated with VF with drug resistance. People with low CD4 cell count before ART or with suboptimal CD4 cell count recovery on treatment should be a priority for regimens with high genetic barrier to resistance. Keywords: antiretroviral therapy, ART, drug resistance, HIV, NNRTI, NRTI, viral failure, viral suppression

Introduction

Amongst people diagnosed with HIV in whom there is initial viral suppression, subsequent virological failure (VF) rates on modern ART regimens are low [1]. However, there remains interest in identifying those people living with HIV (PLHIV) at highest risk of VF, particularly that with emergence of drug resistance. The incidence of acquired drug resistance has been falling in resource-rich countries [2,3], but preservation of future treatment options in PLHIV is important, given that people are likely to need antiretroviral therapy (ART) for life. Although it has been argued that routine monitoring of CD4 cell count observations could be reduced for PLHIV on suppressive ART [4,5], the CD4 cell count remains an important marker of immunological status [6], and so there is a motivation to further investigate associations between baseline and post-treatment CD4 cell counts and risk of VF and acquired drug resistance. It has been previously found that low baseline CD4 cell count (<200 cells/μL) and high baseline viral load (VL) (≥100,000 copies/mL) are risk factors for acquired drug resistance following ART initiation [3,7,8]. The expected level of CD4 cell count recovery on virally suppressive ART is strongly dependent on the baseline observation at ART initiation [9–11], and so CD4 cell count recovery itself needs to be evaluated relative to that expected, given the baseline value. One option for evaluation of CD4 cell count response is to track centile values with reference to population charts [13], and another approach is to model CD4 cell count recovery conditional on baseline using mixed-effects models [14,15]. Using the latter approach, it can be shown that there is considerable between-person variation in CD4 cell count recovery that is not explained by baseline characteristics and also differences in the variability of observations over time [15].

There is some evidence from randomised controlled trials that clinical and CD4 cell count monitoring of response to ART is not inferior to VL monitoring with respect to clinical endpoints within a few years of treatment initiation [16,17]. It is also known that CD4 cell count recovery provides important prognostic information for the outcomes of mortality and AIDS progression amongst PLHIV on ART with viral suppression [18], but the available literature suggests only a limited association with risk of VF. Badri et al. found that slope of increase and absolute change in CD4 cell count from baseline were not predictive of VF [19], and immunological criteria have shown poor performance as a direct proxy for VF on ART [20]. However, it is possible that the association between CD4 cell count recovery and VF could differ according to whether this is coincident with the appearance of acquired drug resistance.

In this paper, we develop a joint competing risks model for CD4 cell count measurements on ART and occurrence of VF with or without emergence of drug resistance mutations. This approach allows estimation of associations between the events of interest and baseline CD4 cell count and VL, CD4 cell count response relative to that expected, given the baseline level, and CD4 cell count
variability over time, as well as other individual characteristics. We investigate PLHIV on first-line efavirenz + tenofovir disoproxil fumarate + emtricitabine (EFV+TDF+FTC), an established regimen with widespread global use.

Methods

We conducted an analysis of pseudo-anonymised clinical records of PLHIV included in the UK Collaborative HIV Cohort [21] (CHIC) linked to viral sequences collected by the UK HIV Drug Resistance Database [22]. Data from the UK Register of Seroconverters [23] (UKR) cohort were also used to calibrate parameters of statistical models developed.

The primary analyses included PLHIV in UK CHIC with viral sequence showing the absence of reverse transcriptase major drug resistance mutations (following the International Antiviral Society–USA list [24]) prior to the initiation of first-line ART. PLHIV were included if they started ART on EFV+TDF+FTC in the period 2004–2014 and were observed to achieve virological suppression (defined as single VL measurement <50 copies/mL) within 6 months of initiation. All CD4 cell counts and VF data were censored at change to or interruption (≥214 days) of ART regimen, and CD4 cell counts observed on or after the date of an observed VF (≥200 copies/mL) were also excluded. Only a very small number of people in the UKR and UK CHIC cohorts with nonsexual acquisition of HIV met the inclusion criteria for each stage of the analysis, and so they were excluded.

The statistical methodology was developed using a ‘calibration’ dataset comprising 339 seroconverters (with well-estimated dates of seroconversion) from the UKR cohort who started ART on EFV+TDF+FTC. The purpose of the additional calibration step was to provide information regarding model parameters for variance components and those linking CD4 cell count and VL at treatment initiation to the expected trajectory of CD4 cell count recovery, for use in the primary analyses; fitting of the primary analysis models without this was found to be unstable.

Statistical methods

All models were developed within a Bayesian framework using the Stan probabilistic programming language [25] run on a cluster computer. Full technical details of the statistical models developed are given in Supplementary Appendix S1A, with files to simulate data and run the models also provided. We conducted modelling using the square-root scale for CD4 cell counts and log_{10} scale for VL.

Calibration analysis

Models were fitted to pre- and post-treatment CD4 cell counts in the UKR ‘calibration dataset’ for the specified ART regimen based on those previously developed by Stirrup et al. [14,15,26]. Briefly, the methodology constitutes an extension of the nonlinear mixed-effects framework in which characteristics of CD4 cell count recovery are modelled conditional on latent variables representing ‘true’ baseline CD4 cell count and VL at treatment initiation. Following previous work [14,27], the pretreatment model comprised a ‘random intercepts and slopes model’ with fractional Brownian motion stochastic processes included in the variance structure alongside the measurement error term, and a simple asymptotic curve is used for the CD4 cell count recovery submodel [14].

Primary analyses

The median post-treatment CD4 cell count recovery for sero-prevalent PLHIV was also modelled using a simple asymptotic curve. The true baseline CD4 cell count (square-root scale) and VL (log_{10} scale) were assumed to follow a bivariate normal distribution. The closest CD4 cell count and VL observation within 6 months prior to (or on the day of) treatment initiation were used as baseline observations, and PLHIV without these were excluded. The baseline CD4 cell count measurement was included as the t = 0 observation for the asymptotic recovery model, whilst the baseline VL observation was modelled as following a normal distribution conditional on the ‘true baseline VL’ latent variable [28]. Informative priors were used based on the posterior of the calibration model for residual variance parameters and for those linking the shape of the median CD4 cell count recovery to true baseline CD4 cell count and VL.

The main outcome for the primary analysis was observation of VF, defined as a single VL measurement of ≥200 copies/mL with or without observation of any new major resistance mutation at resistance test using a blood sample obtained within 6 months. These two outcomes were assessed using Weibull survival models, defined relative to initial viral suppression, following a competing risks approach. For cases in which a viral sequence was recorded in the database after ART initiation but prior to any VL observations ≥200 copies/mL, the VF date was set at the date of blood sampling for resistance testing (unless later than the last possible UK CHIC follow-up for most sites: 31 December 2014). VF events with no viral sequence within 6 months were included in the analyses by treating the event as having a masked/missing cause of failure [29,30].

The VF model was fitted jointly with the nonlinear mixed-effects model for CD4 cell count recovery. The hazard ratios (HRs) for each VF outcome were estimated for the level of CD4 cell count recovery relative to that expected, given the baseline value, the degree of CD4 cell count variability over time (in comparison to a smooth curve) and the true baseline CD4 cell count and VL, each of these predictive variables is not directly observed but rather represented by a latent variable in the mixed-effects model (illustrated in Figure 1). The analysis therefore constitutes a joint modelling approach to longitudinal measurements and competing risks failure time data [31], with the novel feature that one of the latent variables included relates to differences in variability over time.

Baseline true CD4 cell count and VL follow a bivariate normal distribution as described, shift in long-term median CD4 cell count relative to that expected (‘CD4 cell count recovery’) is normally distributed and CD4 cell count variability takes the form of a gamma-distributed variable. Effects on hazard of VF were estimated for each latent variable transformed to a standard normal scale for ease of comparison, that is, effect estimates are reported for a difference of 1 SD from the mean in the studied population (on square-root scale for CD4 cell count and log_{10} scale for VL). The fitted models were used to generate cumulative incidence functions for VF with or without resistance for specific baseline CD4 cell count values.

Models were fitted including parameters linking the following individual characteristics to the asymptotic long-term median post-ART CD4 cell count and hazard functions for VF with and without resistance: age at treatment initiation (linear effect centred at 38 years), men who have sex with women, women who have sex with men, black African ethnicity, black Caribbean ethnicity, any other nonwhite or unknown ethnicity, and viral subtype.

Results

There were 3640 PLHIV on first-line EFV+TDF+FTC included in the primary analysis, with VF observed in 338 of these at a
median of 1.2 (interquartile range 0.6–2.6) years. The overall median follow-up time for the analysis was 2.4 (IQR 0.9–4.6) years. A summary of the study population is given in Table 1. A viral resistance test was available in 134 (40%) of PLHIV with VF, and in 36 (27%) of these, there was at least one resistance mutation observed (mutations listed in Supplementary Appendix S1B). Viral subtype was available in all but three PLHIV, and so the potential associations between individual characteristics other than CD4/VL and VF outcomes were evaluated on a complete case basis.

A plot of estimated associations between VL and CD4 cell count characteristics and the hazard of VF without adjustment for demographic variables is presented in Figure 2. The event of VF
Plots of the estimated cumulative incidence of PLHIV experiencing VF with or without the appearance of resistance mutations, unadjusted and with adjustment for demographic and viral characteristics are given in Supplementary Appendix S1C.

The addition of predictive variables relating to age at ART, sex/mode of infection, ethnicity and viral subtype did not have a substantial impact on the estimated associations between VL and CD4 cell count (Table 2) and the events of VF with or without resistance, but credibility intervals for individual factors were wide, and so the fitted model is not inconsistent with strong associations being present.

Table 1. Characteristics of people living with HIV starting ART on efavirenz+tenofovir disoproxil fumarate+emtricitabine included in the primary analysis (n=3640)

| Sex/mode of infection group | n (%) or median (IQR) |
|-----------------------------|-----------------------|
| MSM                         | 2666 (73.2)           |
| MSW                         | 469 (12.9)            |
| WSM                         | 505 (13.9)            |

Ethnicity

| Black African               | 636 (17.5) |
| Black Caribbean             | 113 (3.1)  |
| Other/unknown               | 525 (14.4) |
| White                       | 2366 (65.0) |

Viral subtype

| A                           | 147 (4.0) |
| B                           | 2458 (67.6) |
| C                           | 448 (12.3) |
| CRF                         | 444 (12.2) |
| Other                       | 136 (3.7)  |
| Unknown                     | 3 (0.1)    |

Age at ART initiation (years)

| 2004                        | 72 (2.0)   |
| 2005                        | 183 (5.0)  |
| 2006                        | 160 (4.4)  |
| 2007                        | 213 (5.9)  |
| 2008                        | 583 (16.0) |
| 2009                        | 576 (15.8) |
| 2010                        | 541 (14.9) |
| 2011                        | 443 (12.2) |
| 2012                        | 407 (11.2) |
| 2013                        | 342 (9.4)  |
| 2014                        | 120 (3.3)  |

Year of ART initiation

| Year of ART initiation     | Baseline cD4 cell count* |
|-----------------------------|--------------------------|
| 2004                        | 1.52 (1.24–1.89)         |
| 2005                        | 0.30 (0.09–0.62)         |
| 2006                        | 1.71 (1.15–2.54)         |
| 2007                        | 0.04 (0.00–0.17)         |
| 2008                        | 0.41 (0.22–0.64)         |
| 2009                        | 4.40 (1.22–12.68)        |
| 2010                        | 2.23 (1.7–2.97)          |
| 2011                        | 1.10 (0.34–2.58)         |

VF without resistance

| Unadjusted model            | VF without resistance |
|-----------------------------|-----------------------|
| Baseline CD4 cell count*    | 1.59 (1.29–1.97)      |
| CD4 cell count recovery*    | 1.63 (1.11–2.52)      |
| CD4 cell count variability* | 0.41 (0.2–0.63)       |
| Baseline VL*                | 2.4 (1.79–3.18)       |
| Age at ART initiation years†| 0.99 (0.97–1.01)      |

VF with resistance

| Adjusted model              | VF with resistance    |
|-----------------------------|-----------------------|
| Baseline CD4 cell count*    | 0.27 (0.06–0.64)      |
| CD4 cell count recovery*    | 0.01 (0–0.03)         |
| CD4 cell count variability* | 8.18 (1.47–28.22)     |
| Baseline VL*                | 0.96 (0.87–1.05)      |

Mode of transmission

| MSM                         | Reference |
|-----------------------------|-----------|
| MSW                         | 0.95 (0.49–1.63) |
| WSM                         | 0.95 (0.46–1.77) |
| Other                       | 3.29 (0.21–13.42) |
| Other/unknown               | 6.28 (0.63–30.58) |

Ethnicity

| White                      | Reference |
|---------------------------|-----------|
| Black Caribbean           | 14.34 (0.67–69.23) |
| Black African             | 2.13 (0.19–8.41)  |
| Other/unknown             | 1.17 (0.12–4.99)  |

Viral subtype

| A                         | 4.82 (0.22–25.43) |
| B                         | Reference         |
| C                         | 4.9 (0.42–23.39)  |
| CRF                       | 1.75 (0.08–8.26)  |
| Other                     | 0.69 (0.02–3.48)  |

VF, virological failure; VL, viral load; WsM, women who have sex with men; MsW, men who have sex with women; VF, virological failure; VL, viral load; WsM, women who have sex with men.

Results reported as posterior expectation of hazard ratio (95% credibility interval).

*Modelled latent variable on standard normal scale, effect estimate reported for a difference of 1 SD from the mean (on square-root scale for CD4 cell count and log_{10} scale for VL).

†Centred at 38 years.

without any resistance mutations was associated with higher baseline CD4 cell count (HR 1.52, 1.24–1.89), CD4 cell count recovery (1.71, 1.15–2.54) and baseline VL (2.23, 1.70–2.97) and lower CD4 cell count variability (0.41, 0.22–0.64). Conversely, VF with resistance was associated with lower baseline cD4 cell count (0.04, 0.00–0.17) and higher cD4 cell count variability (4.40, 1.22–12.68). Further details of the fitted model are given in Supplementary Appendix S1C.

The addition of predictive variables relating to age at ART, sex/mode of infection, ethnicity and viral subtype did not have a substantial impact on the estimated associations between VL and CD4 cell count (Table 2) and the events of VF with or without resistance, but credibility intervals for individual factors were wide, and so the fitted model is not inconsistent with strong associations being present.
Some additional details and sensitivity analyses are presented in a supplementary file: the diagnostic performance of our model to predict resistance status at VF (Supplementary Appendix S1D), VL values at VF (Supplementary Appendix S1E), an extended model with quadratic associations between CD4 cell count and VL characteristics and risk of VF (Supplementary Appendix S1F), and results from alternative simplified models (Supplementary Appendix S1G). The relative importance of predictive factors for VF without drug resistance varied under the sensitivity analyses (Supplementary Appendix S1G); the positive association with CD4 cell count recovery found in the primary analysis was less strong if cases of VF with unknown resistance status were excluded, censored or assumed to have no resistance, and the association with baseline VL was weaker and that with baseline CD4 cell count absent using a competing risks approach considering only observed baseline measurements. However, baseline CD4 cell count showed a strong negative relationship with the hazard of VF with drug resistance for all sensitivity analyses that included post-treatment CD4 cell counts.

**Discussion**

We have found that for PLHIV who achieve initial viral suppression on EFV+TDF+FTC, the characteristics of CD4 cell count response to first-line ART are strongly associated with the risk of VF with emergence of drug resistance. Our results also suggest that, in this cohort, there was a different set of factors associated with the event of VF without drug resistance. We used the model developed to investigate the cumulative incidence of VF according to baseline CD4 cell count level and found the incidence of VF with resistance to be substantially lower for baseline CD4 cell count levels of 350 cells/μL or above.

The finding that low baseline CD4 cell count is a risk factor for acquired drug resistance on first-line EFV+TDF+FTC is consistent with previous research on this particular regimen [32] and that on combination ART more generally both in the UK [7,8,33] and elsewhere [3]. Previous studies have also found an association between high baseline VL and risk of acquired drug resistance [3,7,8,34], which we did not observe. However, we considered only resistance tests within 6 months of the first observed VF unlike some previous studies [3,7,8], and we did find high baseline VL to be associated with VF without resistance in our primary analysis. We considered only the first VF event in each person and did not assess whether people went on to develop resistance mutations at a later date; the rationale for this is that adherence interventions or treatment changes would be possible once VF is detected, but it would be useful to be able to identify high-risk individuals before VF occurs. Furthermore, we only included PLHIV with initial viral suppression, differing from Fogel et al. [34], who observed most cases of acquired drug resistance in PLHIV who never achieved suppression.

The model developed predicts a cumulative incidence of VF with emergence of resistance below 2% at 3 years from initial suppression for a baseline CD4 cell count level of ≥350 cells/μL compared with around 6% for a baseline of 100 cells/μL, despite
a fairly consistent cumulative incidence of VF without resistance of 7%–8% across CD4 cell count levels. Our modelling framework has the advantage that it takes the occurrence of VF events with unknown resistance status into account, and so our estimate of the cumulative incidence of VF with resistance includes cases that may not be identified within 6 months of a detectable VL.

For the estimated associations between CD4 cell count response on ART and the risks of VF with or without resistance, interpretation is made difficult by a lack of information on drug adherence for the studied PLHIV. Poor drug adherence is known to predict both VF overall [35] and the emergence of drug resistance [3,36]. It is also known that low or inconsistent ART adherence is associated with reduced CD4 cell count recovery [37,38], and so the association that we have identified between lower than expected CD4 cell count response and the emergence of drug resistance may be due to consistent poor adherence in the affected PLHIV. However, new drug resistance mutations can nonetheless occur in PLHIV with perfect self-reported adherence [36].

The level of CD4 cell count recovery was not found to be negatively associated with the risk of VF without resistance, which could indicate that these events were primarily caused by short-term lapses in adherence in our study population. The fact that we identified distinct sets of associations for the events of VF with and without resistance suggests that they are linked to different combinations of biological and behavioural factors, but we do not know whether differences in adherence fully explain the findings in our studied cohort or whether there could also be a physiological basis for the link between low CD4 cell count and the emergence of drug resistance.

The variability in CD4 cell counts over time was also found to be associated with the risk of VF with emergence of resistance in the primary analysis; it may seem that erratic CD4 cell count trajectories are likely due to inconsistent treatment adherence, but similar differences between PLHIV in the level of CD4 cell count variability can also be observed in pretreatment data [14,27], indicating that this could reflect a biological characteristic of immune response.

A limitation of this study is that it made use of classical Sanger consensus sequences, both for the inclusion criterion of confirmed lack of resistance mutations at baseline and for the classification of VF events. There is evidence that the presence of minority variants with resistance mutations at baseline is a risk factor for subsequent VF [39,40]. A study of men who have sex with men in the UK with probable recent HIV infection in 2011–2013 using next-generation sequencing (NGS) found minority variant (2%–20% thresholds) transmitted drug resistance in 2.3% of PLHIV for nucleoside reverse transcriptase inhibitor and in 1.4% for non-nucleoside reverse-transcriptase inhibitor mutations [41]. It is therefore possible that new drug resistance mutations observed at VF in the studied cohort could have been present as an undetected minority variant prior to the initiation of ART. Although we cannot therefore be sure whether suboptimal CD4 cell count recovery represents a cause of new drug resistance or an effect of pre-existing minority drug resistance mutations in each individual, our results would still be of clinical relevance if the latter were true in the absence of routine NGS screening; in this scenario, suboptimal CD4 cell count recovery would be predictive of VF caused by pre-existing but undetected drug resistance.

The EFV+TDF+FTC regimen investigated in this study is no longer recommended as first-line ART in the UK [42]. Dolutegravir, in particular, is now being used as the basis for first-line treatment in both low-/middle- and high-income countries [42,43]. It will be several years before enough follow-up data would be available for an equivalent analysis to be conducted for PLHIV starting first-line dolutegravir in the UK, and this drug is known to have a higher genetic barrier to resistance [44] than does EFV, meaning that there are likely to be fewer cases of acquired resistance. Our results suggest that a high genetic barrier to resistance should be a particular priority when deciding on treatment for people with low baseline CD4 cell count. PLHIV with viral suppression but lower than expected CD4 cell count recovery might also benefit from a switch to such a regimen, whatever the underlying cause of their suboptimal recovery and particularly if adherence issues can be ruled out.

This study included PLHIV starting ART in the years 2004–2014 and during this time, the guidelines for ART initiation in the UK shifted from starting when PLHIV have a CD4 cell count that has dropped below 350 cells/μL [45] to starting at any CD4 cell count following diagnosis [42]. Public Health England has also recently reported that improved uptake of regular testing has led to an increase in the proportion of PLHIV diagnosed with high baseline CD4 cell count in some centres [46]. We would therefore expect a substantially higher average baseline CD4 cell count for PLHIV now starting first-line ART in the UK. In our analyses, we did not account for the possibility that the risk of VF might differ for PLHIV in whom ART is initiated close to the date of infection, as this would have been a rare event in the cohort under investigation, and this warrants further investigation. However, in the UK and worldwide, there will continue to be large numbers of PLHIV in whom HIV is not diagnosed early and who will initiate ART at a level comparable to the cohort in this analysis.

There is limited information available in the literature regarding the link between CD4 cell response to treatment and the risk of VF and acquired drug resistance. This is due in part to the fact that it is difficult to appropriately quantify the level of an individual’s CD4 cell response, as the expected recovery is dependent on their baseline characteristics and individual trajectories can be highly erratic. The modelling framework that we have developed has identified an association between lower than expected CD4 cell count response and the risk of VF with emergence of drug resistance for PLHIV on first-line EFV+TDF+FTC. Our results suggest that policies to ensure that people who acquire HIV are diagnosed early and initiate ART at as high a CD4 cell count level as possible have the potential to substantially further reduce the incidence of acquired drug resistance, and that people with a low CD4 cell count at ART initiation or with suboptimal CD4 cell count recovery on treatment might benefit from the use of an ART regimen with higher genetic barrier to resistance.

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Conflicts of interest

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Supplementary files
Appendix S1 Appendix containing further details of statistical methodology and fitted models is available at the following website link: https://doi.org/10.6084/m9.figshare.9884627.v1