Investigation of Efavirenz Discontinuation in Multi-ethnic Populations of HIV-positive Individuals by Genetic Analysis

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ABSTRACT

Background: Efavirenz (EFV) based antiretroviral therapy is expanding worldwide. However discontinuation of EFV containing regimens is common in some patients, particularly black patients, due most often to neuropsychiatric side effects. These adverse drug effects often result in premature drug discontinuation, as well as considerable morbidity.

Methods: We genotyped CYP2A6, CYP2B6 and CYP3A4, which encode enzymes principally involved in EFV metabolism, from patients enrolled in the multinational SMART, FIRST and ESPRIT studies, for whom outcome data of treatment adherence was available. Patients with loss or decrease of function single nucleotide polymorphisms (SNPs) in the above genes were assigned a risk score based upon the number of SNPs present weighted relative to whether CYP2B6 (main metabolism pathway) and/or CYP2A6 and CYP3A4 (accessory pathways) were involved. Cox regression models were used to study the association between high genetic risk and time from initiation to EFV discontinuation. Failure was defined as discontinuation of an antiretroviral regimen other than for virologic failure or protocol determined discontinuation.

Findings: Patients with highest pharmacogenetic risk, as defined by cumulative SNPs in CYP2A6, CYP2B6 and CYP3A4, have an increased risk of discontinuation of EFV containing therapy compared to patients with lower genetic risk scores (adjusted HR 1.9, 95% CI 1.2, 3.1, P = 0.009). High genetic risk was not associated with an increased risk of discontinuing atazanavir or nevirapine. High genetic risk was present more often in blacks compared to non-blacks (Adjusted OR 4.5, 95% CI: 1.9, 10.5), and treatment discontinuation was also increased in blacks overall (Adjusted HR 1.4, 95% CI 1.0, 1.9). However, high genetic risk was more associated with treatment discontinuation than race alone for both blacks (Adjusted OR 1.9, 95% CI 0.8, 4.8) and non-blacks (Adjusted OR 5.3, 95% CI 1.5, 18.0).

Interpretation: Premature discontinuation of ART delays the time to effective long term viral suppression, and is associated with significant morbidity. Pharmacogenetic testing may predict those with a high risk of EFV discontinuation, and therefore should be considered in patients in whom initiation of EFV based ART is being considered.

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1. Introduction

Effective combination antiretroviral therapy (cART) has dramatically changed the clinical course of HIV infection. However, this clinical success requires affordable access to medications, and lifelong adherence. Specific antiretroviral agents may have high rates of adverse drug effects (ADEs), which lead to discontinuation of otherwise effective (i.e., virologically suppressive) treatment regimens in up to 40% of patients within 1 year (Durability of first ART regimen and risk factors for modification, interruption or death in HIV-positive patients starting ART in Europe and North America, 2002–2009, 2013). The World Health
EFV undergoes hepatic metabolism catalyzed by cytochromes P450 CYP2B6 (main pathway), and CYP2A6 and CYP3A4 (accessory pathways) (Desta et al., 2007; Telenti and Zanger, 2008). Single nucleotide polymorphisms (SNPs) in CYP2B6, CYP2A6 and CYP3A4 exist that result in loss of function (LOF) or decrease of function (DOF), which associate with slower EFV metabolism and consequently increased drug levels (di Iulio et al., 2009; Arab-Alameddine et al., 2009). Because the risk of EFV associated neuro-psychiatric symptoms is increased in patients with higher plasma concentrations (Marzolini et al., 2001) (Csajka et al., 2003) (Gounden et al., 2010) (Nanzigu et al., 2010) (Nanzigu et al., 2012; Gutierrez et al., 2005), it is likely that patients who have SNPs in CYP2B6, CYP2A6 and CYP3A4, will have a higher incidence of EFV intolerance. Indeed, in 831 participants from three AIDS Clinical Trials group studies, SNPs in CYP2B6 were associated with an increased likelihood of a CNS adverse effect from EFV (Ribaudo et al., 2010), and in a separate study of 577 patients, SNPs in all three enzymes, CYP2A6, CYP2B6 and CYP3A4, were associated with discontinuation of EFV-based regimes within 12 months of initiation (Lubomirov et al., 2011).

In the studies referenced above, the majority of subjects were non-black (66% in (Ribaudo et al., 2010) and 80% in (Lubomirov et al., 2011)), yet the greatest increase in EFV use is likely in populations that are of broader ethnicity, thus it is of importance to determine whether SNP analysis is associated with EFV discontinuation in mixed ethnicity populations. We therefore sought to determine if pharmacogenetic testing of select SNPs in CYP2B6, CYP2A6, and CYP3A4 would be associated with premature treatment discontinuation of virologically suppressive, EFV-containing ART regimes in a multi-national, mixed ethnicity cohort of patients with a long duration of follow up.

2. Materials and Methods

2.1. Participants

Participants included in this study were HIV-positive patients who participated in studies conducted by INSIGHT (International Network

| Table 1 |
|---------------------------------------------|
| Genetic risk score for premature discontinue of efavirenz. |
| Score 1 (reference score): Homozygous for the reference allele in all 3 genes |
| Score 2: Homozygous for the reference allele for CYP2B6, and 1 to 4 LOF/DOF alleles for CYP2A6 and CYP3A4 |
| Score 3: 1 LOF/DOF allele for CYP2B6 but no LOF/DOF allele for CYP2A6 and CYP3A4 |
| Score 4: 1 LOF/DOF allele for CYP2B6 and 1 to 4 LOF/DOF alleles for CYP2A6 and CYP3A4 |
| Score 5: 2 LOF/DOF alleles for CYP2B6 but no LOF/DOF allele for CYP2A6 and CYP3A4 |
| Score 6: 2 LOF/DOF alleles for CYP2B6 and 1 to 4 LOF/DOF alleles for CYP2A6 and CYP3A4 |

**Fig. 1.** Participant eligibility and exclusion stratified by study (SMART, ESPRIT and FIRST).
2.3. Statistical Analysis

Descriptive statistics were used to describe baseline characteristics of study participants. For ART-naïve patients, characteristics at study entry are given; for those that were cART-experienced, characteristics at the time the EFV or ATV regimen was initiated during follow-up are given. Logistic regression models were used to study factors measured at treatment initiation associated with genetic risk score. Unadjusted and adjusted odds ratios (OR) (genetic score of 6 versus 1–5) are given with 95% confidence intervals (CIs).

Time to event methods (Kaplan–Meier survival scores and Cox regression) were used to compare time from initiation to discontinuing EFV according to genetic risk score. Discontinuation of a single drug for any reason was considered because detailed information regarding reasons for discontinuation was not collected. In the Cox regression models, the following baseline covariates were considered: age, gender, race, CD4+ T cell count, HIV RNA, BMI, and co-infection with hepatitis B or C to estimate adjusted hazard ratios (HRs) of discontinuing EFV (genetic risk score of 6 versus 1–5) (Lubomirov et al., 2011). These models were stratified by study (SMART, ESPRIT, and FIRST). Separate and combined models for ART-naïve and ART-experienced patients were considered. To increase confidence that the associations found were due to EFV, as negative controls, we also estimated the risk of discontinuing nevirapine (NVP) and atazanavir (ATV) associated with the genetic risk score. A priori, no association of the genetic risk score with discontinuation of these treatments was expected. For these analyses, expanded Cox models with interaction terms were used to assess whether the risk of discontinuation of EFV associated with the genetic risk score differed from that of NVP and ATV.

We also carried out pooled analyses using individual level data previously published from the Swiss Cohort Study (Lubomirov et al., 2011). For this analysis, a 12 month follow-up period was considered in both studies. Logistic regression was used to study the association of genetic risk score with EFV discontinuation by 12 months. Odds ratios (ORs) and 95% CIs are cited for scores of 1 through 5, each versus a score of 6. The logistic model was stratified by study and included covariates corresponding to age, gender, race, CD4 + T cell count, HIV RNA level, BMI, and hepatitis co-infection. The pooled analyses were also carried out for self-identified blacks and non-blacks separately.

Two-sided p-values less than 0.05 was considered statistically significant. Statistical analyses were performed using SAS software (version 9.3).

Table 2a

| Characteristic | Score 1–5 | Score 6 | OR (95% CI) score 6 vs 1–5a | OR (95% CI) score 6 vs 1–5b |
|---------------|-----------|---------|---------------------------|---------------------------|
| No.           | 1         | 2       | 3                         | 4                         | 5                         |
| Age in years (median, IQR; OR per 10 year increase) | 40 (34, 45) | 37 (34, 41) | 0.8 (0.5, 1.1) | 0.8 (0.5, 1.1) |
| Female (%)    | 21.3      | 47.5    | 3.3 (1.7, 6.4) | 2.1 (1.0, 4.3) |
| Black race (%)| 22.1      | 65.0    | 5.5 (2.6, 12.0) | 4.5 (1.9, 10.5) |
| CD4 T cell count in cells/mm³ (median, IQR; OR per 100 cell increase) | 414 (280, 571) | 312 (136, 520) | 0.9 (0.8, 1.1) | 1.0 (0.8, 1.1) |
| HIV RNA (× 500 copies) | 44.3 | 22.5 | 0.6 (0.2, 1.4) | 0.7 (0.3, 1.9) |
| BMI kg/m² (median, IQR; OR per 5 kg/m² increase) | 24.0 (21.8, 26.4) | 23.9 (22.0, 27.7) | 1.1 (0.8, 1.6) | 1.0 (0.7, 1.3) |
| Hepatitis B or C co-infection (%) | 13.1 | 10.0 | 1.1 (0.4, 3.4) | 1.1 (0.4, 3.6) |

a Unadjusted, stratified by study.

b Adjusted for age, gender, race, CD4 T cell count, HIV RNA, BMI, and hepatitis co-infection and stratified by study.
3. Results

1134 participants were identified as meeting inclusion criteria, whereas 1204 participants did not. Of these, 761 (67%) participants had DNA of sufficient quantity and quality to perform the genotyping assay. After genotyping, 3 participants were excluded due to uninterpretable assay results. Thus, the analyses in this report are based on a total of 758 patients (See Fig. 1 for flow diagram).

Of the 758 patients, 131 (17%) were ART naïve and initiated EFV as their first regimen and 315 (42%) were ART experienced who switched to EFV from another regimen. Eighty (11%) participants were ART naïve and initiated nevirapine (NVP) and 232 (31%) participants were ART experienced who switched to azatavir (ATV) from another regimen. The characteristics of these patients at the time their cART regimen was initiated are summarized in Supplemental Tables 1 and 2. Of interest, 24% of all patients were black, which is a population known to have a greater incidence of premature cART discontinuation (Ribaudo et al., 2013).

### 3.1. Pre-treatment Factors Associated With High Genetic Risk Score

Genetic risk score was calculated based on accumulation of LOF and DOF SNPs in CYP2A6, CYP2B6 and CYP3A4 as previously described (see Table 1 and [Lubomirov et al., 2011]). Overall, 40 patients (5.3%) had a genetic risk score of 6 (Fig. 2), 26 of whom were black. The prevalence of a high genetic risk in blacks was 26/185 (14.1%), whereas for non-blacks it was 14/573 (2.4%) (unadjusted OR (black/non-black) for a genetic risk score of 6 was 5.5; 95% CI:2.6–12.0; p = 0.001 Tables 2a and 2b). Therefore while EFV toxicity occurs commonly in blacks, the prevalence of high genetic risk remains uncommon in blacks, and even less common in non-blacks. Apart from the black race, and gender (female vs male unadjusted OR 3.3 (1.7–6.4), p = 0.001; adjusted OR 2.1 (1.0, 4.3), p = 0.04) there were not significant associations with the genetic risk score.

#### 3.2. Association of Genetic Risk Score With Treatment Discontinuation

Participants with genetic risk scores of 1–5 had similar rates of discontinuation (range; 14 to 26 per 100 person years, p = 0.10 for difference), thus those groups were combined. Participants with a genetic risk score of 6 had a significantly increased risk of discontinuing effective ART regimens containing EFV compared to participants with risk scores of 1–5 (HR 2.0 (95% CI 1.2, 3.1); P = 0.004). Conversely patients with a high genetic risk were not more likely to discontinue ATV or NVP (HR 0.6 (95% CI 0.1, 4.5) P = 0.64 and HR 1.2 (0.6, 2.6) P = 0.54 respectively). This effect was apparent in both ART naïve participants who initiated EFV based regimens (HR 2.5 (95% CI 1.2, 5.4); P = 0.02) and in ART experienced patients who switched to EFV based regimens (HR 1.7 (95% CI 0.9, 3.0); P = 0.08). The increased risk for EFV discontinuation in participants with risk score of 6 persisted after adjustment for age, gender, race, CD4 T cell count, HIV RNA, body mass index, hepatitis co-infection and stratified by study (HR 1.9 (95% CI 1.2, 3.1); P = 0.009, Table 3). Importantly, black subjects were only slightly more likely to discontinue EFV than non-blacks, (HR 1.4, 95% CI 1.0, 1.9) indicating that genetic risk score was superior to race in associating with which patients discontinued EFV. EFV discontinuation occurred as early as two months after starting EFV containing therapy and continued to occur up until to 60 months of follow up (Fig. 3).

#### 3.3. Pooled Analysis With Swiss Cohort

A pooled analysis of the CPCRA and INSIGHT studies together with the Swiss Cohort (Gutierrez et al., 2005) was carried out to increase the power to determine if there was a graded relationship of the score with risk of discontinuation of EFV (Table 4). Each of the lower scores, 1–5, was associated with a reduced risk of EFV discontinuation compared to a score of 6. However, the risk associated with scores 1–5 did not vary (p = 0.15).

### Table 2b
Baseline characteristics of participants by genetic risk score (Swiss Cohort).

| Characteristic | Scores 1–5 | Score 6 | OR (95% CI) score 6 vs 1–5<sup>a</sup> | OR (95% CI) score 6 vs 1–5<sup>b</sup> |
|---------------|------------|---------|----------------------------------|----------------------------------|
| No.           | 259        | 13      | 0.7 (0.4, 1.3)                   | 1.2 (0.6, 2.5)                   |
| Age in years  | 39 (34–47) | 36 (32–42) | 4.7 (1.5, 14.8)                  | 1.8 (0.5, 6.8)                   |
| Female (%)    | 25.5       | 61.5     | 19.4 (5.1, 73.7)                 | 17.5 (3.6, 84.4)                 |
| Black race (%)| 14.7       | 76.9     | 0.9 (0.4, 1.7)                   | 0.9 (0.3, 2.0)                   |
| CD4 T cell count in cells/mm³ (median, IQR; OR per 100 cell increase) | 207 (119, 269) | 204 (152, 248) | 0.8 (0.4, 1.5) | 0.8 (0.3, 2.0) |
| BMI kg/m² (median, IQR; OR per 5 kg/m² increase) | 22.6 (20.9, 24.6) | 23.0 (21.4, 25.3) | 1.0 (0.5, 2.2) | 0.9 (0.4, 2.3) |
| Hepatitis B or C co-infection (%) | 45.6 | 53.8 | 1.4 (0.5, 4.3) | 0.9 (0.3, 3.1) |

<sup>a</sup> Unadjusted.

<sup>b</sup> Adjusted for age, gender, race, CD4 T cell count, HIV RNA, BMI, and hepatitis co-infection.

### Table 3
Risk of premature treatment discontinuation of effective antiretroviral therapy according to genetic risk score.

| Patient group | N (rate) with scores 1–5 who discontinued | N (rate) with score 6 who discontinued | Unadjusted HR (95% CI) for discontinuation of ART, score 6 vs 1–5 | P value | Adjusted<sup>b</sup> HR (95% CI) for discontinuation of ART, score 6 vs 1–5 | P value |
|---------------|----------------------------------------|---------------------------------------|---------------------------------------------------------------|---------|-----------------------------------------------------------------------------|---------|
| ART naïve who started EFV (N = 131) | 85 (25.1) | 7 (69.4) | 2.5 (1.2, 5.4) | 0.02 | 2.2 (1.0, 4.9) | 0.05 |
| ART experienced who switched to EFV (N = 315) | 174 (21.4) | 13 (38.9) | 1.7 (0.9, 3.0) | 0.08 | 1.6 (0.9, 3.0) | 0.13 |
| All who started EFV (N = 446) | 259 (22.5) | 20 (45.9) | 2.0 (1.2, 3.1) | 0.004 | 1.9 (1.2, 3.1) | 0.009 |
| ART naïve who started NVP (N = 80) | 56 (34.9) | 9 (37.7) | 1.2 (0.6, 2.6) | 0.54 | 1.5 (0.6, 3.7) | 0.35 |
| ART experienced who switched to ATV (N = 232) | 91 (16.6) | 1 (9.6) | 0.6 (0.1, 4.5) | 0.64 | 0.6 (0.1, 4.8) | 0.65 |

<sup>a</sup> Per 100 person-years.

<sup>b</sup> Adjusted for age, gender, race, CD4 T cell count, HIV RNA, BMI, and hepatitis co-infection and stratified by study.
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Fig. 3. Kaplan–Meier estimates of the cumulative percentage patients on EFV-containing regimens who discontinued the regimen comparing high genetic risk patients (Score 6) to average genetic risk patients (Scores 1 to 5).

3.4. Analysis by Population and Study Stratification

Because high genetic risk score was over-represented in black participants, we conducted population stratification analyses based on race and study (Tables 5a and 5b). The risk of discontinuation of EFV was increased for those with high genetic risk score for both blacks (Adjusted OR 1.9 (p = 0.18)) and non-blacks (Adjusted OR 5.3 (p = 0.008)), indicating that pharmacogenetic prediction was associated with increased risk of EFV discontinuation independent of self-identified race.

4. Discussion

EFV-based regimens are recommended as first-line and command a substantial market share of current ART use; yet as EFV is now off patent and generic versions are available at lower cost, it is likely that the use of EFV containing regimens will increase in resource limited settings where cost of medications has prohibited widespread access to therapy. However EFV discontinuation rates for non-virologic reasons (i.e., for reasons other than viral resistance) can reach as high as 20% and therefore being able to a priori discriminate those who are more likely to tolerate EFV based therapy is of great global health importance. Herein we demonstrate in a multiethnic population, individuals with loss or decrease of function alleles for 2 or more EFV metabolizing enzymes, in-cluding CYP2B6, are at –2-fold increased risk of premature discontinuation of EFV, irrespective of race or any other factor.

As EFV becomes a more affordable and widespread option for HIV care, a pharmacogenetic test that accurately discriminates those patients who will continue EFV for ADE reasons could be an important addition to the clinician’s decision tools for selecting cART regimens for individual patients. HLA-B*5701 testing to predict abacavir hypersensitivity significantly influenced the care of HIV, by allowing the safe use of a medication that had life threatening ADE potential. Notably, the frequency of the highest genetic risk score in the present study (5.3%) is similar to the reported frequency of HLA-B*5701 (Orkin et al., 2010). Being able to determine who will tolerate EFV may enhance the ability of patients who take EFV to tolerate EFV, lower risk of developing NNRTI resistance due to missed doses, and reduced morbidity due to ADEs. Each of these predictions is testable and warrants further study. This may lead to cost savings through less work and school absences, less need to switch cART regimens and incur the additional expense and inconvenience of doctor visits and lab tests needed to initiate and monitor a therapy change. This may not necessarily be the case though; the rate per 100 person years for stopping EFV (including ART experienced and naïve combined) in our study was 23.3. The corresponding rate for stopping NVP was 35.3; however, better tolerated agents are available now, including integrase inhibitors, which could be used instead of EFV or NVP. An alternative strategy could be reducing EFV dose. Evidence supporting reduced dosing for EFV is found in the ENCORE1 trial where reduced dose EFV (400 mg) was non-inferior to 600 mg EFV for virologic suppression, and study-drug related ADEs (Puls et al., 2014); it would be of great interest to stratify such an analysis by genetic risk score.

In our study, those participants with the highest genetic risk score of 6 had an increased risk for EFV discontinuation compared to those participants with risk scores 1–5. We therefore performed a post hoc analysis of pooled data of 781 patients starting EFV-based regimens from our cohort and the patients in the Swiss Cohort (Lubomirov et al., 2011) and that showed the risk of EFV discontinuation did not change in patients with genetic risk score of 1–5, likely reflecting the known redundancy in EFV metabolizing pathways, and is consistent with data in patients with CYP2B6 polymorphisms 516G > T and 983 T > C where plasma EFV plasma concentrations were elevated only in those patients who also had other accessory pathway mutations (Haas et al., 2014).

Black participants in our cohort had a higher prevalence (14.1%) of high genetic risk compared to other races (2.4%), consistent with reported population allele frequencies for variants in those genes (http://www.ncbi.nlm.nih.gov/snp/). A high prevalence of CYP2B6 516G > T (rs3745274) has been previously reported in Ghanaian patients (Sarfo et al., 2014), and racial differences in the prevalence are evident in HapMap and 1000 Genomes data (35–42% in Sub-Saharan Africans, 23–27% in Europeans, 15–18% in Asians). Thus if an individual with this allele also happens to have other LOF/DOF alleles in EFV metabolizing enzymes, it is logical that they might be intolerant to EFV. It is noteworthy however that race alone did not predict EFV discontinuation in our analyses — indicating that the pharmacogenetic risk stratification employed in our study is more discriminatory than determination of race alone. In addition, it is likely that factors other than genetic risk contribute to disparities in treatment discontinuation which could contribute to an attenuation of observed genetic risk.

There are potential limitations of our study. Our study focused on three CYP enzymes, and thus on pharmacokinetic pharmacogenetics. There might be other pharmacokinetic factors, e.g., genetically

Table 4

Risk of premature treatment discontinuation of effective antiretroviral therapy according to genetic risk score — pooled analysis with Swiss Cohort.

| Genetic risk score | N (%) who discontinued within first year: INSIGHT | N (%) who discontinued within first year: Swiss Cohort | Unadjusted OR (95% CI) for discontinuation in first year, vs. score of 6 | P value | Adjusted OR (95% CI) for discontinuation in first year, vs. score of 6 | P value |
|--------------------|-----------------------------------------------|-----------------------------------------------|-------------------------------------------------|--------|-------------------------------------------------|--------|
| Score 1            | 31 (28.4)                                     | 22 (30.6)                                     | 0.38 (0.19, 0.79)                                | 0.009  | 0.41 (0.18, 0.90)                                | 0.03   |
| Score 2            | 30 (28.6)                                     | 16 (28.6)                                     | 0.38 (0.18, 0.79)                                | 0.01   | 0.36 (0.17, 0.77)                                | 0.009  |
| Score 3            | 16 (18.4)                                     | 14 (21.9)                                     | 0.21 (0.11, 0.40)                                | 0.001  | 0.24 (0.10, 0.54)                                | 0.001  |
| Score 4            | 29 (27.6)                                     | 19 (35.2)                                     | 0.41 (0.20, 0.85)                                | 0.02   | 0.39 (0.18, 0.82)                                | 0.01   |
| Score 5            | 2 (12.5)                                      | 3 (23.1)                                      | 0.19 (0.06, 0.60)                                | 0.005  | 0.20 (0.06, 0.65)                                | 0.008  |
| Score 6            | 12 (50.0)                                     | 7 (53.8)                                      | 1.0                                              | –      | 1.0                                              | –      |
| Total              | 120 (26.9)                                    | 81 (29.8)                                     | 1.0                                              | –      | –                                                | –      |

* Stratified by study.

b Adjusted for age, gender, race, CD4 T cell count, HIV RNA, BMI, and hepatitis co-infection and stratified by study.
polymorphic transporters, that contribute to premature discontinuation of EFV that were not assessed here. It is also conceivable that some of the side effects might also be influenced by pharmacodynamic pharmacogenetics — i.e., genetic variation in the targets for the drug. In addition, since we included only those participants with 12 months of follow up data, there is the potential for survivorship bias. Finally, data was not available in all studies regarding pregnancy as a potential cause for premature treatment discontinuation. Future studies should take these potential factors into account.

In conclusion, given the significant association of high genetic risk score with EFV but not NVP or ATZ discontinuation in a multiethnic cohort, assessment of this score is warranted in large prospective international cohorts. The cost effectiveness of this strategy would need to be determined, particularly in resource-limited settings.

Conflict of Interest

JKR has received honoraria for speaking at educational events or consulting from AbbVie, Bionor, Boehringer-Ingelheim, BMS, Gilead, Janssen, Merck, Tibotec, and ViV. MB has received honoraria from AbbVie, Boehringer-Ingelheim, Bristol Myers Squibb, Gilead, Janssen-Cilag and Merck and grant funding from Gilead and Merck. All other authors declare no conflict of interests.

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Portions of the data were previously presented at the Individualizing Medicine Conference 2013 in Rochester, MN, USA.

Appendix A. Supplementary Data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ebiom.2015.05.012.

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Table 5a

Risk of premature treatment discontinuation of effective antiretroviral therapy according to genetic risk score – Pooled analysis with Swiss Cohort – Black race (N = 166).

| Genetic Risk Score | N (%) who discontinued within first year: INSIGHT | N (%) who discontinued within first year: Swiss Cohort | Unadjusted OR (95% CI) for discontinuation in first year, vs. score of 6 | P value | Adjusted OR (95% CI) for discontinuation in first year, vs. score of 6 | P value |
|-------------------|-----------------------------------------------|-----------------------------------------------|-------------------------------------------------|--------|-------------------------------------------------|--------|
| Score 1           | 2 (28.6)                                       | 1 (100.0)                                     | 0.96 (0.18, 5.04)                                | 0.96   | 0.60 (0.08, 4.47)                                | 0.62   |
| Score 2           | 11 (29.7)                                      | 1 (9.1)                                       | 0.44 (0.16, 1.24)                                | 0.12   | 0.37 (0.12, 1.14)                                | 0.08   |
| Score 3           | 2 (50.0)                                       | 0 (0)                                         | 1.44 (1.17, 12.4)                                | 0.74   | 2.46 (0.24, 25.1)                                | 0.45   |
| Score 4           | 14 (25.9)                                      | 10 (41.7)                                     | 0.58 (0.23, 1.47)                                | 0.25   | 0.54 (0.20, 1.46)                                | 0.23   |
| Score 5           | 1 (100.0)                                      | 1 (50.0)                                      | 1.97 (0.16, 24.7)                                | 0.60   | 2.87 (0.17, 48.1)                                | 0.46   |
| Score 6           | 7 (46.7)                                       | 7 (40.0)                                      | 1.0                                             | –      | 1.0                                             | –      |
| Total             | 37 (31.4)                                      | 17 (35.4)                                     | 1.71 (0.72, 4.08)                                | 0.23   | 1.89 (0.75, 4.78)                                | 0.18   |

a Adjusted for age, gender, CD4 T cell count, HIV RNA, BMI, and hepatitis co-infection and stratified by study.

Table 5b

Risk of premature treatment discontinuation of effective antiretroviral therapy according to genetic risk score – pooled analysis with Swiss Cohort – non-black race (N = 552).

| Genetic risk score | N (%) who discontinued within first year: INSIGHT | N (%) who discontinued within first year: Swiss Cohort | Unadjusted OR (95% CI) for discontinuation in first year, vs. score of 6 | P value | Adjusted OR (95% CI) for discontinuation in first year, vs. score of 6 | P value |
|-------------------|-----------------------------------------------|-----------------------------------------------|-------------------------------------------------|--------|-------------------------------------------------|--------|
| Score 1           | 29 (28.4)                                     | 21 (20.6)                                     | 0.21 (0.06, 0.72)                                | 0.01   | 0.24 (0.07, 0.84)                                | 0.03   |
| Score 2           | 19 (27.9)                                     | 15 (33.3)                                     | 0.23 (0.06, 0.81)                                | 0.02   | 0.24 (0.07, 0.85)                                | 0.03   |
| Score 3           | 14 (16.9)                                     | 14 (21.9)                                     | 0.12 (0.03, 0.43)                                | 0.001  | 0.13 (0.04, 0.47)                                | 0.002  |
| Score 4           | 15 (20.4)                                     | 9 (30.0)                                      | 0.23 (0.06, 0.82)                                | 0.02   | 0.23 (0.06, 0.85)                                | 0.03   |
| Score 5           | 1 (6.7)                                       | 2 (18.2)                                      | 0.07 (0.01, 0.36)                                | 0.002  | 0.07 (0.01, 0.38)                                | 0.002  |
| Score 6           | 5 (55.6)                                      | 3 (100.0)                                     | 1.0                                             | –      | 1.0                                             | –      |
| Total             | 83 (25.3)                                     | 64 (28.6)                                     | 5.59 (1.66, 18.8)                                | 0.006  | 5.27 (1.54, 18.0)                                | 0.008  |

a Adjusted for age, gender, CD4 T cell count, HIV RNA, BMI, and hepatitis co-infection and stratified by study.
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