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Impact of Efavirenz Metabolism on Loss to Care in Older HIV+ Africans

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Abstract

Background: Efavirenz is commonly used in Africa and is frequently associated with neurocognitive toxicity, which may compromise clinical outcomes. Older individuals are at increased risk for drug toxicity and clinical outcomes may be worse in older age, particularly among those individuals with cytochrome P450 (CYP) 2B6 polymorphisms associated with slower efavirenz metabolism.

Methods: We conducted a prospective cohort study of 914 treatment-naïve HIV+ adults initiating efavirenz-based antiretroviral treatment at public HIV clinics in Gaborone, Botswana between 2009 and 2013. Older age, defined as age ≥ 50 years, was the primary exposure and loss to care at six months was the primary outcome. Interaction between age and CYP2B6 516G>T and 983T>C polymorphisms, defined as extensive, intermediate, and slow metabolism, was assessed.

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Compliance with Ethical Standards

Conflict of Interest: The authors declare there is no conflict of interest.

Ethical Standards: The parent study was approved by the Institutional Review Board at the University of Pennsylvania and by the Botswana Ministry of Health. Informed consent was obtained from all participants included in this study. Funding agencies had no involvement in the analysis, interpretation of results, or development of this manuscript.

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Neurocognitive toxicity was measured using a symptom questionnaire. Age-stratified logistic regression was performed to identify factors associated with loss to care.

Results: Older age was associated with loss to care (OR: 1.95, 95% CI: 1.30–2.92). Age modified the effect of CYP2B6 genotype on loss to care with older, slow metabolizers at over four-fold higher risk when compared to older, intermediate metabolizers (OR: 4.06 95% CI: 1.38, 11.89); neurocognitive toxicity did not mediate this risk. CYP2B6 metabolism genotype did not increase risk of loss to care in younger participants.

Conclusion: Older age was associated with loss to care, especially among those with slow efavirenz metabolism. Understanding the relationship between older age and CYP2B6 genotype will be important to improving outcomes in an aging population initiating efavirenz-based ART in similar settings.

1 INTRODUCTION

Efavirenz, a non-nucleoside reverse transcriptase inhibitor, is an integral component of first-line antiretroviral therapy (ART) for the treatment of HIV in resource-limited settings [1]. While efavirenz is highly effective, more than 50% of people initiating efavirenz-containing ART regimens report a spectrum of distressing neurocognitive symptoms with upwards of 10% requiring efavirenz discontinuation due to these adverse effects [2].

Efavirenz toxicity has been associated with increased plasma concentration and diminished clearance, suggesting individual metabolic factors likely mediate drug toxicity [3]. Over the past decade, pharmacogenetic predictors of impaired efavirenz metabolism have been identified within the family of cytochrome P450 (CYP) enzymes [4,5]. Efavirenz undergoes extensive hepatic metabolism via CYP enzymes and glucuronidation; renal metabolism is insignificant with less than 1% of free efavirenz excreted in the urine [6]. CYP2B6 is the predominant isoenzyme responsible for primary and secondary metabolism, with smaller contributions by CYP3A4/5 and CYP2A6 [4,7]. The single nucleotide polymorphism (SNP) CYP2B6 516G>T has been strongly associated with increased efavirenz plasma concentrations and, in some studies, has correlated with increased toxicity, and increased risk of treatment discontinuation [8–10]. This polymorphism may have practical implications as the prevalence of the CYP2B6 516G>T polymorphism ranges from 25–60% in African and Asian populations [5,11]. In addition, the CYP2B6 983T>C SNP has been described to have similar impact on efavirenz plasma concentration and may contribute to increased drug toxicity and subsequent discontinuation [12,13]. While less prevalent than the 516G>T polymorphism, the 983T>C polymorphism is found most commonly in African populations at frequencies as high as 7.5% [14]. The slow efavirenz metabolism conferred by these polymorphisms may impact drug tolerability and potentially compromise adherence and virologic control.

Older age may also differentially impact CYP-based drug metabolism and tolerability, but the effect of older age has not been rigorously studied in HIV-infected patients on efavirenz [15]. While the effect of older age on the expression of CYP2B6 is unclear, the process of aging in general confers increased risk of drug toxicity due to physiologic changes that occur with advancing age including alterations in drug absorption, volume of distribution,

and decreased organ mass and perfusion [16]. Similarly, changes in neurotransmission and reduced synaptic plasticity observed in older age may increase the vulnerability of older people to medication-induced central nervous system toxicity [17,18]. These biologic changes associated with aging may substantially impact both efavirenz pharmacokinetics and pharmacodynamics and may ultimately impact clinical response above and beyond pharmacogenetic predispositions. As the HIV-infected population in resource-limited settings ages, older age may become increasingly relevant as a risk factor for adverse treatment outcomes. To this end, we aimed to determine if the CYP2B6 polymorphisms differentially impacted loss to care in older people.

2 METHODS

We conducted a secondary analysis of a prospective cohort study of 941 HIV positive adults initiating efavirenz-based ART in Botswana between June 2009 and February 2013. Details of the study design were previously published; briefly, people age 21 and older were eligible for enrollment if they intended to initiate efavirenz-based ART, were not pregnant, and planned to remain in the local area for at least six months following treatment initiation [19]. The baseline study visit occurred immediately prior to initiation of ART and blood samples were collected for CD4+ T-lymphocyte count, quantitative HIV RNA, and participant DNA for CYP2B6 516G>T and 983T>C genotyping. Baseline demographic data were obtained and participants completed both Patient Health Questionnaire 9 (PHQ-9) and Alcohol Use Disorders Identification Test (AUDIT-C) questionnaires. Subsequent study visits occurred at one month and six months following initiation of ART. During subsequent visits, participants completed a 35-item Subject Experience Questionnaire (SEQ) to assess severity of adverse experiences, including 19 items regarding neurocognitive symptoms, and pharmacy refill data were obtained to calculate ART medication possession ratio [20,21]. All study questionnaires were completed by the participants in English or Setswana. At the final six month visit, blood was collected for CD4 count and HIV RNA measurements. A window period of three months was allotted to complete the final six-month assessment.

2.1 Definitions

Older age, defined as age 50 years or greater at the time of ART initiation, was the primary exposure for this analysis. This age cut off is clinically significant as prior studies have indicated a blunted immunologic recovery in adults age 50 or greater, despite appropriate virologic response following ART initiation [22]. CYP P450 enzymatic activity within the hepatic microsomes has similarly shown a functional decline beginning in the sixth decade of life [23]. The primary outcome was composite loss to care, defined as participant death or no identifiable clinical interaction following enrollment with the participant during the final assessment window period. Per protocol, study personnel reviewed medical records, contacted participant family members, and employed community outreach to confirm vital status at the study end point to ensure accurate recording of deaths and losses to follow-up care. Virologic failure was defined as quantitative HIV RNA ≥ 25 copies/mL at six months. While some guidelines define virologic failure as ≥ 400 copies/mL, low-level viremia has previously been associated with subsequent treatment failure, thus a more stringent quantitative virologic threshold was used [24,25]. As those individuals who had virologic

failure at six months were still retained in care, virologic failure was analyzed as a separate outcome from loss to care. All participants were screened for active tuberculosis; those who screened positive were initiated on antituberculosis treatment prior to initiation of ART. Hazardous alcohol use was defined as binge drinking or 7 drinks/week for women or 14 drinks/week for men. Depression was defined as a score of 10 on PHQ-9 questionnaire at baseline. Efavirenz-associated neurocognitive toxicity was defined by the cumulative score for the 19 neurocognitive items within the SEQ at one month following efavirenz initiation and analyzed as a continuous variable [26].

2.2 Laboratory methods

Quantification of HIV RNA was performed using NucliSENS Easy Q HIV-1 (BioMérieux) on plasma, with a lower limit of quantification of 25 copies/ml. Genotyping of the CYP2B6 516G>T (rs3745274) and 983T>C (rs28399499) SNPs were completed using DNA extracted from whole blood and assayed by the Taqman Genotyper software, version 1.3 (Life Technology) measuring allele-specific fluorescence. CYP2B6 allelic variants were defined as extensive (516GG+983TT), intermediate ([516GT+983TT] or [516GG+983CT]), and slow (516TT or 983CC or [516GT+983CT]) (19). Efavirenz concentration was measured at the Month 1 follow up visit and reflected steady state plasma concentrations confirmed by patient dosing records and presuming adherence [3,6,8,9]]. Plasma efavirenz concentrations were assayed using high performance liquid chromatography tandem mass spectrometry [19].

2.3 Statistical Analysis

Baseline demographics were compared using the Student's T-test or ANOVA for comparison of means, the Mann-Whitney test for comparison of medians, and Chi-Square test for comparisons of proportions, as appropriate. To determine the effect of age on loss to care, we calculated unadjusted odds ratios of loss to care. We then used the test for homogeneity from the Mantel-Haenszel method to evaluate a potential interaction between age and CYP2B6 polymorphism when analyzing the risk of loss to care. Stratified odds ratios were generated for the association between age and loss to care by CYP2B6 polymorphism and homogeneity of odds was assessed with the Chi-Square test. We fit a multivariate logistic regression model to adjust for potential confounders and forced sex into this model given prior observations of differential outcomes by sex [27]. To assess the potential for efavirenz-associated neurocognitive toxicity as a potential mediator of loss to care, we performed an exploratory analysis adjusting the multivariate model for SEQ score [28]. We performed sensitivity analyses to address the effect of missing SEQ scores on loss to care among older participants through three scenarios: 1) multiple imputation to derive missing SEQ scores, 2) "worst case" in which all missing SEQ values were replaced with most extreme SEQ score observed, and 3) "best case" in which all missing SEQ values were replaced with zero.

2.4 Power Calculation

Given a sample size of 914, including 125 older adults, with 30% loss to care, we had over 80% power to detect an OR of 1.75 of loss to care when comparing older adults to younger adults. A priori, we set an alpha level of 0.05 for two sided tests of hypothesis and all statistical analyses were performed using Stata version 13 [29].

3 RESULTS

Of the 941 participants enrolled in this study, 914 (97.1%) had age recorded and were included in the analysis. Of the 914 participants included, 789 (86.3%) were age 21–49 years and 125 (13.7%) were age 50 years or older (Table 1). Prevalence of baseline depression and underweight BMI were similar between age groups, but hazardous alcohol use in the past year was more commonly reported in the younger age group. Median CD4 counts and HIV viral loads prior to ART initiation were similar by age. Seven hundred and ninety (86.4%) had CYP2B6 polymorphisms available with similar distributions observed across age groups (Chi Square test; $p=0.87$). Efavirenz concentration varied by CYP2B6 phenotypes; however, efavirenz concentration did not differ by age (Figure 1).

Overall, 216 (23.9%) were lost to care, including 38 (17.6%) with confirmed deaths and 178 (82.4%) who were lost to follow-up at the end of the study. Participants age 50 years or greater had nearly twice the odds of being lost to care at six months when compared to participants age 21–49 years (Table 2). Older people had a greater odds of dying when compared to younger participants. Of the 687 retained in care with HIV viral load assessed, 103 (15%) had detectable HIV RNA at six months. Of those with virologic failure, median viral load in older and younger participants was 52 copies/mL (IQR: 34–200) and 85 copies/mL (IQR: 45, 160), respectively (Mann-Whitney test: $p=0.18$), with only two (2.6%) older participants and 15 (2.5%) younger participants with viral loads of ≥ 400 copies/mL. Odds of virologic failure were not statistically different by age group (Table 2).

When stratified by age, intermediate metabolizers had a reduced risk of loss to care when compared to extensive metabolizers among participants age 21–49 years, although no statistically significant difference was observed for the slow metabolizers in this age group (Figure 2). However, in participants age 50 years or greater, there was a dose-response association observed across CYP2B6 metabolism genotypes: extensive metabolizers had 0.6 odds of being lost to care and slow metabolizers had nearly three times the odds of being lost to care when compared to older, intermediate metabolizers. Age modified the effect of CYP2B6 metabolism genotype on loss to care with a statistically significant test for homogeneity (Mantel–Haenszel test of homogeneity: $p=0.02$).

Among older participants, sex, baseline depression, baseline CD4 count and viral load, active tuberculosis, and hazardous alcohol use during the preceding year were not statistically significantly associated with increased risk of loss to care in univariate analysis (Table 3). Underweight BMI was associated with increased odds of loss to care among older participants; however, this association was not observed among younger participants (data not shown). After controlling for sex, BMI, and severe immunosuppression defined by baseline CD4 <50 cells/mm³, older, slow metabolizers remained significantly more likely to be lost to care when compared to older, intermediate metabolizers (Table 3). Older, extensive metabolizers were 0.68 times less likely to be lost to care compared to older, intermediate metabolizers in the multivariate analysis, but this association was not statistically significant.

To explore potential mediators of loss to care, we evaluated efavirenz adherence and efavirenz associated neurocognitive toxicity in the subset that remained in care for the one-

month follow-up visit. Median ART adherence in those with at least one adherence assessment (n=858) was over 98% one month into therapy in both younger and older participants and not statistically different by age. Neurocognitive toxicity, as measured by SEQ, was overall mild with mean cumulative score of 2.2 and 2.6 in younger and older participants, respectively (Student's T-test; $p=0.40$) (Supplementary Table 1). In this subset with available data, neurocognitive toxicity did not mediate the association between genotype and loss to care in older individuals as there was no statistically significant difference in loss to care by increasing SEQ score among older participants when this variable was retained in the multivariate model (Supplemental Table 2). Sensitivity analyses suggest even in the setting of "worst case" SEQ score among older individuals lost to care, slow CYP2B6 metabolism genotype remained independently associated with loss to care. When stratified by genotype, mean SEQ score among the older people was lowest in the slow metabolizers, although this trend was not statistically significant (ANOVA test: $p=0.06$) (Supplementary Table 3).

4 DISCUSSION

In this observational study from a routine public clinic-based setting in Botswana, approximately a quarter of patients were lost to care within the first six months after initiating ART. Furthermore, adults aged 50 and older initiating efavirenz-based ART regimens were two times more likely to die or become lost to follow-up after ART initiation. CYP2B6 SNPs conferring slow efavirenz metabolism were strongly associated with loss to care in older individuals.

Approximately 9% of older participants died during follow-up, and mortality on ART accounted for one quarter of loss to care in those aged 50 years and older. Our results are consistent with several prior observational studies of HIV+ adults in sub-Saharan Africa, which have similarly noted increased short-term mortality in older individuals [30–36]. We found older participants had a higher risk of becoming lost to follow-up with over a quarter of those over 50 years of age lost to follow-up at six months, and it is possible that in this setting many of those lost to follow-up had actually died [37]. Differential participant relocation could also potentially explain the unusually high attrition rate among older participants; however, this is less likely as study enrollment was limited to participants intending to remain in the local area throughout the study duration. Our findings suggest factors impacting retention in care among older people in resource limited settings may present unique barriers and highlight the need for further understanding of these dynamics.

We found CYP2B6 genotype impacted risk of loss to care differentially by age in that older individuals with slow efavirenz metabolism were at over four-fold increased risk of loss to care when compared to older individuals with intermediate efavirenz metabolism. In contrast, this association between slow efavirenz metabolism and clinical outcome was not observed in people age 21–49 years. The rationale to evaluate the effect of genotype in younger and older individuals separately was based on a hypothesis including both pharmacokinetic and pharmacodynamic concepts, wherein older age would be associated with both slower metabolism within specific genotypes, resulting in increased drug concentration, and increased susceptibility to CNS toxicity at any given drug concentration.

However, this mechanism is unlikely to explain the association observed as efavirenz concentrations were not different by age group after accounting for CYP2B6 genotype, suggesting higher extracellular drug concentrations cannot account for this observation. In addition, increased severity of adverse events among older people may not explain this association as SEQ scores did not significantly differ by age group. In fact, among older people, SEQ scores showed a trend towards a lower score in intermediate and slow metabolizers suggesting there is less reported neurocognitive toxicity in older, slower metabolizers, consistent with prior findings in this cohort [19]. While the differential loss to care may be a source of potential bias, sensitivity analyses performed suggest even in the hypothetical setting of extreme neurocognitive toxicity, the magnitude and significance of the association between loss to care and slow efavirenz metabolism in older individuals remains significant.

Other potential mechanisms driving the association between older age, slow efavirenz metabolism and loss to care include unmeasured toxicity or unmeasured drug-drug interactions. While our study has relied on a self-reported questionnaire previously designed for HIV+ individuals, efavirenz-associated neurocognitive toxicity may manifest in other cognitive domains not formally assessed in this study [21,26]. Other studies have suggested executive function, attention, and language are adversely impacted in patients on efavirenz-based ART and may be most severe in HIV+ adults > 65 years [38,39]. Drug-drug interactions may occur more often in older, slow CYP2B6 metabolism genotypes when taking efavirenz-based ART by virtue of potentiated toxicity. For example, cardiac arrhythmias may be potentiated in such patients when efavirenz-based ART is co-administered with QT-prolonging agents, including azoles, macrolides, fluoroquinolones, trimethoprim-sulfamethoxazole, chloroquine, and pentamidine, agents commonly given the high prevalence of opportunistic and other infections in similar populations [40–45]. Herb-drug interactions may be another source of toxicity that may be exacerbated in older, slow CYP2B6 metabolism genotypes given the pervasive use of herbal medicinals in African countries [46,47]. *Sutherlandia frutescens*, an herbal medicinal commonly used by HIV+ people, has been demonstrated to inhibit CYP isozymes including CYP2B6, and may potentiate herbal and/or ART toxicity and may further exacerbate neuroinflammation in HIV-infected people [48–50]. While the exact mechanism is unclear, our data suggest that the associations between efavirenz metabolism, older age, and clinical outcomes are complex and future investigations evaluating loss to care in older adults should consider herbal-drug interactions.

We also found underweight BMI was associated with loss to care in older adults, independent of CYP2B6 metabolism genotype and sex, and severe baseline immunosuppression. This is an intriguing finding as underweight BMI may be a marker of food insecurity, frailty, or other multimorbidity and may impact ART metabolism through altered volume of distribution and may ultimately impact clinical outcomes. Prior cohort studies in sub-Saharan Africa similarly note underweight BMI increases risk for death; however, the contribution of these age-related issues has not been rigorously investigated in resource-limited settings and warrants further study [51–53].

The primary strength of this study is the large size of this African cohort, allowing for thorough evaluation of the impact of efavirenz pharmacogenetics on clinical outcomes in older adults treated in a routine care setting. It is estimated that 3.9 million people living with HIV worldwide are age 50 or older; in sub-Saharan Africa, this age group is projected to increase 190% by 2040 with 9.1 million older people living with HIV in this region alone [54]. As the CYP2B6 516G>T and 983T>C SNP are highly prevalent in this region, our findings raise concern for the safety and effectiveness of efavirenz-based therapy in the increasing number of older HIV+ individuals [5,11]. While the use of efavirenz in first-line regimens will likely soon be replaced by less toxic agents, given the projected increase in older HIV+ people initiating ART in the immediate future, additional study of efavirenz pharmacokinetics and pharmacodynamics accounting for CYP2B6 metabolism genotypes is necessary to ensure safe treatment and successful retention of this growing population.

Designed as a post-hoc analysis, our findings are limited by the fact that statistically significant results may be observed by chance alone. In addition, the actual cause of loss to care was not evaluated so we cannot comment on the mechanism by which slow efavirenz metabolism might account for this loss. Despite these potential limitations, there remains a need to understand barriers to retaining older people in care in addition to ART pharmacokinetics and pharmacodynamics in this growing population. Effective strategies to minimize loss to follow up among older HIV+ Africans are undefined in current practice and warrant intensive evaluation. Assessment of efavirenz-associated toxicity was limited to subjective assessment of neurocognitive symptoms at one month and six months following efavirenz initiation and may have not captured interval neurocognitive symptoms, or other adverse effects that may lead to self-discontinuation of efavirenz-based ART. In addition, the SEQ employed to assess efavirenz-associated neurocognitive toxicity in this study has been previously validated; however, the construct validity of this tool has not been established in African populations [21].

5 CONCLUSION

Older HIV+ people are at increased risk of loss to care after ART initiation and altered pharmacokinetics and unmeasured toxicity may increase this risk in older people with slow efavirenz metabolism genotypes. With efavirenz an integral component of first-line ART in resource-limited settings, understanding why slow efavirenz metabolism might cause loss to care in older adults will be critical for interventions to improve retention and allow providers to tailor HIV therapy in similar settings. Quantifying age-associated clinical outcomes is critical to maximize patient safety, adherence, and control of HIV in older people, a demographic that will continue to grow as people living with HIV are aging successfully.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Guideline On When To Start Antiretroviral Therapy And On Pre-exposure Prophylaxis For HIV. Geneva: World Health Organization; 2015 http://apps.who.int/iris/bitstream/10665/186275/1/9789241509565_eng.pdf?ua=1, accessed 25 August 2016
2. Munoz-Moreno JA, Fumaz CR, Ferrer MJ, et al. Neuropsychiatric Symptoms Associated with Efavirenz: Prevalence, Correlates and Management. A Neurobehavioral Review. AIDS Rev 2009; 11:103–109 [PubMed: 19529750]
3. Marzolini C, Telenti A, Decosterd LA, et al. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. AIDS. 2001; 15:71–75 [PubMed: 11192870]
4. Ward BA, Gorski JC, Jones DR, et al. The cytochrome P450 2B6 (CYP2B6) is the main catalyst of efavirenz primary and secondary metabolism: implication for HIV/AIDS therapy and utility of efavirenz as a substrate marker of CYP2B6 catalytic activity. J Pharmacol Exp Ther. 2003; 306:287–300 [PubMed: 12676886]
5. Klein K, Lang T, Saussele T, et al. Genetic variability of CYP2B6 in populations of African and Asian origin: allele frequencies, novel functional metabolizers, and possible implications for anti-HIV therapy with efavirenz. Pharmacogenet Genomics. 2005; 15:861–873 [PubMed: 16272958]
6. Sustiva (efavirenz) [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 10 2017 http://packageinserts.bms.com/pi/pi_sustiva.pdf, accessed 6 August 2018
7. Ogburn ET, Jones DR, Masters AR, et al. Efavirenz Primary and Secondary Metabolism In Vitro and In Vivo: Identification of Novel Metabolic Pathways and Cytochrome P450 2A6 as the Principal Catalyst of Efavirenz 7-Hydroxylation. Drug Metabolism and Disposition. 2010; 38(7): 1218–29 [PubMed: 20335270]
8. Rotger M, Colombo S, Furrer H, et al. Influence of CYP2B6 polymorphism on plasma and intracellular concentrations and toxicity of efavirenz and nevirapine in HIV-infected patients. Pharmacogenet Genomics 2005; 15(1):1–5 [PubMed: 15864119]
9. Gounden V, van Niekerk C, Syma T, et al. Presence of the CYP 2B6 516G>T polymorphism, increased plasma Efavirenz concentrations and early neuropsychiatric side effects in South Africa HIV-infected patients. AIDS Res Ther 2010; 7:32 [PubMed: 20723261]
10. Cummins NW, Neuhaus J, Chu H, et al. Investigation of Efavirenz Discontinuation in Multi-ethnic Populations of HIV-positive Individuals by Genetic Analysis. EBioMedicine 2015; 12:706–12
11. Nwogu JN, Ma Q, Babalola CP, et al. Pharmacokinetic, Pharmacogenetic, and Other Factors Influencing CNS Penetration of Antiretrovirals. AIDS Res Treat 2016; 2016:2587094 [PubMed: 27777797]
12. Wyen C, Hendra H, Vogel M, et al. Impact of CYP2B6 983T>C polymorphism on non-nucleoside reverse transcriptase inhibitor plasma concentrations in HIV infected patients. J Antimicrob Chemother 2008; 61(4):914–918 [PubMed: 18281305]
13. Ribaud HJ, Liu H, Schwab M, et al. Effect of CYP2B6, ABCB1, and CYP3A5 Polymorphisms on Efavirenz Pharmacokinetics and Treatment Response: An AIDS Clinical Trials Group Study. J Infect Dis 2010; 202(5):717–722 [PubMed: 20662624]
14. Mehlotra RK, Bockarie MJ, Zimmerman PA. CYP2B6 983T>C polymorphism is prevalent in West Africa but absent in Papua New Guinea: implications for HIV/AIDS treatment. Br J Clin Pharmacol 2007; 64(3):391–5 [PubMed: 17391322]
15. Schoen JC, Erlandson KM, Anderson PL. Clinical Pharmacokinetics of Antiretroviral Drugs in Older Persons. Expert Opin Drug Metab Toxicol. 2013; 9(5): 573–588 [PubMed: 23514375]

16. Pharmacokinetics Klotz U. and drug metabolism in the elderly. *Drug Metabol Rev* 2009; 41: 67–76
17. Moore AR, O’Keeffe ST. Drug-Induced Cognitive Impairment in the Elderly. *Drugs & Aging* 1999; 15(1): 15–28 [PubMed: 10459729]
18. von Moltke LL, Greenblatt DJ, Romach MK, et al. Cognitive toxicity of drugs used in the elderly. *Dialogues Clin Neurosci.* 2001; 3(3):181–90 [PubMed: 22034128]
19. Gross R, Bellamy SL, Ratshaa B, et al. CYP2B6 Genotypes and Early Efavirenz-based HIV Treatment Outcomes in Botswana. *AIDS.* 2017; 31(15):2107–2113 [PubMed: 28692529]
20. Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. *Clin Ther* 1999; 21(6):1074–90 [PubMed: 10440628]
21. Clifford DB, Evans S, Yang Y, Acosta EP, Goodkin K, Tashima K, et al. Impact of efavirenz on neuropsychological performance and symptoms in HIV-infected individuals. *Ann Intern Med* 2005, 143:714–721 [PubMed: 16287792]
22. Nogueras M, Navarro G, Anton E, et al. Epidemiological and clinical features, response to HAART, and survival in HIV-infected patients diagnosed at the age of 50 or more. *BMC Infect Dis.* 2006; 6:159 [PubMed: 17087819]
23. Sotaniemi EA, Arranto AJ, Pelkonen O, Pasanen M. Age and cytochrome P450-linked drug metabolism in humans: an analysis of 226 subjects with equal histopathologic conditions. *Clin Pharmacol Ther.* 1997; 61(3):331–9 [PubMed: 9091249]
24. Ryscavage P, Kelly S, Li JZ, et al. Significance and clinical management of persistent low-level viremia and very-low-level viremia in HIV-1-infected patients. *Antimicrob Agents Chemother* 2014; 58(7):3585–98 [PubMed: 24733471]
25. Botswana National HIV & AIDS Treatment Guidelines. Gabarone: Ministry of Health; 2012 https://aidsfree.usaid.gov/sites/default/files/tx_botswana_2012.pdf, accessed 8 August 2018
26. Joska JA, Westgarth-Taylor J, Hoare J, et al. Neuropsychological outcomes in adults commencing highly active anti-retroviral treatment in South Africa: a prospective study. *Br J Clin Pharmacol.* 2013; 75(4):997–1006 [PubMed: 22957905]
27. Beckham SW, Beyrer C, Luckow P, et al. Marked sex differences in all-cause mortality on antiretroviral therapy in low- and middle-income countries: a systematic review and meta-analysis. *J Int AIDS Soc.* 2016; 19(1):21106 [PubMed: 27834182]
28. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol.* 1986; 51(6): 1173–82 [PubMed: 3806354]
29. StataCorp. 2013 Stata Statistical Software: Release 13. College Station, TX: StataCorp LP
30. Vinikoor MJ, Joseph J, Mwale J, et al. Age at antiretroviral therapy initiation predicts immune recovery, death, and loss to follow-up among HIV-infected adults in urban Zambia. *AIDS Res Hum Retroviruses.* 2014; 30(10):949–55 [PubMed: 24998881]
31. Maskew M, Brennan AT, MacPhail AP, et al. Poorer ART outcomes with increasing age at a large public sector HIV clinic in Johannesburg, South Africa. *J Int Assoc Physicians AIDS Care (Chic).* 2012; 11(1):57–65 [PubMed: 21951728]
32. Mutevedzi PC, Lessells RJ, Rodger AJ, Newell M-L. Association of age with mortality and virological and immunological response to antiretroviral therapy in rural South African adults. *PLoS ONE* 2011; 6:e21795 [PubMed: 21747959]
33. Semeere AS, Lwanga I, Sempa J, et al. Mortality and Immunological Recovery Among Older Adults on Antiretroviral Therapy at a Large Urban HIV Clinic in Kampala, Uganda. *J Acquir Immune Defic Syndr* 2014; 67:382–9 [PubMed: 25171733]
34. Bakandaa C, Birungia J, Mwesigwa R, et al. Association of aging and survival in a large HIV-infected cohort on antiretroviral therapy. *AIDS* 2011; 25:701–5 [PubMed: 21160412]
35. Eduardo E, Lamb MR, Kandula S, et al. Characteristics and Outcomes among Older HIV-Positive Adults Enrolled in HIV Programs in Four Sub-Saharan African Countries. *PLoS ONE* 2014; 9(7): e103864 [PubMed: 25075743]
36. Cornell M, Johnson LF, Schomaker M, et al. Age in antiretroviral therapy programmes in South Africa: a retrospective, multicentre, observational cohort study. *Lancet HIV* 2015; 2:e368–75 [PubMed: 26423550]

37. Bisson GP, Gaolathe T, Gross R, et al. Overestimates of survival after HAART: implications for global scale-up efforts. *PLoS One*. 2008; 3(3):e1725 [PubMed: 18320045]
38. Ma Q, Vaida F, Wong J, et al. Long-term efavirenz use is associated with worse neurocognitive functioning in HIV-infected patients. *J Neurovirol* 2016; 22:170–178 [PubMed: 26407716]
39. Ciccarelli N, Fabbiani M, Di Giambenedetto S, et al. Efavirenz associated with cognitive disorders in otherwise asymptomatic HIV-infected patients. *Neurology* 2011; 76:1403–1409 [PubMed: 21502598]
40. Akinyemi JO, Ogunbosi BO, Fayemiwo AS, et al. Demographic and epidemiological characteristics of HIV opportunistic infections among older adults in Nigeria. *Afr Health Sci*. 2017; 17(2):315–321 [PubMed: 29062325]
41. Sani MU, Okeahialam BN. QTc interval prolongation in patients with HIV and AIDS. *J Natl Med Assoc*. 2005; 97(12):1657–61 [PubMed: 16396057]
42. Nachimuthu S, Assar MD, Schussler JM. Drug-induced QT interval prolongation: mechanisms and clinical management. *Ther Adv Drug Saf*. 2012; 3(5):241–253 [PubMed: 25083239]
43. Ogunmola OJ, Oladosu YO, Olamoyegun MA. QTc interval prolongation in HIV-negative versus HIV-positive subjects with or without antiretroviral drugs. *Ann Afr Med*. 2015; 14(4):169–76 [PubMed: 26470741]
44. Abdelhady AM, Shugg T, Thong N, et al. Efavirenz Inhibits the Human Ether-A-Go-Go Related Current (hERG) and Induces QT Interval Prolongation in CYP2B6*6*6 Allele Carriers. *J Cardiovasc Electrophysiol*. 2016; 27(10):1206–1213 [PubMed: 27333947]
45. Lopez JA, Harold JG, Rosenthal MC, et al. QT prolongation and torsades de pointes after administration of trimethoprim-sulfamethoxazole. *Am J Cardiol* 1987; 59:376–377 [PubMed: 3492908]
46. Thomford NE, Dzobo K, Chopera D, et al. Pharmacogenomics Implications of Using Herbal Medicinal Plants on African Populations in Health Transition. *Pharmaceuticals (Basel)*. 2015; 8(3):637–63 [PubMed: 26402689]
47. Hughes GD, Puoane TR, Clark BL, et al. Prevalence and predictors of traditional medicine utilization among persons living with AIDS (PLWA) on antiretroviral (ARV) and prophylaxis treatment in both rural and urban areas in South Africa. *Afr J Tradit Complement Altern Med*. 2012; 9(4):470–84 [PubMed: 23983383]
48. Mills E, Foster BC, van Heeswijk R, et al. Impact of African herbal medicines on antiretroviral metabolism. *AIDS*. 2005; 19(1):95–97 [PubMed: 15627040]
49. Fasinu PS, Gutmann H, Schiller H, et al. The potential of *Sutherlandia frutescens* for herb-drug interaction. *Drug Metab Dispos*. 2013; 41(2):488–97 [PubMed: 23209194]
50. Africa LD, Smith C. *Sutherlandia frutescens* may exacerbate HIV-associated neuroinflammation. *J Negat Results Biomed*. 2015; 14:14 [PubMed: 26187042]
51. O'Brien D, Spelman T, Greig J, et al. Risk factors for mortality during antiretroviral therapy in older populations in resource-limited settings. *J Int AIDS Soc*. 2016; 19(1):20665 [PubMed: 26782169]
52. Greig J, Esther C, Casas EC, O'Brien DP, et al. Association between older age and adverse outcomes on antiretroviral therapy: a cohort analysis of programme data from nine countries. *AIDS* 2012; 26 (Suppl 1):S31–S37 [PubMed: 22781173]
53. Pathai S, Gilbert C, Weiss HA, et al. Frailty in HIV-infected adults in South Africa. *J Acquir Immune Defic Syndr*. 2013; 62(1):43–51 [PubMed: 23018372]
54. Hontelez JA, de Vlas SJ, Baltussen R, et al. The impact of antiretroviral treatment on the age composition of the HIV epidemic in sub-Saharan Africa. *AIDS*. 2012; 26 Suppl 1:S19–30 [PubMed: 22781175]

Key points:

- Certain CYP2B6 genotypes are associated with slow efavirenz metabolism and these genotypes are very common in sub-Saharan Africa.
- People age 50 years and older comprise an increasing proportion of people living with HIV in sub-Saharan Africa and few studies have evaluated drug effects in this population.
- People age 50 and older are twice as likely to die or be lost to follow-up after start of efavirenz-based antiretroviral treatment, especially those older people with the slow efavirenz metabolism CYP2B6 genotypes.

Figure 1.

Boxplot of efavirenz concentration at Month 1 by CYP2B6 phenotype and age. Box is bounded by 25% percentile and 75% percentile with median value represented by horizontal line; whiskers extend to values 1.5x the interquartile range; isolated dots reflect outlier values. EFV: efavirenz.

Figure 2.

Odds of loss to care by age and CYP2B6 metabolism genotype. Whiskers reflect 95% confidence interval. * Chi-Square p-value for test of homogeneity of odds by age strata presented. ART: antiretroviral therapy.

Table 1.

Baseline Characteristics by Age

Characteristic	Age 21–49 years n=789	Age 50 years n=125	<i>p</i> ^a
Median age, years (IQR)	36 (32, 41)	54 (52, 57)	--
Male, n(%)	398 (50)	65 (52)	0.75
BMI 18.5 kg/m ² , n(%)	129 (16)	17 (14)	0.48
Active tuberculosis, n(%)	33 (4)	2 (6)	0.16
Depression ^b , n(%) ^b	115 (15)	20 (16)	0.83
Hazardous alcohol use ^c , n(%) ^c	343 (44)	35 (28)	<0.01
Median CD4 cells/mm ³ (IQR)	195 (110, 254.5)	194 (111, 242.8)	0.67
Median HIV-1 RNA copies/mm ³ (IQR)	4.9 (4.3, 5.4)	5.0 (4.2, 5.5)	0.34
CYP2B6 metabolism ^d , n(%) ^d			0.52
Extensive	179 (23)	29 (23)	
Intermediate	344 (43)	49 (39)	
Slow	164 (21)	25 (20)	
Genotype not defined	102 (13)	22 (18)	

Abbreviations: BMI: body mass index; CYP: cytochrome; IQR: interquartile range

^a Chi Square test for comparison of proportions and Student's T-test for comparison of means

^b Depression as defined by positive PHQ-9

^c Hazardous alcohol use past year defined as binge drinking or 7 drinks/week for women or 14 drinks/week for men

^d Extensive = CYP2B6 516GG+983TT; Intermediate = CYP2B6 516GT+983TT or 516GG+983CT; Slow = CYP2B6 516GT+983 CT or 516TT or 983CC

Table 2.

Unadjusted Odds Ratio of Outcomes by Age

Variable	Age 21–49 years n=789	Age 50 years n=125	OR (95% CI)
Composite Loss to Care	172 (22%)	44 (35%)	1.95 (1.30, 2.92)
Death	27 (3%)	11 (9%)	2.70 (1.31, 5.60)
Loss to Follow-up	145 (18%)	33 (26%)	1.72 (1.10, 2.68)
Virologic Failure^a	94 (15%)	9 (12%)	0.71 (0.34, 1.48)

^aVirologic failure defined as HIV RNA > 25 copies/mL (n=687)

Table 3.

Odds Ratio of Composite Failure Among Older Participants

Variable	Retained n = 81	Lost to Care n=44	Unadjusted OR (95% CI)	Adjusted OR ^a (95% CI)
Male, n (%)	40 (49)	25 (57)	1.35 (0.64, 2.82)	1.02 (0.40, 2.62)
BMI < 18.5 kg/m ^{2b} , n (%)	5 (6)	12 (27)	5.70 (1.86, 17.51)	8.03 (2.07, 31.12)
CD4 < 50 cells/mL ^b , n (%)	6 (7)	6 (14)	1.97 (0.60, 6.53)	1.31 (0.27, 6.27)
HIV RNA >5 log ₁₀ copies/mL ^b , n (%)	40 (51)	23 (52)	1.04 (0.50, 2.18)	--
Active tuberculosis, n (%)	2 (2)	0	--	--
Depression, n (%)	11 (14)	9 (20)	1.66 (0.63, 4.39)	--
Hazardous alcohol use, n (%)	21 (26)	14 (32)	1.33 (0.60, 2.98)	--
Month 1 SEQ Score, mean (SD)	2.6 (5.1)	2.6 (4.7)	1.00 (0.92, 1.10)	--
ART adherence 95%, n (%)	54 (68)	21 (48)	0.97 (0.41, 2.32)	--
CYP2B6 metabolism ^c , n (%)				
Extensive	23 (28)	6 (14)	0.59 (0.20, 1.75)	0.68 (0.21, 2.20)
Intermediate	34 (42)	15 (34)	ref	ref
Slow	11 (14)	14 (32)	2.88 (1.06, 7.81)	4.06 (1.38, 11.89)

Abbreviations: ART: antiretroviral therapy; BMI: body mass index; SEQ: symptom experience questionnaire

^a. Model adjusted for sex, BMI, baseline CD4 <50 cells/mL, and CYP2B6 metabolism genotype^b. Baseline assessment^c. Genotype not defined in 9 (20%) lost to care and 13 (16%) retained in care; inclusion of undefined genotypes did not significantly change parameter estimates.