

Efavirenz-metabolizing polymorphisms, viral suppression, and depressive symptoms in individuals initiating antiretroviral therapy in Uganda

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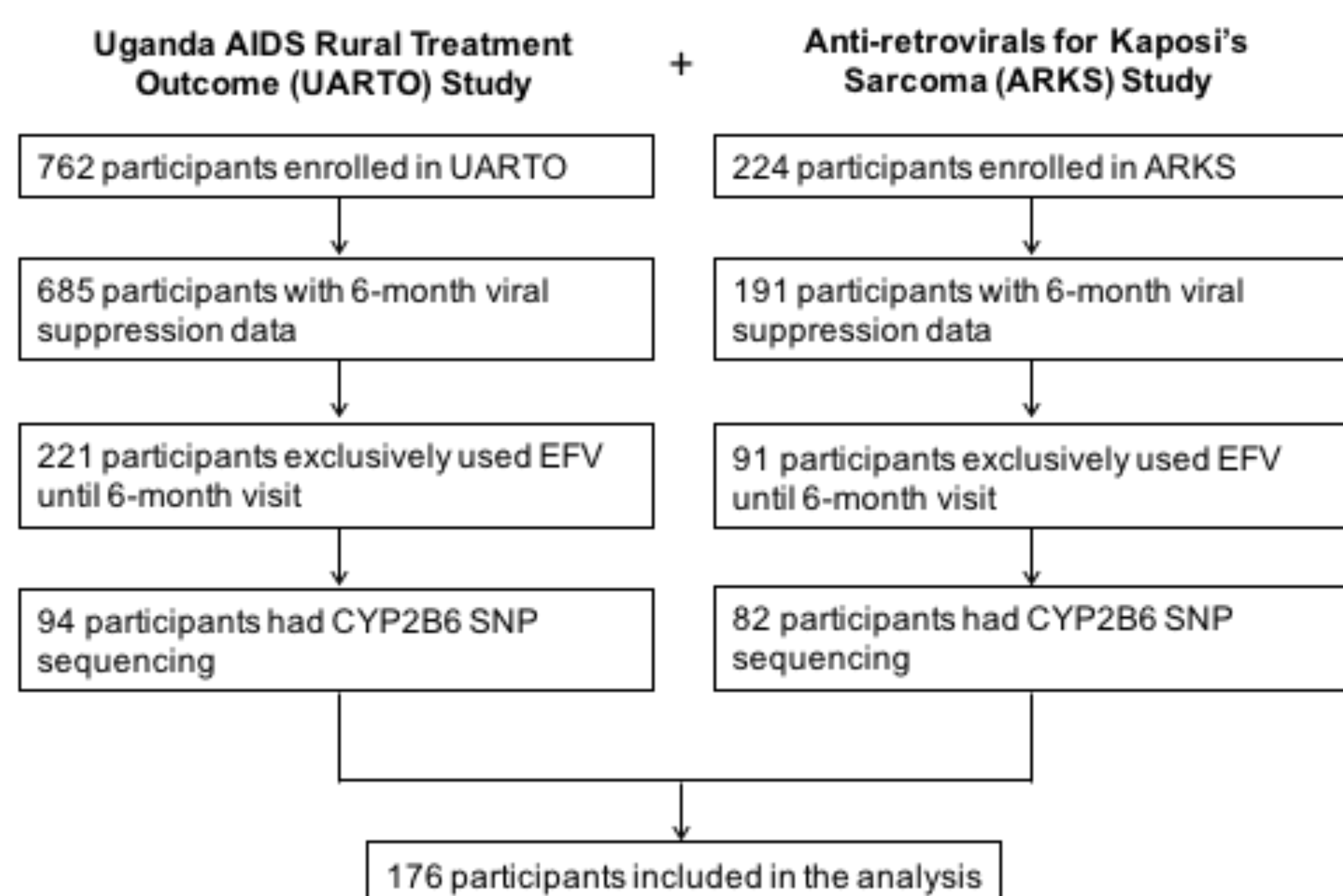
Introduction

- Three polymorphisms in *CYP2B6* (rs4803419, rs3745274, and rs28399499) define a 10-fold range in trough plasma efavirenz concentrations¹
- There is conflicting evidence on the effect of these polymorphisms on clinical outcomes in efavirenz users and limited data in sub-Saharan Africa.

Methods

- We pooled data from the UARTO and ARKS clinical cohorts including individuals in Ugandan initiating efavirenz (EFV)-containing antiretroviral therapy with genome array data, including three SNPs in *CYP2B6* (rs3745274, rs28399499, and rs4803419)
- Participants were grouped into pharmacokinetic strata (extensive, intermediate, and slow metabolizers) based on SNPs based on prior published pharmacogenomic relationships¹
- We fit regression models with viral suppression at six months and depressive symptom score (Hopkins Symptom Checklist) as the outcome of interest and metabolizer strata as the primary exposure of interest

Figure 1. Flow diagram for selection of final sample



Results

Table 1. Summary Characteristics for Study Cohort at Enrollment

| Variable | Metabolizer level | | | P |
|--|-------------------|---------------------|-------------------|------|
| | Fast (n=55) | Intermediate (n=90) | Slow (n=31) | |
| Age (years), median (IQR) | 36 (29, 41) | 35 (28, 43) | 35 (30, 44) | 0.61 |
| Female, n (%) | 26 (47%) | 48 (53%) | 13 (42%) | 0.51 |
| Married, n (%) | 40 (73%) | 53 (59%) | 22 (71%) | 0.18 |
| Secondary education, n (%) | 21 (38%) | 38 (42%) | 11 (35%) | 0.77 |
| Asset index, n (%) | | | | |
| 1 st quintile (most poor) | 7 (13%) | 11 (12%) | 4 (13%) | 0.99 |
| 2 nd quintile | 11 (20%) | 19 (21%) | 6 (19%) | |
| 3 rd quintile | 11 (20%) | 17 (19%) | 8 (26%) | |
| 4 th quintile | 11 (20%) | 20 (22%) | 4 (13%) | |
| 5 th quintile (least poor) | 15 (27%) | 23 (26%) | 9 (29%) | |
| Year of enrollment | | | | |
| 2005-2007 | 10 (18%) | 14 (16%) | 5 (16%) | 0.99 |
| 2008-2010 | 26 (47%) | 42 (47%) | 14 (45%) | |
| 2011-2013 | 19 (35%) | 34 (38%) | 12 (39%) | |
| Depressed, n (%) | 12 (22%) | 25 (28%) | 7 (23%) | 0.68 |
| Depressive symptom score, median (IQR) | 1.33 (1.07, 1.67) | 1.33 (1.13, 1.8) | 1.27 (1.13, 1.73) | 0.91 |
| Heavy drinking, n (%) | 11 (20%) | 19 (21%) | 3 (11%) | 0.45 |
| Physical health summary score, n (%) | | | | 0.11 |
| 1 st quartile (least healthy) | 21 (39%) | 26 (29%) | 7 (23%) | 0.78 |
| 2 nd quartile | 6 (11%) | 21 (23%) | 4 (13%) | |
| 3 rd quartile | 9 (17%) | 14 (16%) | 11 (35%) | |
| 4 th quartile (most healthy) | 10 (33%) | 29 (32%) | 9 (29%) | |
| CD4 count (cells/mm ³), median (IQR) | 199 (53, 336) | 168 (59, 290) | 150 (56, 326) | 0.78 |
| Viral load (log ₁₀ copies/mL), median (IQR) | 5.1 (4.6-5.4) | 5.1 (4.7, 5.6) | 5.3 (4.8, 5.8) | 0.23 |

Table 2. Allelic frequencies for the three *CYP2B6* single-nucleotide polymorphisms (SNP)

| <i>CYP2B6</i> SNP | Minor allelic frequency |
|----------------------|-------------------------|
| rs4803419 (15582C>T) | 6.0% |
| rs3745274 (516G>T) | 34.9% |
| rs28399499 (983T>C) | 7.7% |

Table 3. Poisson regression model for 6-month viral suppression

| Metabolizer strata | Unadjusted IRR (95% CI) | P | Adjusted IRR (95% CI) | P |
|--------------------|-------------------------|-------|-----------------------|-------|
| Fast | REF | -- | REF | -- |
| Intermediate | 1.02 (0.88, 1.18) | 0.759 | 1.00 (0.88, 1.15) | 0.947 |
| Slow | 1.04 (0.87, 1.25) | 0.658 | 1.05 (0.88, 1.26) | 0.576 |

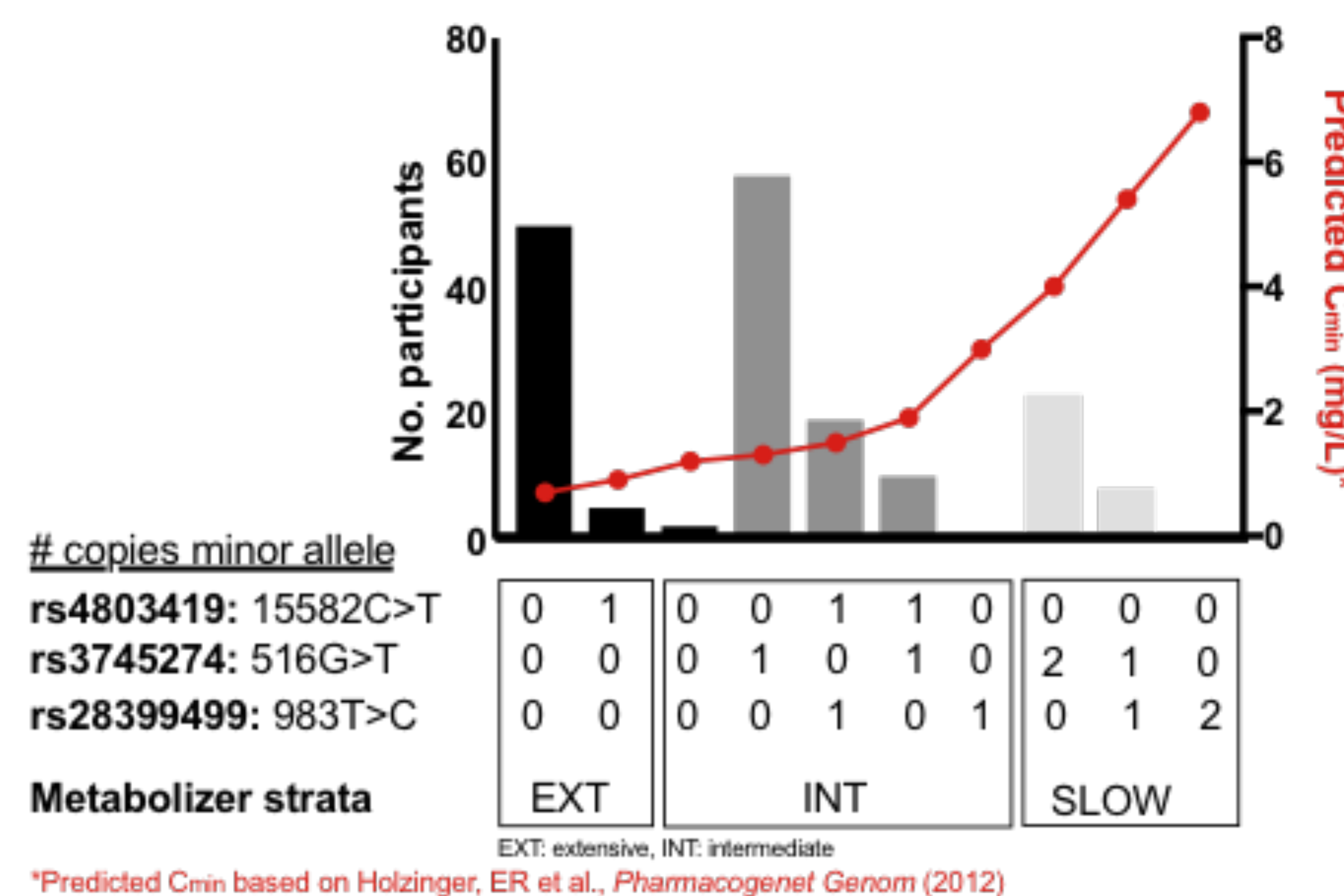
*Adjusted for covariates with $P < 0.25$ in unadjusted analyses: sex, secondary education, asset index, and year of enrollment

Table 4. Linear regression model for 6-month depressive symptom score

| Metabolizer strata | Unadjusted coeff. (95% CI) | P | Adjusted coeff. (95% CI) | P |
|--------------------|----------------------------|-------|--------------------------|-------|
| Fast | REF | -- | REF | -- |
| Intermediate | 0.10 (0.020, 0.19) | 0.015 | 0.10 (0.018, 0.18) | 0.016 |
| Slow | 0.088 (-0.020, 0.20) | 0.110 | 0.079 (-0.029, 0.19) | 0.150 |

*Adjusted for covariates that reached a significance of $P < 0.25$ in unadjusted analyses, which were the following: age, secondary education, asset index, enrollment depressive symptom score, viral suppression at six months, heavy drinking, and physical health summary score

Figure 2. Efavirenz-metabolism strata and genotypic correlates



Discussion

- We found no association between previously reported EFV metabolism –determining alleles and virologic suppression, but a slight increase in depression scores among slower metabolizers
- Further studies should investigate longer-term outcomes and the effect of de novo *CYP2B6* alleles in this sub-Saharan African population

References:

1. Holzinger ER, Grady B, Ritchie MD, Ribaldo HJ, Acosta EP, Morse GD, et al. Genome-wide association study of plasma efavirenz pharmacokinetics in AIDS Clinical Trials Group protocols implicates several *CYP2B6* variants. *Pharmacogenet Genomics*. 2012;22(12):858–67

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