Risk of Suicidal Behavior with Use of Efavirenz: Results from the START Trial

A. Arenas-Pinto[1], B. Grund[2], S. Sharma[3], E. Martinez[4], N. Cummins[5], J. Fox[6], K.L. Klingman[7], D. Sedlacek[8], S. Collins[9], P. Flynn[10], W. Chasanov[11], E. Kedem[12], C. Katlama[13], J. Sierra-Madero[14], C. Afonso[15], P. Brouwers[7], D.A. Cooper[16] for the INSIGHT START study group.

[1]Medical Research Council Clinical Trials Unit at UCL, University College London, UK
[2]University of Minnesota, School of Statistics, Minneapolis, USA
[3]University of Minnesota - Division of Biostatistics, Minneapolis, USA
[4]Hospital Clinic, Barcelona Spain
[5]Mayo Clinic, Rochester, MN, USA
[6]Guy's and St.Thomas' NHS Foundation Trust, London, UK
[7]Division of AIDS, National Institute of Allergy & Infectious Diseases, NIH, Bethesda, MD, USA
[8]University Hospital Plzen, Plzen, Czech Republic
[9]HIV i-Base, London, UK
[10]St. Jude Children's Research Hospital, Memphis, TN, US
[11]Cooper University Hospital, Camden, NJ, US
[12]Clinical Immunology Unit, Rambam Health Care Center, Haifa, Israel
[13]Hospitalier Pitié-Salpétrière, Paris, France
[14]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Tlalpan, México
[15]Hospital de Santa Maria, Lisbon, Portugal
[16]The Kirby Institute, University of New South Wales, Sydney, NSW, Australia

Correspondence:
Dr Alejandro Arenas-Pinto,
MRC-Clinical Trials Unit at UCL,
Institute of Clinical Trials and Methodology,
90 High Holborn, London WC1V 6XX
Telephone number: +44 (0)20 7670 4716.
Email: A.Arenas-Pinto@ucl.ac.uk

Short summary:
We compared the incidence of suicidal behavior events between participants with high CD4 count who were started on ART immediately or at CD4 cell count below 350 cell/mL. Participants with pre-existing psychiatric conditions and those started on efavirenz-based, but not other ART combinations, had increased risk of suicidal behavior.

Abstract

Background: Randomized trials have shown increased risk of suicidality associated with efavirenz (EFV). The START trial randomized treatment-naïve HIV-positive adults with high CD4 cell counts to immediate versus deferred antiretroviral therapy (ART).

Methods: The initial ART regimen was selected prior to randomization ("pre-specified"). We compared the incidence of suicidal and self-injurious behaviour ("suicidal behavior") between the immediate versus deferred ART groups using proportional hazards models, separately for those with EFV and other pre-specified regimens, by intention-to-treat, and after censoring participants in the deferred arm at ART initiation.

Results: Of 4684 participants, 271 (5.8%) had a prior psychiatric diagnosis. EFV was pre-specified for 3515 participants (75%); less often in those with psychiatric diagnoses (40%) than without (77%). While the overall intention-to-treat comparison showed no difference in suicidal behavior between arms (53 events, hazard ratio [HR]=1.07, p=0.81), subgroup analyses suggest that initiation of EFV, but not other ART, is associated with increased risk of suicidal behavior. In particular, when censoring follow-up at ART initiation in the deferred group, the immediate versus deferred HR among those who were pre-specified EFV was 3.31 (p=0.03) and the HR among those with other pre-specified ART was 1.04 (p=0.93) (p=0.07 for interaction). Risk was higher among those with prior psychiatric diagnoses, 12.5 and

9.3 times among those with pre-specified EFV and other ART, respectively, in the immediate group.

Conclusions: Participants who used EFV in the immediate ART group had increased risk of suicidal behavior compared to ART-naïve controls. Those with prior psychiatric diagnoses were at higher risk.

Funding: The START study is primarily funded by the National Institute of Allergy and Infectious Diseases of the NIH.

Efavirenz (EFV) has been a preferred option for first-line anti-retroviral therapy (ART) and is recommended in the WHO guidelines for all HIV-positive adults and adolescents (1), preferably as part of a fixed-dose combination (2). EFV is usually well tolerated but neuropsychiatric adverse-effects can result in treatment switching (3) or serious clinical complications. A meta-analysis of four trials in ART-naïve patients showed an increased risk of suicidality in those randomized to EFV-based ART compared to other regimens (4). In contrast, several observational studies found no associations of EFV with suicidality (5-7), possibly because, consistent with some prescribing guidelines (8), providers avoided EFV in patients who were at increased risk of suicidality resulting in a higher proportion of high-risk participants in non-EFV control groups which might bias observational studies.

The Strategic Timing of Antiretroviral Treatment (START) trial demonstrated clear clinical benefit of immediate ART by decreasing the risk of serious AIDS and serious non-AIDS conditions by 57% in HIV-positive adults with near-normal CD4 cell counts (9). In START, "suicidal behavior" was the second most frequent type of serious event reported and 75% of participants randomized to immediate ART initiation used EFV-based ART. We investigated whether initiating EFV increased risk of "suicidal behavior" more than initiating other ART, by utilizing START's randomized design to find appropriate control groups.

Methods

Study design and participants

The START trial has been described previously (9, 10). In brief, HIV-positive, ART-naïve individuals with high CD4 cell counts and no previous AIDS-defining conditions were randomized to initiating ART immediately versus deferring ART until the CD4 cell count dropped below 350 cells/μL or AIDS developed (Supplemental Appendix, Figure S1). Each participant's ART regimen was selected prior to randomization ("pre-specified") by site investigators from a table of recommended initial regimens (Supplemental Appendix, section 1). START enrolled between 2009 and 2013. This analysis uses data accrued through May 26, 2015, the day before the START study results were unblinded and participants in the deferred ART group were recommended starting ART (9).

Outcomes

The START study reported "serious events" that were not related to AIDS irrespective of exposure to ART. These included deaths, unscheduled hospitalizations and grade 4 Adverse Events according to the NIH Division of AIDS toxicity table (11) (Supplemental Appendix, Table S1). All serious events were coded using the *Medical Dictionary for Regulatory Activities* (MedDRA®), version 19.1, by staff blinded to treatment assignments and ART regimens. The primary endpoint for this analysis are events coded as the MedDRA high-level group term "suicidal and self-injurious behavior", referred to as "suicidal behavior".

Baseline Covariates

Age, gender, HIV risk group, prior psychiatric diagnosis (major depression, bipolar disorder, or psychotic disorder including schizophrenia), and current use of psychotropic drugs (benzodiazepines, antidepressants, antipsychotic drugs [neuroleptics], other drugs for bipolar mood disorders, methadone, other prescribed opiates) were obtained by chart abstraction or participant self-report. History of recreational drug use (amphetamines, methamphetamines/ecstasy, cocaine, ketamine, opiates) and heavy alcohol consumption within the past month were estimated from a self-administered questionnaire (Supplemental Appendix, section 2).

Statistical analysis

Our primary goal was to assess whether use of EFV-based ART regimens increased the risk of suicidal behavior, compared with no ART use, or with other ART. To investigate whether participants who were pre-specified EFV prior to randomization had the same *a-priori* risk of suicidal behavior as those with other ART, we considered the follow-up in the deferred ART group accrued prior to ART initiation, and compared the two subgroups for the incidence of suicidal behavior using Kaplan-Meier estimates and a log-rank test (Figure 1). A direct comparison of participants who used EFV versus those who used other ART would be confounded by the differences in *a-priori risk*. To avoid such bias, we used a series of intention-to-treat comparisons between the randomized immediate and deferred ART groups to assess the effect of EFV use (in the immediate ART group) versus an appropriate control group. First, we compared the incidence of suicidal behavior in the immediate versus

the deferred ART groups using Cox proportional hazards models, overall, and separately within the two subgroups of participants by pre-specified ART type (EFV-based, and other ART) (Figure 2). These treatment comparisons are protected by randomization, because the subgroups were defined before randomization. Because most participants in the immediate group started their pre-specified regimen (Figure 3), the intention-to-treat comparisons within the two subgroups are an approximate comparison of immediate EFV (or other ART) use versus deferring EFV (or other ART). In the second analysis, we restricted follow-up to year 1, since only few participants in the deferred group initiated ART in the first year (Figure 3). This analysis provides a better approximation of comparing EFV (or other ART) use to no ART while maintaining the protection by randomization. In the third analysis, in order to compare EFV (or other ART) use directly to no ART, we censored follow-up in the deferred group at ART initiation; in the immediate ART group, we started follow-up at ART initiation. Consequently, in the "pre-specified EFV" (other ART) subgroup, all participants in the immediate ART group initiated EFV (other ART) at time 0, and were compared to similar participants in the deferred group without ART. In the "pre-specified other ART" subgroup, we also censored follow-up at any EFV initiation in the immediate group. For this third analysis, which is not protected by randomization, we provided Kaplan-Meier estimates of the cumulative proportions of participants with suicidal behavior. The three analyses were repeated for participants with or without prior psychiatric diagnoses, because the rates of suicidal behavior were higher among those participants.

In all three analyses, we compared the hazard ratios (immediate versus deferred ART) across the two subgroups (pre-specified EFV or other ART) by including the interaction between the treatment group and subgroup indicators in expanded Cox proportional hazards models. To estimate the effect of EFV compared with other ART, we calculated the corresponding ratio of hazard ratios (immediate versus deferred ART) for the "pre-specified EFV" subgroup over the "pre-specified other ART" subgroup (Figure 2).

Event rates were estimated without adjustments for baseline characteristics. However, proportional hazards models comparing immediate versus deferred ART were stratified by history of psychiatric diagnoses. We compared baseline characteristics between participants who were pre-specified EFV versus other ART using Kruskal-Wallis tests for medians and chi-squared tests for proportions. We described ART use through follow-up by plotting the proportion of participants using any EFV, other ART, and no ART in one-month intervals, and by calculating the percentage of total follow-up time during which EFV, other ART, and no ART was used.

To identify predictors for suicidal behavior with EFV use, we restricted the analyses to participants in the immediate ART group who were pre-specified and started EFV, and estimated associations in Cox proportional hazards models. Initially, we included baseline variables (age, sex, HIV risk group, race/ethnicity, geographic region [high vs low-middle income], prior psychiatric diagnoses, psychotropic drug treatment, recreational drug use, heavy alcohol use) and a time-updated indicator variable for

EFV use. In the final model, we retained age, sex, HIV risk group, and the time-updated EFV indicator, in addition to those baseline factors that were independently associated with the risk of suicidal behavior in the initial, model. Using predictors with $p<0.10$ in the final model for EFV, we repeated the analyses for participants pre-specified other ART. For the strongest predictor (prior psychiatric diagnoses), we tested whether associations with suicidal behavior differed by pre-specified ART type in the immediate ART group by testing for an interaction between ART type and predictor.

Statistical analyses were performed using SAS versions 9.3 and 9.4 (SAS Institute, Cary, NC) and R version 3 (12). All tests are 2-sided; p-values ≤ 0.05 denote statistical significance.

Results

Baseline Characteristics

The START study enrolled 4684 participants at 215 sites in 35 countries. Baseline characteristics were described previously (9, 13). The "pre-specified" ART regimen included EFV in 3515 (75%) participants. Table 1 shows the baseline characteristics by type of pre-specified ART. Participants with pre-specified EFV less frequently lived in high-income countries (34% versus 81%), were less likely to be current smokers (29% versus 42%), and less likely to have used recreational drugs (24% versus 38%). Within the two subgroups, the immediate and deferred treatment

groups were well-balanced for baseline characteristics (Supplemental Appendix, Table S2).

Pre-existing psychiatric diagnoses were less common in those with pre-specified EFV compared to other ART (3.1% versus 13.9%), as was use of psychotropic medication (5.2% versus 16.8%) (Table 1). The prevalence of psychiatric conditions at baseline was higher in high-income regions (U.S.A., Europe and Australia) compared to low-middle income regions (Latin America, Africa and Asia) (11% and 1.4%, respectively).

ART use through follow-up

Figure 3A shows the use of EFV and other ART over time in the immediate and deferred ART groups, separately for participants with pre-specified EFV and other ART. Among those pre-specified EFV in the immediate ART group, 94% were using ART by month 4 and 82% were on EFV (Figure 3A, upper-left panel); in the deferred arm, median time to ART initiation was 3.2 years, 46% ever initiated ART, and 31% initiated EFV (upper-right panel). Among those with other ART pre-specified, ART use in both treatment groups was slightly higher, and a few participants also used EFV (Figure 3A, lower panels).

Figure 3B shows cumulative ART use as proportion of follow-up time accrued. Among those with EFV pre-specified, ART was used for 94% of follow-up time in the immediate group versus 26% in the deferred group, and EFV was used for 76% and 15%, respectively. Among those with other ART pre-specified, ART was used for 95%

and 35% of time in the immediate and deferred groups, respectively. EFV was used for 6% and 4% of time, respectively.

Suicidal behavior

Suicidal behavior was reported for 28 participants in the immediate ART group and 25 in the deferred group over a mean follow-up of 3.2 years, rates of 0.39 and 0.34 per 100 person-years (PY), respectively. The estimated HR (immediate versus deferred group) was 1.07 (95% CI: 0.6 to 1.8); there was no evidence for a treatment difference (p=0.81). Among those with EFV pre-specified, 19 participants in the immediate ART group reported suicidal behavior versus 12 in the deferred group, rates of 0.35 and 0.22 per 100 PY, respectively, (HR=1.38; 95% CI: 0.7 to 2.9) (Table 2). Among those with other ART pre-specified, 9 (rate 0.50 per 100 PY) and 13 participants (rate 0.69 per 100 PY) had suicidal behavior, respectively (HR=0.74; 95% CI: 0.3 to 1.7). The ratio between the HRs, comparing the pre-specified EFV subgroup versus the other ART subgroup for "excess risk" of suicidal behavior in the immediate group, was not significant (HR ratio=1.86, p=0.24).

We repeated the analyses for the first year of follow-up only. Among those with EFV pre-specified, the HR was 3.74 (95% CI 0.8-17.5; p=0.09), compared with HR=1.02 among those with other ART pre-specified (Table 2). However, event numbers were small in this analysis, confidence intervals were large, and there was insufficient evidence for heterogeneity between the sub-groups (HR ratio = 3.67, p=0.15).

In the third analysis, we compared EFV (or other ART) use to no ART, by starting follow-up in the immediate group at ART initiation, and censoring follow-up in the deferred group at ART initiation. Among those with EFV pre-specified, 18 participants (0.36 per 100 PY) experienced suicidal behavior in the immediate group (one event occurred in a participant who was excluded in this analysis because never used EFV), compared with 4 (0.10 per 100 PY) in the deferred group (HR=3.31; 95% CI: 1.1 to 9.9; p=0.03). Among those with other ART pre-specified, rates in both treatment groups were higher (0.56 and 0.66 per 100 PY), but the hazard ratio was 1.04 (95% CI: 0.4 to 2.7, p=0.93). The excess risk of suicidal behavior in the immediate ART group versus no ART was 3.18-fold higher among those with EFV pre-specified compared with the other ART subgroup, but there was insufficient evidence for heterogeneity between subgroups (p=0.07) (Table 2). For the last comparison, Kaplan-Meier estimates for the cumulative proportion of participants with suicidal behavior are shown in Figure 4.

Of the 53 “suicidal behavior” events, 3 were completed suicide, all in the deferred ART group and after ART initiation. Two of these participants had pre-existing depression and anxiety/depression and were treated for these. Both were on Truvada plus darunavir/ritonavir. The third participant had a history of alcohol abuse, and started EFV-based ART 18 months before the suicide. Table 3 shows the components of “suicidal behavior” by MedDRA® Preferred Term, for each of the comparisons in table 2.

The incidence of suicidal behavior was substantially higher among the 371 participants with prior psychiatric diagnosis; among those pre-specified other ART, 8 of 162 participants with prior psychiatric diagnoses experienced an event (1.7 per 100 PY) compared with 14 of 1007 without diagnoses (0.5 per 100 PY) (p=0.003). Supplemental Tables S3 and S4 show the event rates and HRs from Table 2 for participants with and without prior psychiatric diagnoses, respectively. Among the 109 participants with prior psychiatric diagnoses who were pre-specified EFV, none experienced suicidal behavior in the deferred ART group, compared with 6 (2.7 per 100 PY) in the immediate group after starting EFV (Table S3).

Predictors of suicidal behavior

A prior psychiatric diagnosis was the strongest predictor of suicidal behavior among participants in the immediate group who started ART, both among those who were pre-specified EFV, HR=12.5 (95% CI: 4.7 to 33.6, p<0.001) (Table 4), and those pre-specified other ART, HR=9.3 (95% CI: 2.4 to 36.4, p=0.001) (Supplemental Table S5); there was no evidence for a difference by ART type (p=0.79 for interaction). Among those who were pre-specified EFV, heavy alcohol and recreational drug use were independently associated with increased risk (HR of 4.6 and 2.6, respectively), while the risk decreased with age (HR=0.51 per 10 years older). The time-updated indicator for EFV use was not associated with risk of suicidal behavior (HR=1.4, p=0.74); however, power for this variable was low because almost all participants started EFV shortly after randomization (Table 4). Median time from EFV start to suicidal behavior was 10.2 months.

Discussion

In START there was no overall difference between the immediate versus deferred ART groups in the incidence of suicidal behavior events. However, among participants whose pre-specified ART regimen contained EFV, those in the immediate arm who started EFV had higher risk of suicidal behavior (HR=3.31; 95%CI: 1.19.9; p=0.03) compared to those who were randomized to the deferred arm and were not yet using any ART. Conversely, among participants who were pre-specified other ART, there was no excess risk of suicidal behavior in the immediate ART group (HR=1.04). This is consistent with a post-hoc meta-analysis that combined data from four ART-naïve trials (4). In contrast, cohort analyses and data extracted from regulatory agencies databases have failed to observe any excess risk of suicidality associated with EFV (5-7). Observational studies comparing EFV use to other ART are unreliable, however, because EFV is often avoided for patients with elevated risk of suicidal behavior, resulting in higher *a-priori* risk of suicidal behavior in the other ART group. This higher *a-priori* risk was evident in the START study (Figure 1). We minimized bias by utilizing the randomized design of the study to identify control groups for EFV (or other ART) prior to randomization.

In the general population, patients with severe depression and other serious psychiatric conditions are at higher risk for suicidality (14-16). In our study, the strongest predictor of suicidal behavior in the immediate ART group was a pre-existing psychiatric diagnosis, both among those using EFV and those with other ART. Given the higher absolute risk of suicidal behavior among those with psychiatric

conditions, the association between EFV exposure and suicidal behavior supports the recommendation in national and regional guidelines to avoid prescribing EFV to patients with past or current psychiatric conditions (8, 17, 18). Recreational drugs use, including alcohol, was also independently associated with suicidal behavior, which is also consistent with findings in the general population and those with other chronic conditions, particularly at younger age (15, 19, 20).

In a recent systematic review and meta-analysis, a higher incidence of severe neuropsychiatric adverse events but not suicidality was observed in ART-naïve adults randomized to EFV-based ART compared to other regimens. However, there were no completed suicides in the meta-analysis studies and the overall rate of suicidal ideation was extremely low (0.6%), affecting their power to investigate differences between groups (21).

Screening for psychiatric conditions (mainly depression) before prescribing EFV could reduce the risk of suicidality. However, screening may not be feasible or affordable, particularly in low-middle income countries where EFV continues to be frequently used in first-line ART. The Encore1 Trial reported a lower rate of EFV-related adverse events in patients treated with reduced compared to standard doses (22), suggesting that lower doses of EFV may provide a better safety profile.

The main strengths of our study are the use of START's randomized design, and the standardized reporting of serious suicidal behavior events. Our study had several limitations. First, this is a post-hoc analysis of a trial in which EFV exposure was not

the randomized intervention. However, by comparing the immediate versus deferred treatment groups within subgroups by pre-specified ART type, we estimated the effect of EFV (and other ART) versus randomized control groups, thus minimizing selection bias. Second, not all participants in the immediate group started their pre-specified regimen, and some discontinued pre-specified EFV. Adherence overall was high, however (Figure 3). Third, participants in the deferred group gradually started ART; while we censored follow-up at ART start in the third analysis, this censoring compromises the protection by randomization. Fourth, NRTIs differed between the EFV and other ART groups. Finally, the number of events was low, which limited the power; therefore, results need to be interpreted with caution.

In conclusion, in START, ART-naïve participants using EFV in the immediate ART group had an increased risk of suicidal behavior compared to ART naïve controls. Pre-existing psychiatric conditions were the strongest predictor of suicidal behavior. Therefore, screening for major psychiatric conditions before EFV initiation would be advisable.

Role of the funding source

The funder had a role in study design and interpretation of data and the writing of the report through the membership of KLK and PB in the Writing Committee. The funder had no role in the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Acknowledgments

We gratefully acknowledge the commitment of the participants and investigators in the START study, without whom this analysis would not have been possible. Investigators in the START Study Group were listed previously (9).

The START study was funded by the National Institute of Allergy and Infectious Diseases (UM1-AI068641 and UM1-AI120197), National Institutes of Health Clinical Center, National Cancer Institute, National Heart, Lung, and Blood Institute, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institute of Mental Health, National Institute of Neurological Disorders and Stroke, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (France), National Health and Medical Research Council (Australia), National Research Foundation (Denmark), Bundes ministerium für Bildung und Forschung (Germany), European AIDS Treatment Network, Medical Research Council (United Kingdom), National Institute for Health Research, National Health Service (United Kingdom), and University of Minnesota. Antiretroviral drugs were donated to the central drug repository by AbbVie, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmith-Kline/ViiV Healthcare, Janssen Scientific Affairs, and Merck.

Authors' contributions

Conception and design: AAP, NC, EM, DAC, BG, SS. Analysis and interpretation of the data: BG, SS. Drafting of the article: AAP, BG, SS. Provision of study materials or patients: PMF, WMC, CK, JF, VO, CA, DS, JSM, EK. Collection and assembly of data:

PMF, WMC, CK, JF, VO, CA, DS, JSM, EK. Critical revision of the article for important intellectual content: SC, NC, PB, KLK, EM, DAC. Final approval of the article: All coauthors.

Potential conflicts of interest. AAP has received grants from ViiV Healthcare, Janssen Cilag, and Pfizer, outside the submitted work. AAP, BG and SS (or the institutions where they work) have received grants from NIH, during the conduct of the study. EM has received grants from Merck and Janssen outside the submitted work. PMF has received personal fees from Merck outside the submitted work. CK has received consultancy fees and/or travel grants outside the submitted work. JSM has received grants from Fundación IBIS/CICAL, during the conduct of the study and grants from Pfizer, Stendahl, Gilead, Abbvie, BMS, and GSK, outside the submitted work. CA has received a grant from University of Minnesota during the conduct of the study. PB is an employee of the US Department of Health and Human Services, National Institutes of Mental Health. NC, JF, KLK,DS, SC, WC, EK and DAC have nothing to disclose.

References

1. Organization WH. Consolidated Guidelines on the use of Antiretroviral Drugs for Treating and Preventing HIV Infection. Recommendations for a Public Health Approach. June 2016 ed. Layout L'IV Com Sàrl, Villars-sous-Yens, Switzerland.: WHO Press; 2016. p. 480.
2. Nelson LJ, Beusenberg M, Habiyambere V, Shaffer N, Vitoria MA, Montero RG, et al. Adoption of national recommendations related to use of antiretroviral therapy before and shortly following the launch of the 2013 WHO consolidated guidelines. AIDS. 2014;28 Suppl 2:S217-24.
3. Scourfield A, Zheng J, Chinthapalli S, Waters L, Martin T, Mandalia S, et al. Discontinuation of Atripla as first-line therapy in HIV-1 infected individuals. AIDS. 2012;26(11):1399-401.

4. Mollan KR, Smurzynski M, Eron JJ, Daar ES, Campbell TB, Sax PE, et al. Association between efavirenz as initial therapy for HIV-1 infection and increased risk for suicidal ideation or attempted or completed suicide: an analysis of trial data. Ann Intern Med. 2014;161(1):1-10.
5. Nkhoma ET, Coumbis J, Farr AM, Johnston SS, Chu BC, Rosenblatt LC, et al. No Evidence of an Association Between Efavirenz Exposure and Suicidality Among HIV Patients Initiating Antiretroviral Therapy in a Retrospective Cohort Study of Real World Data. Medicine (Baltimore). 2016;95(3):e2480.
6. Napoli AA, Wood JJ, Coumbis JJ, Soitkar AM, Seekins DW, Tilson HH. No evident association between efavirenz use and suicidality was identified from a disproportionality analysis using the FAERS database. J Int AIDS Soc. 2014;17:19214.
7. Smith C, Ryom L, Monforte A, Reiss P, Mocroft A, El-Sadr W, et al. Lack of association between use of efavirenz and death from suicide: evidence from the D:A:D study. J Int AIDS Soc. 2014;17(4 Suppl 3):19512.
8. Waters L AN, Angus B, Boffito M, Bower M, Churchill D, Dunn D, Edwards S, Emerson C, Fidler S, Fisher M, Horne R, Khoo S, Leen C, Mackie N, Marshall N, Monteiro F, Nelson M, Orkin C, Palfreeman A, Pett S, Phillips A,, Post F PA, Reeves I, Sabin C, Trevelion R, Walsh J, Wilkins E, Williams I, Winston A. BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015 (2016 interim update). In: (BHIVA) BHA, editor. London. UK: BHIVA; 2016.
9. Group ISS, Lundgren JD, Babiker AG, Gordin F, Emery S, Grund B, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N Engl J Med. 2015;373(9):795-807.
10. Group ISToATS, Lundgren J, Babiker A, Gordin F, Emery S, Fatkenheuer G, et al. Why START? Reflections that led to the conduct of this large long-term strategic HIV trial. HIV Med. 2015;16 Suppl 1:1-9.
11. Department of Health and Human Services NIoH, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS table for grading the severity of adult and pediatric adverse events, version 1.0. In: National Institutes of Health NIoAaID, Division of AIDS., editor. 2014.
12. Group ES, Carey D, Puls R, Amin J, Losso M, Phanupak P, et al. Efficacy and safety of efavirenz 400 mg daily versus 600 mg daily: 96-week data from the randomised, double-blind, placebo-controlled, non-inferiority ENCORE1 study. Lancet Infect Dis. 2015;15(7):793-802.
13. Sharma S, Babiker AG, Emery S, Gordin FM, Lundgren JD, Neaton JN, et al. Demographic and HIV-specific characteristics of participants enrolled in the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial. HIV Med. 2015;16 Suppl 1:30-6.
14. Katon WJ. Epidemiology and treatment of depression in patients with chronic medical illness. Dialogues Clin Neurosci. 2011;13(1):7-23.
15. Singhal A, Ross J, Seminog O, Hawton K, Goldacre MJ. Risk of self-harm and suicide in people with specific psychiatric and physical disorders: comparisons between disorders using English national record linkage. J R Soc Med. 2014;107(5):194-204.

16. Cho SE, Na KS, Cho SJ, Im JS, Kang SG. Geographical and temporal variations in the prevalence of mental disorders in suicide: Systematic review and meta-analysis. J Affect Disord. 2016;190:704-13.
17. Africa DoHRoS. National Consolidated Guidelines for the Prevention of Mother-to-Child transmission of HIV and the management of HIV in Children, Adolescents and Adults. In: Health Do, editor. Pretoria, 0001, South Africa: Department of Health, Republic of South Africa; 2015. p. 136.
18. (EACS) EACS. EACS Guidelines. In: (EACS) EACS, editor.: European AIDS Clinical Society (EACS); 2016.
19. McGirr A, Renaud J, Bureau A, Seguin M, Lesage A, Turecki G. Impulsive-aggressive behaviours and completed suicide across the life cycle: a predisposition for younger age of suicide. Psychol Med. 2008;38(3):407-17.
20. Dumais A, Lesage AD, Alda M, Rouleau G, Dumont M, Chawky N, et al. Risk factors for suicide completion in major depression: a case-control study of impulsive and aggressive behaviors in men. Am J Psychiatry. 2005;162(11):2116-24.
21. Ford N, Shubber Z, Pozniak A, Vitoria M, Doherty M, Kirby C, et al. Comparative Safety and Neuropsychiatric Adverse Events Associated With Efavirenz Use in First-Line Antiretroviral Therapy: A Systematic Review and Meta-Analysis of Randomized Trials. J Acquir Immune Defic Syndr. 2015;69(4):422-9.
22. Group ES, Puls R, Amin J, Losso M, Phanuphak P, Nwizu C, et al. Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naive adults (ENCORE1): a randomised, double-blind, placebo-controlled, non-inferiority trial. Lancet. 2014;383(9927):1474-82.

Table 1. Baseline characteristics by pre-specified ART regimen.

	EFV + NRTIs (n=3515)	Other ART[a] + NRTIs (n=1169)	P-value[b]	Total (n=4684)
Age, median years [IQR]	36 [29, 43]	36 [29, 45]	0.010	36 [29, 44]
Female, n (%)	995 (28.3)	262 (22.4)	<0.001	1257 (26.8)
Race, n (%)				
Asian	349 (9.9)	39 (3.3)	<0.001	388 (8.3)
Black	1158 (32.9)	250 (21.4)	<0.001	1408 (30.1)
Latino/Hispanic	527 (15.0)	110 (9.4)	<0.001	637 (13.6)
White	1339 (38.1)	748 (64.0)	<0.001	2087 (44.6)
Other	142 (4.0)	22 (1.9)	<0.001	164 (3.5)
Geographic region, n (%)				
Africa	897 (25.5)	102 (8.7)	<0.001	999 (21.3)
Asia	326 (9.3)	30 (2.6)	<0.001	356 (7.6)
Australia	51 (1.5)	58 (5.0)	<0.001	109 (2.3)
Europe and Israel	871 (24.8)	668 (57.1)	<0.001	1539 (32.9)
South America	1086 (30.9)	88 (7.5)	<0.001	1174 (25.1)
United States	284 (8.1)	223 (19.1)	<0.001	507 (10.8)
Income region, n (%)				
High (US/Europe/Australia)	1206 (34.3)	949 (81.2)	<0.001	2155 (46.0)
Low-moderate (Latin America/Africa/Asia)	2309 (65.7)	220 (18.8)	<0.001	2529 (54.0)
Likely mode of HIV infection, n (%)				
Sexual contact with same sex	1831 (52.1)	756 (64.7)	<0.001	2587 (55.2)
Sexual contact with opposite sex	1466 (41.7)	322 (27.5)	<0.001	1788 (38.2)
Injection drug use	21 (0.6)	43 (3.7)	<0.001	64 (1.4)
Blood products/other/unknown	197 (5.6)	48 (4.1)	0.046	245 (5.2)
Time since HIV diagnosis, median years [IQR]	1.0 [0.3, 3.1]	1.1 [0.4, 3.0]	0.068	1.0 [0.4, 3.1]
CD4[c], median cells/μL [IQR]	651 [583, 768]	652 [585, 755]	0.753	651 [584, 765]
HIV RNA, median copies/mL [IQR]	12225 [2879, 41562]	14304 [3738, 47703]	0.022	12761 [3025, 43482]
Current smoker, n (%)	1012 (28.8)	487 (41.7)	<0.001	1499 (32.0)
Pre-specified ART regimen, n (%)				
EFV + NRTIs	3515 (100.0)	0 (0.0)	<0.001	3515 (75.0)
Other NNRTI not EFV + NRTIs	0 (0.0)	171 (14.6)	<0.001	171 (3.6)
PI + NRTIs	0 (0.0)	815 (69.7)	<0.001	815 (17.4)
INSTI + NRTIs	0 (0.0)	183 (15.7)	<0.001	183 (3.9)
Psychiatric diagnosis or current psychotropic drug treatment, n (%)	224 (6.4)	260 (22.2)	<0.001	484 (10.3)
Prior psychiatric diagnosis[d]	109 (3.1)	162 (13.9)	<0.001	271 (5.8)
Any psychotropic drug use	183 (5.2)	196 (16.8)	<0.001	379 (8.1)
Antidepressants	120 (3.4)	150 (12.8)	<0.001	270 (5.8)
Benzodiazepines	62 (1.8)	50 (4.3)	<0.001	112 (2.4)

Antipsychotic drugs (neuroleptics)	15 (0.4)	19 (1.6)	<0.001	34 (0.7)
Other drugs for bipolar mood disorder	5 (0.1)	13 (1.1)	<0.001	18 (0.4)
Methadone	1 (0.0)	8 (0.7)	<0.001	9 (0.2)
Other opiates	18 (0.5)	25 (2.1)	<0.001	43 (0.9)
Ever use of recreational drugs[e], n (%)	858 (24.4)	442 (37.8)	<0.001	1300 (27.8)
Heavy alcohol use, n (%)	155 (4.4)	45 (3.8)	0.41	200 (4.3)

[a] Ritonavir-boosted PI, INSTI, or NNRTI other than EFV.
[b] P-values are for comparisons between the EFV+NRTIs and Other ART + NRTIs groups. Medians were compared using Kruskall-Wallis tests, percents were compared using chi-squared tests.
[c] Average of two screening values
[d] Including major depression, bipolar disorder, psychotic disorder including schizophrenia. These diagnoses were not collected separately.
[e] Amphetamines and methamphetamines/ecstasy, cocaine, ketamine and opiates.

ART = antiretroviral therapy; EFV = efavirenz; INSTI = integrase strand transfer inhibitor; IQR = inter quartile range; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor.

Table 2. Suicidal and self-injurious behavior, by randomization arm and pre-specified ART groups; Cox proportional hazards models.

	N	Immediate ART		Deferred ART		HR[a]	95% CI	P	HR Ratio[b]	Int. P[c]
		No. of pts with events	Rate per 100 PY	No. of pts with events	Rate per 100 PY					
Intention to treat (ITT) analysis, mean follow-up 3 years										
EFV pre-specified	3515	19	0.35	12	0.22	1.38	(0.7, 2.9)	0.39	1.86	0.24
Other ART pre-specified	1169	9	0.50	13	0.69	0.74	(0.3, 1.7)	0.49		
ITT analysis, follow-up truncated at 1 year after randomization										
EFV pre-specified	3515	9	0.52	2	0.11	3.74	(0.8, 17.5)	0.09	3.67	0.15
Other ART pre-specified	1169	7	1.25	7	1.19	1.02	(0.4, 2.9)	0.96		
Censoring deferred arm participants at ART initiation										
EFV pre-specified[d]	3394	18	0.36	4	0.10	3.31	(1.1, 9.9)	0.03	3.18	0.07
Other ART pre-specified[e]	1137	9	0.56	8	0.66	1.04	(0.4, 2.7)	0.93		

[a] HR(Immediate/Deferred), estimated in Cox proportional hazards models, stratified by history of psychiatric diagnosis.
[b] Ratio of HRs (Immediate/Deferred) within the EFV pre-specified subgroup over the Other ART pre-specified subgroup.
[c] P-value for the interaction between indicators for treatment group and pre-specified ART regimen; compares HRs (Imm/Def) between subgroups by pre-specified ART.
[d] Of these events, 6 and 0, in the immediate vs deferred arms, respectively, occurred among 100 participants with prior psychiatric diagnoses. The immediate group excludes participants who did not start ART. Follow-up time starts at EFV start date. Of the 3515 participants with EFV in the pre-specified regimen, 117 in the immediate arm were excluded (32 never started ART, 85 never used EFV), and 4 in the deferred arm were excluded (3 started ART at randomization, 1 participant was lost to follow-up at randomization).
[e] Of these events, 5 and 2, in the immediate vs deferred arms respectively, occurred among 161 participants with prior psychiatric diagnoses. Of the 1169 participants without EFV in the pre-specified regimen, 32 were excluded (in the immediate group, 7 never started ART, and for 25, the first ART regimen contained EFV). The immediate group excludes participants who did not start ART. Follow-up time starts at ART start date and was censored at EFV start.

ART=antiretroviral therapy; CI=confidence interval; EFV=efavirenz, HR=hazard ratio; NRTI=nucleoside reverse transcriptase inhibitor.

Table 3. Number of participants with "suicidal and self-injurious behavior" included in each of the three analyses in Table 2, and the composition of these events by MedDRA Preferred Terms.

		Complete Follow-up, ITT Analysis		First Year, ITT Analysis		Deferred Arm Censored at ART Initiation[a]	
		Imm.	Def.	Imm.	Def.	Imm.	Def.
Suicidal Behavior Events							
All participants		28	25	16	9	27	12
EFV+NRTIs pre-specified		19	12	9	2	18	4
Other ART+NRTIs pre-specified		9	13	7	7	9	8
Breakdown of Suicidal Behavior by MedDRA Preferred Term							
All participants	Completed suicide	0	3	0	0	0	0
	Intentional self-injury	0	1	0	0	0	0
	Self-injurious ideation	0	1	0	1	0	1
	Suicidal ideation	10	6	4	1	10	3
	Suicide attempt	18	14	12	7	17	8
EFV+NRTIs pre-specified	Completed suicide	0	1	0	0	0	0
	Intentional self-injury	0	1	0	0	0	0
	Suicidal ideation	6	3	1	1	6	2
	Suicide attempt	13	7	8	1	12	2
Other+NRTIs pre-specified	Completed suicide	0	2	0	0	0	0
	Self-injurious ideation	0	1	0	1	0	1
	Suicidal ideation	4	3	3	0	4	1
	Suicide attempt	5	7	4	6	5	6

[a] In this analysis, follow-up in the immediate ART group is started at EFV (ART) initiation, which excludes participants who did not start EFV (ART) or had experienced suicidal behavior before initiating EFV (ART).

ART=antiretroviral therapy, EFV=efavirenz, NRTI=nucleoside reverse transcriptase inhibitor.

Table 4. Factors associated with suicidal and self-injurious behavior among participants in the immediate ART group who were pre-specified EFV+NRTIs, and who started ART.

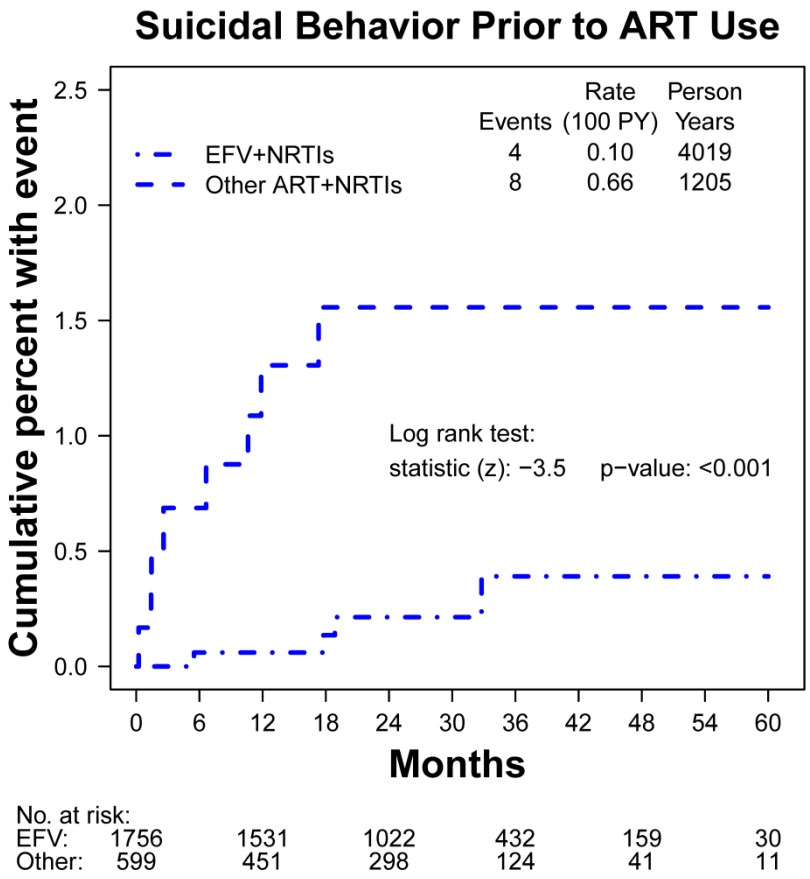
	Multivariate analysis[a]		
	HR	**95% CI**	**P-value**
Age (per 10 yrs older)	0.51	(0.29, 0.89)	0.018
Gender & risk group			
Female vs male	0.68	(0.19, 2.47)	0.55
MSM vs other male	0.49	(0.15, 1.59)	0.23
Prior psychiatric diagnosis[b]	12.49	(4.65, 33.59)	<0.001
Recreational drug use, ever	2.58	(0.96, 6.95)	0.06
Heavy alcohol use	4.62	(1.46, 14.61)	0.009
EFV started (time-updated)[c]	1.42	(0.18, 11.08)	0.74
No. of participants		***1723***	
No. of suicidal behavior events		***19***	

[a] HRs from one multivariate Cox proportional hazards regression model with all listed variables.
[b] Diagnosis of major depression, bipolar disorder, or psychotic disorder including schizophrenia
[c] Indicator variable, switches from 0 to 1 at the date of EFV start (if ever).

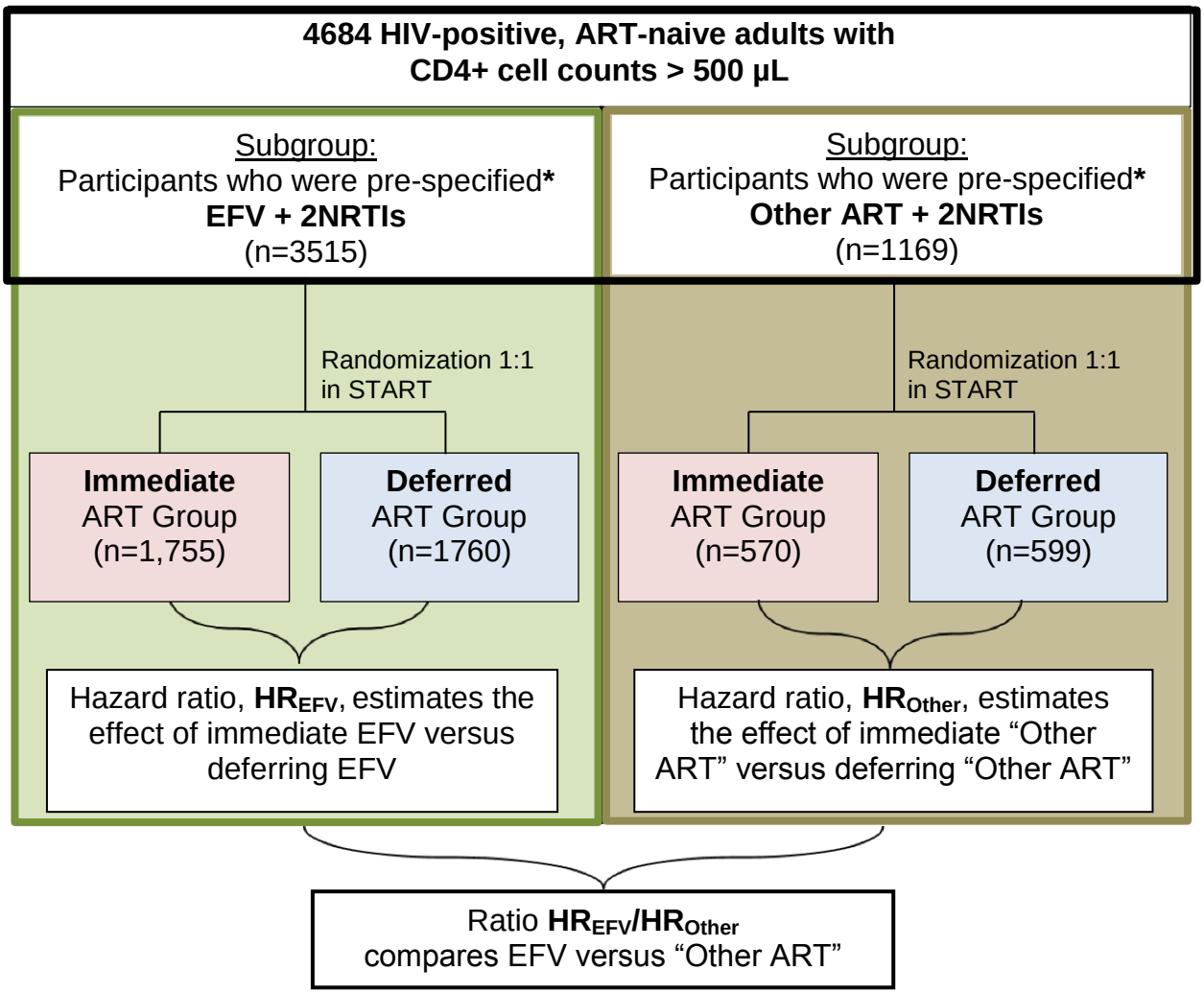
Number in group (number of events) for categorical variables: female=484 (3); MSM= 909 (12); other male=330 (4); prior psychiatric diagnosis= 70 (9); ever use of recreational drugs=409 (11); heavy alcohol use=76 (4).

ART=antiretroviral therapy; CI=confidence interval; EFV=efavirenz, HR=hazard ratio; MSM=men who have sex with men; NRTI=nucleoside reverse transcriptase inhibitor.

Figure 1. Kaplan-Meier estimates of the cumulative percent of participants with suicidal or self-injurious behavior in the deferred ART group prior to any ART use, within subgroups by pre-specified ART type (EFV versus other ART). Follow-up is censored at ART initiation. The difference between the curves (p<0.001) indicates that participants who were pre-specified EFV-containing regimens had a lower *a-priori* risk of suicidal behavior compared with those pre-specified other ART.



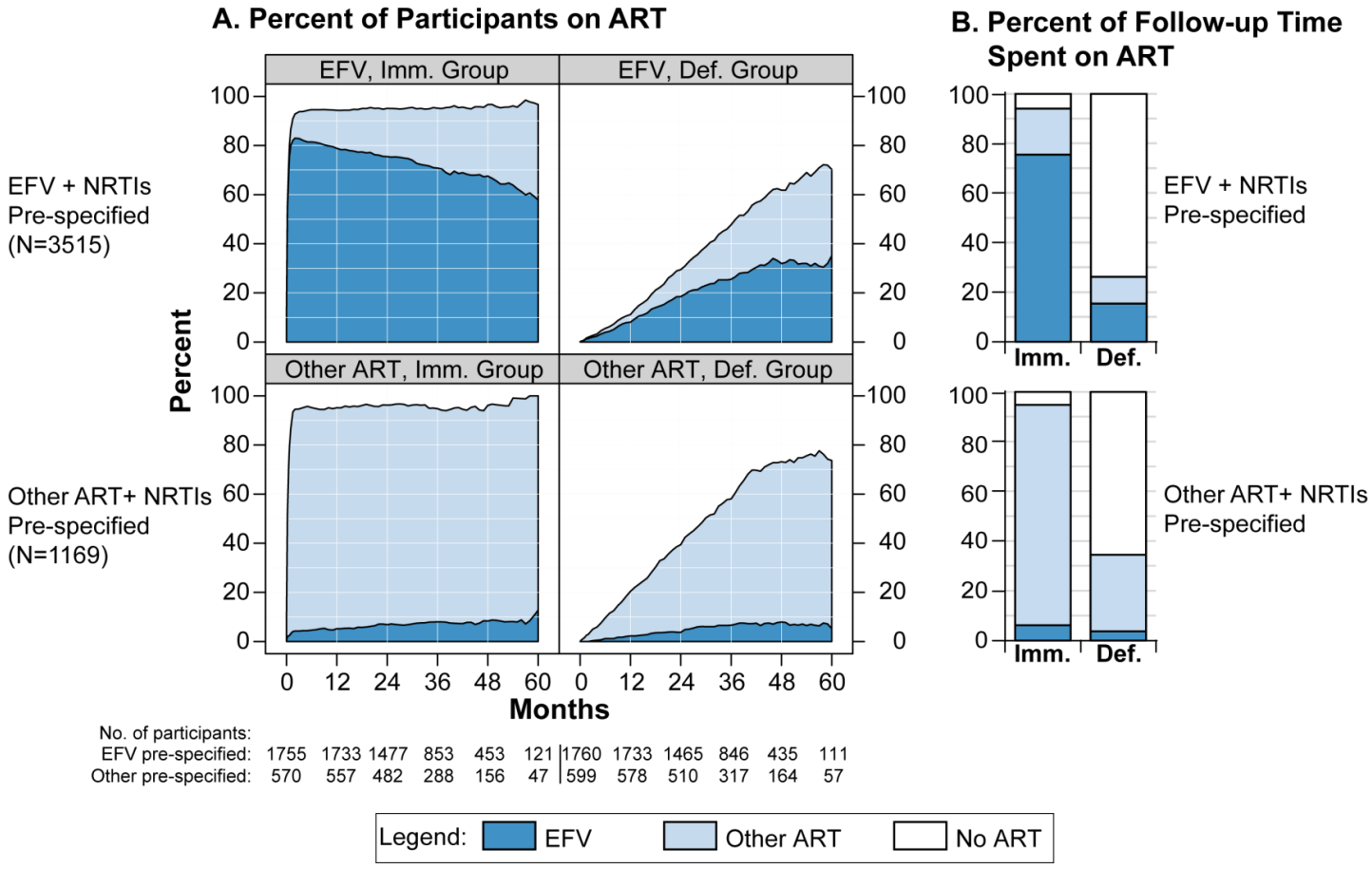
ART = antiretroviral therapy; EFV=efavirenz; NRTI = nucleoside reverse transcriptase inhibitor; PY = person years



***** ART regimens were pre-specified by the provider in consultation with participants and reported prior to randomization. ART was pre-specified prior to randomization to enable randomized comparisons of immediate versus deferred use of specific drugs, by restricting analyses to those who were pre-specified the drug(s).

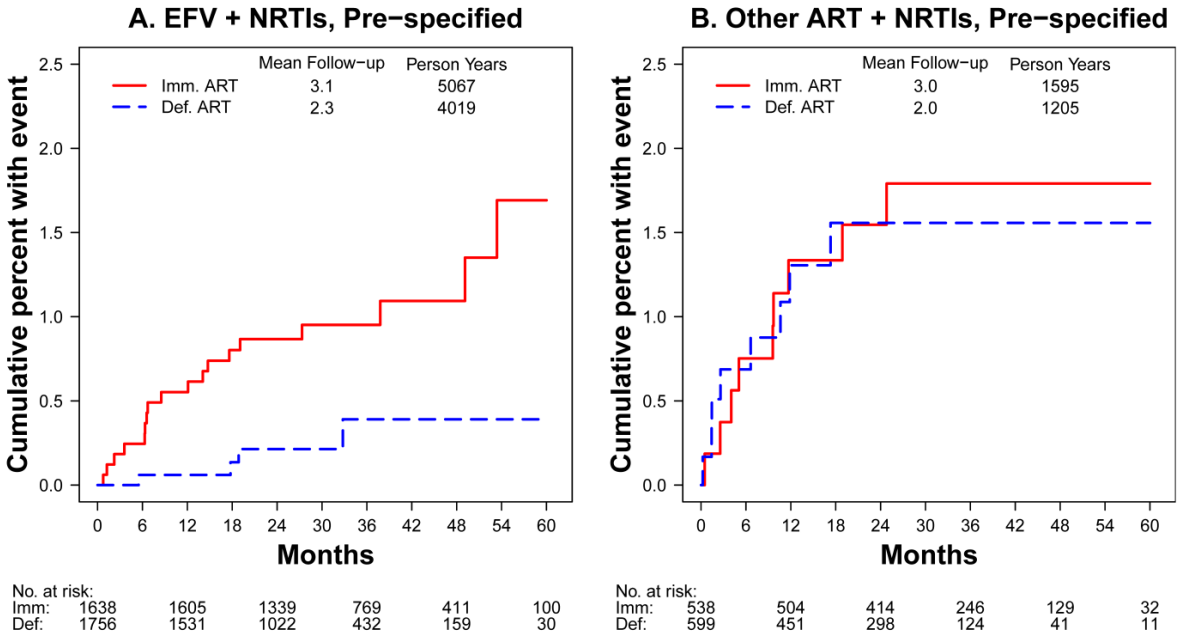
Study Design: The study is a post-hoc analysis of "**suicidal or self-injurious behavior**". The outcome consists of all events that were reported as "serious event" and were classified under the MedDRA® High-Level Group Term "suicidal and self-injurious behavior". In START, "serious events" were reported throughout follow-up, irrespective of ART use.

Figure 3. ART and EFV use in the immediate and deferred ART groups, within subgroups by pre-specified ART type. **(A)** Percent of participants using ART and EFV. **(B)** Percent of follow-up time during which ART and EFV were used.



ART = antiretroviral therapy; EFV=efavirenz; NRTI = nucleoside reverse transcriptase inhibitor

Figure 4. Kaplan-Meier estimates of the cumulative percent of participants with suicidal or self-injurious behavior, within subgroups by pre-specified ART type. In the deferred ART group, follow-up is censored at ART initiation. **(A)** Kaplan-Meier estimates for participants who were pre-specified EFV-containing ART regimens. In the immediate ART group, follow-up time is started at EFV initiation, excluding 116 (6.6%) participants who never initiated EFV. **(B)** Kaplan-Meier estimates for participants whose pre-specified regimen did not contain EFV. In the immediate group, follow-up time is started at ART initiation, excluding 32 participants who never initiated ART or whose first regimen contained EFV; for the 31 participants who started EFV, follow-up is censored at EFV start.



ART = antiretroviral therapy; EFV=efavirenz; NRTI = nucleoside reverse transcriptase inhibitor