Supplemental Appendix

to

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

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Section 1. Recommendations of Antiretroviral Drugs to be Used When Initiating Antiretroviral Treatment in START

Recommendations as of 26 May 2015:

Antiretroviral Components Required for the Initial Regimen in START
29 May 2014 [1]

To construct the initial antiretroviral regimen in START, select one component from Column A and one component from Column B		
Column A **NNRTI, PI or INSTI Options** **(alphabetical order)**	**+**	**Column B** **Dual-NRTI Options** [2] **(alphabetical order)**
NNRTI: or PI: or INSTI: efavirenz atazanavir + ritonavir (once daily) dolutegravir rilpivirine darunavir + ritonavir (once daily) elvitegravir + lopinavir/ritonavir (once or twice daily) cobicistat [3] raltegravir		NRTI: abacavir/lamivudine tenofovir/emtricitabine zidovudine/lamivudine [4]

1. Derived from Table 6 of the Department of Health and Human Services (DHHS) Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents (01 May 2014). Use of fixed-dose combinations of components in Columns A and B or of single formulations of NRTIs in Column B is acceptable except as noted in **3** below.
2. Lamivudine may substitute for emtricitabine or vice versa.
3. Only as part of the fixed-dose combination elvitegravir/cobicistat/emtricitabine/tenofovir (e.g., Stribild[TM] or other approved brand/generic), in individuals with creatinine clearance >70 mL/min
4. As of 01 May 2014, the US DHHS Guidelines no longer recommend zidovudine as part of antiretroviral therapy provided that other and safer alternatives are available. Zidovudine causes excess risk of anemia, neutropenia and lipodystrophy compared with tenofovir and abacavir. Conversely, abacavir is contraindicated in persons with tissue type HLA-B*5701; tenofovir may negatively impact bone physiology and cause renal impairment, and is generally not recommended in individuals with severely impaired kidney function.

Nevirapine (NNRTI) may not be used in the initial antiretroviral regimen in START because it is not recommended for women with a CD4+ cell count > 250 cells/mm^{3} or for men with a CD4+ cell count > 400 cells/mm^{3} due to increased risk of hepatic toxicity.

Not all of the antiretroviral agents listed above may be available from the START Central Drug Repository.

NRTI: nucleoside/nucleotide reverse transcriptase inhibitor   PI: protease inhibitor
NNRTI: non-nucleoside reverse transcriptase inhibitor   INSTI: integrase strand transfer inhibitor

The START study protocol required the use of an approved drug combination derived from the guidelines of the U.S. Department of Health and Human Services as the first antiretroviral treatment (ART) regimen. The table above shows the options for approved ART regimens as of 26 May 2015; the regimens evolved with the guidelines. The above table and a complete history of the approved combinations for the initial regimen in START was published in Section 3 of the Supplemental Appendix to *INSIGHT START Study Group, 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*.

The ART regimen was pre-specified and reported by the clinician **prior to randomization**.

Section 2. Alcohol and Recreational Drug Use

The baseline covariates "History of recreational drug use (amphetamines, methamphetamines/ecstasy, cocaine, ketamine, opiates)" and "heavy alcohol consumption within the past month" were estimated from a participant questionnaire on alcohol and recreational drug use, administered in the START study prior to randomization. Study staff was instructed to give the questionnaire to the participant and have it returned to the study staff in a closed envelope, to be sent to the data management center.

To assess alcohol consumption, the following questions from the questionnaire were used.

We define a drink of alcohol as a bottle, can, or glass of beer (one 12-ounce/355 mL); one glass of wine (4-ounce/118 mL); a mixed drink, or a shot of liquor:

2. How many days **per week**, on average, did you have a drink of alcohol during the **past month**?
    - 0 ☐ None
    - 1 ☐ Less than 1 day per week
    - 2 ☐ 1 to 3 days per week
    - 3 ☐ 4 to 7 days per week

3. When you drink alcohol, how many drinks do you usually have?
    - 0 ☐ None, I do not drink alcoholic beverages
    - 1 ☐ 1
    - 2 ☐ 2 to 4
    - 3 ☐ 5 to 7
    - 4 ☐ 8 or more

We calculated "**heavy alcohol use**" as follows:
> Women: 5 or more drinks on 1-7 days per week OR 2 or more drinks on 4-7 days per week.
> Men: 8 or more drinks on 1-7 days per week OR 5 or more drinks on 4-7 days per week.

These thresholds were chosen based on the definition of **low-risk drinking** by the U.S. National Institute of Alcohol Abuse and Alcoholism (NIAA):

> Women: no more than 3 drinks on any single day and no more than 7 drinks per week.
> Men: no more than 4 drinks on any single day and no more than 14 drinks per week.
> (From https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking, accessed on 12/8/2017).

With our thresholds, we estimated "heavy alcohol use" as a level of alcohol consumption that carries moderate or high risk for developing alcohol use disorder, using the available questionnaire data.

To assess recreational drug use, the following questions from the questionnaire were used.

4. Have you **ever** used any of the following recreational drugs or similar drugs?
 • speed (amphetamines)
 • crystal meth, crank, crystal, tina, ice (methamphetamines)
 • Ecstasy, X (MDMA)
 • powder or crack cocaine
 • Special K, Super K (ketamine)
 • heroin, smack, junk, black tar (opiates)

     0 ☐ No ⟶ **STOP. You have completed this questionnaire.**
     1 ☐ Yes ⟶ **Go to Question 5.**
     2 ☐ I do not want to answer ⟶ **STOP. You have completed this questionnaire.**

5. How many days **per week** on average, did you use any of those recreational drugs during the **past month**?
     0 ☐ None
     1 ☐ Less than 1 day per week
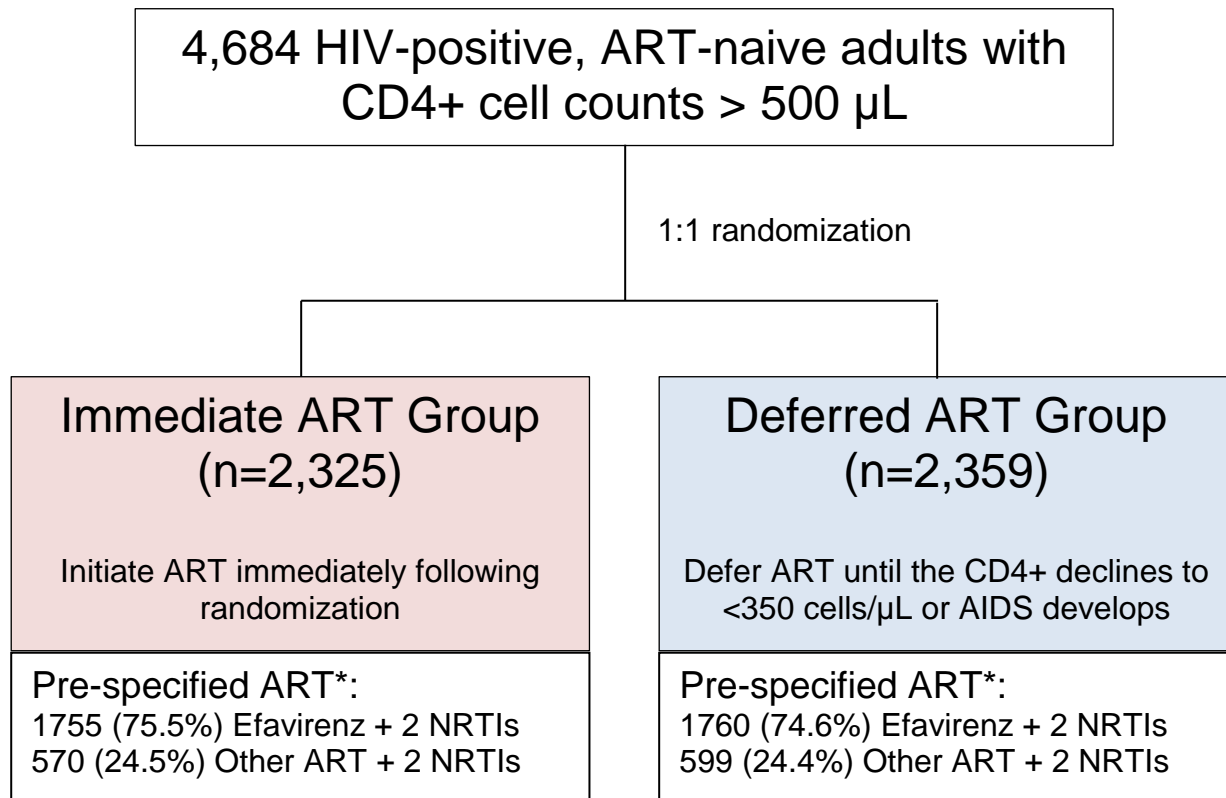   2 ☐ 1 to 3 days per week
     3 ☐ 4 to 7 days per week
     4 ☐ I do not want to answer

We calculated **"ever use of recreational drugs"** as follows:

    Answered "yes" or "I do not want to answer" on item 4 above OR
    indicated any recreational drug use during the past week on item 5, OR
    mode of HIV infection was "injection drug use".

Figure S1. Study design for the START study.

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┌─────────────────────────────────────────────────────┐
│        4,684 HIV-positive, ART-naive adults with      │
│              CD4+ cell counts > 500 µL                │
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1:1 randomization

Immediate ART Group (n=2,325)	Deferred ART Group (n=2,359)
Initiate ART immediately following randomization	Defer ART until the CD4+ declines to <350 cells/µL or AIDS develops
Pre-specified ART*: 1755 (75.5%) Efavirenz + 2 NRTIs 570 (24.5%) Other ART + 2 NRTIs	Pre-specified ART*: 1760 (74.6%) Efavirenz + 2 NRTIs 599 (24.4%) Other ART + 2 NRTIs

* 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).

Primary endpoint of START:
Serious AIDS, serious non-AIDS conditions, and all-cause death.

Secondary endpoints included "**serious events**" not related to AIDS, which were reported for all participants throughout follow-up, irrespective of ART use. "Serious events" included all deaths, life-threatening events, unscheduled hospitalizations, events resulting in significant disability or incapacity, other important medical events that may jeopardize the participant or require intervention to prevent one of those outcomes, and all grade 4 events. "Serious events" were MedDRA® coded centrally.

Table S1. Department of Health and Human Services NIH, National Institute of Allergy and Infectious Diseases, Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (excerpt relevant to grading suicidal and self-harming behavior).

Division of AIDS (DAIDS) Table for
Grading the Severity of Adult and Pediatric Adverse Events
Version 2.0, November 2014

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
ESTIMATING SEVERITY GRADE				
Clinical adverse event NOT identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not warranted	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death
PSYCHIATRIC				
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Alteration causing inability to perform usual social & functional activities Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

Source: https://rsc.tech-res.com/docs/default-source/safety/daids_ae_grading_table_v2_nov2014.pdf
(Accessed 11 December 2017)

Table S2. Baseline characteristics by pre-specified ART regimen and study arm

	EFV + NRTIs		Other ART[a] + NRTIs	
	Immediate (n=*1755*)	Deferred (n=1760)	Immediate (n=570)	Deferred (n=599)
Age, median years [IQR]	36 [29, 43]	36 [29, 43]	36 [29, 45]	36 [29, 45]
Female, n (%)	496 (28.3)	499 (28.4)	128 (22.5)	134 (22.4)
Race, n (%)				
Asian	179 (10.2)	170 (9.7)	19 (3.3)	20 (3.3)
Black	580 (33.0)	578 (32.8)	121 (21.2)	129 (21.5)
Latino/Hispanic	269 (15.3)	258 (14.7)	50 (8.8)	60 (10.0)
White	648 (36.9)	691 (39.3)	368 (64.6)	380 (63.4)
Other	79 (4.5)	63 (3.6)	12 (2.1)	10 (1.7)
Geographic region, n (%)				
Africa	442 (25.2)	455 (25.9)	56 (9.8)	46 (7.7)
Asia	164 (9.3)	162 (9.2)	15 (2.6)	15 (2.5)
Australia	27 (1.5)	24 (1.4)	29 (5.1)	29 (4.8)
Europe and Israel	437 (24.9)	434 (24.7)	326 (57.2)	342 (57.1)
South America	538 (30.7)	548 (31.1)	43 (7.5)	45 (7.5)
United States	147 (8.4)	137 (7.8)	101 (17.7)	122 (20.4)
Income region, n (%)				
High (US/Europe/Australia)	611 (34.8)	595 (33.8)	456 (80.0)	493 (82.3)
Low-moderate (Latin America/Africa/Asia)	1144 (65.2)	1165 (66.2)	114 (20.0)	106 (17.7)
Likely mode of HIV infection, n (%)				
Sexual contact with same sex	925 (52.7)	906 (51.5)	375 (65.8)	381 (63.6)
Sexual contact with opposite sex	718 (40.9)	748 (42.5)	153 (26.8)	169 (28.2)
Injection drug use	13 (0.7)	8 (0.5)	24 (4.2)	19 (3.2)
Blood products/other/unknown	99 (5.6)	98 (5.6)	18 (3.2)	30 (5.0)
Time since HIV diagnosis, median years [IQR]	1.0 [0.3, 3.1]	1.0 [0.3, 3.1]	1.0 [0.4, 2.6]	1.2 [0.4, 3.3]
CD4[b], median cells/µL [IQR]	652 [585, 772]	649 [581, 766]	650 [585, 755]	656 [585, 755]
HIV RNA, median copies/mL [IQR]	12402 [2991, 42680]	12015 [2736, 41000]	14304 [3759, 48400]	14234 [3736, 47700]
Current smoker, n (%)	500 (28.5)	512 (29.1)	232 (40.7)	255 (42.6)
Pre-specified ART regimen, n (%)				
EFV + NRTIs	1755 (100.0)	1760 (100.0)	0 (0.0)	0 (0.0)
Other NNRTI not EFV + NRTIs	0 (0.0)	0 (0.0)	90 (15.8)	81 (13.5)
PI + NRTIs	0 (0.0)	0 (0.0)	386 (67.7)	429 (71.6)
INSTI + NRTIs	0 (0.0)	0 (0.0)	94 (16.5)	89 (14.9)
Psychiatric diagnosis or current psychotropic drug treatment, n (%)	132 (7.5)	92 (5.2)	125 (21.9)	135 (22.5)
Prior psychiatric diagnosis[c]	71 (4.0)	38 (2.2)	81 (14.2)	81 (13.5)
Any psychotropic drug treatment	107 (6.1)	76 (4.3)	90 (15.8)	106 (17.7)

	EFV + NRTIs		Other ART[a] + NRTIs	
	Immediate (n=*1755*)	**Deferred (n=1760)**	**Immediate (n=570)**	**Deferred (n=599)**
Antidepressants	70 (4.0)	50 (2.8)	61 (10.7)	89 (14.9)
Benzodiazepines	37 (100.0)	25 (100.0)	28 (100.0)	22 (100.0)
Antipsychotic drugs (neuroleptics)	11 (0.6)	4 (0.2)	5 (0.9)	14 (2.3)
Other drugs for bipolar mood disorder	2 (0.1)	3 (0.2)	5 (0.9)	8 (1.3)
Methadone	0 (0.0)	1 (0.1)	3 (0.5)	5 (0.8)
Other opiates	9 (0.5)	9 (0.5)	17 (3.0)	8 (1.3)
Ever use of recreational drugs[d], n (%)	418 (23.8)	440 (25.0)	212 (37.2)	230 (38.4)
Heavy alcohol use, n (%)	76 (4.3)	79 (4.5)	22 (3.9)	23 (3.8)

[a] Ritonavir-boosted PI, INSTI, or NNRTI other than EFV.
[b] Average of two screening values
[c] Including major depression, bipolar disorder, psychotic disorder including schizophrenia. These diagnoses were not collected separately.
[d] 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 S3. Suicidal and self-injurious behavior, by randomization arm and pre-specified ART, for 371 participants with a prior psychiatric diagnosis at baseline.

	N	Immediate ART		Deferred ART		HR[a]	95% CI	P
		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[b]	109	7	2.85	0				
Other ART pre-specified	162	5	2.09	3	1.18	1.83	(0.4, 7.7)	0.41
ITT analysis, follow-up truncated at 1 year after randomization								
EFV pre-specified	109	4	6.07	0				
Other ART pre-specified	162	5	6.41	2	2.57	2.48	(0.5, 12.8)	0.28
Censoring deferred arm participants at ART initiation								
EFV pre-specified[c]	100	6	2.7	0				
Other ART pre-specified[d]	161	5	2.3	2	1.35	2.21	(0.4, 11.4)	0.34

[a] Hazard ratio (Immediate/Deferred), estimated in Cox proportional hazards models, unstratified.
[b] Of the 7 participants in the immediate ART group who experienced suicidal behavior, one experienced the event prior to having started EFV.
[c] In the immediate group, participants who did not start ART were excluded, and follow-up time starts at EFV start date.
[d] In the immediate group, participants who did not start ART were excluded, and 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 S4. Suicidal and self-injurious behavior, by randomization arm and pre-specified ART, for 4413 participants without prior psychiatric diagnosis at baseline.

	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	3406	12	0.23	12	0.22	1.02	(0.5, 2.3)	0.95	2.37	0.22
Other ART pre-specified	1007	4	0.26	10	0.61	0.43	(0.1, 1.4)	0.15		
ITT analysis, follow-up truncated at 1 year after randomization										
EFV pre-specified	3406	5	0.30	2	0.12	2.56	(0.5, 13.2)	0.26	6.10	0.13
Other ART pre-specified	1007	2	0.42	5	0.98	0.42	(0.1, 2.2)	0.30		
Censoring deferred arm participants at ART initiation										
EFV pre-specified[d]	3294	12	0.25	4	0.10	2.67	(0.9, 8.3)	0.09	4.17	0.08
Other ART pre-specified[e]	976	4	0.29	6	0.57	0.64	(0.2, 2.3)	0.49		

[a] Hazard ratio (Immediate/Deferred), estimated in Cox proportional hazards models, unstratified.
[b] Ratio of hazard ratios (Immediate/Deferred) within the EFV pre-specified subgroup over the Other ART pre-specified subgroup.
[c] Interaction between indicators for treatment group and pre-specified regimen.
[d] The immediate group excludes participants who did not start ART. Follow-up time starts at EFV start date.
[e] 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 S5. Factors associated with suicidal and self-injurious behavior among participants in the immediate ART group who were pre-specified other ART+NRTIs, and who started ART.

	Multivariate analysis[a]		
	HR	95% CI	P-value
Age (per 10 yrs older)	0.29	(0.11, 0.75)	0.01
Prior psychiatric diagnosis[b]	9.28	(2.37, 36.42)	0.001
Recreational drug use, ever	6.53	(1.32, 32.40)	0.02
Heavy alcohol use	3.62	(0.42, 31.41)	0.24
No. of participants	*563*		
No. of suicidal behavior events	*9*		

[a] HRs were estimated from one multivariate Cox proportional hazards regression model with all listed variables.
[b] Diagnosis of major depression, bipolar disorder, or psychotic disorder including schizophrenia

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