# Risk factors for antiretroviral therapy (ART) discontinuation in a large multinational trial of early ART initiators

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**Objective:** We aimed to investigate potential causes of higher risk of treatment interruptions within the multicountry Strategic Timing of AntiRetroviral Treatment (START) trial in 2015.

**Methods:** We defined baseline as the date of starting antiretroviral therapy (ART) and a treatment interruption as discontinuing ART for at least 2 weeks. Participants were stratified by randomization arm and followed from baseline to earliest end date of the initial phase of START, death, date of consent withdrawn or date of first treatment interruption. Cox regression was used to calculate hazard ratios and 95% confidence intervals for factors that may predict treatment interruptions in each arm.

**Results:** Of the 3438 participants who started ART, 2286 were in the immediate arm and 1152 in the deferred arm. 12.9% of people in the immediate arm and 10.5% of people in the deferred arm experienced at least one treatment interruption by 3 years after starting ART. In adjusted analyses, age [hazard ratio for 35–50 years: 0.75 (95% confidence interval: 0.59–0.97) and >50 years: 0.53 (0.33–0.80) vs. <35 years], education status [hazard ratio for postgraduate education vs. less than high-school education (0.23 (0.10–0.50))] and region [hazard ratio for United States vs. Europe/Israel (3.16 (2.09–4.77))] were significantly associated with treatment interruptions in the immediate arm. In the deferred arm, age and education status were significantly associated with treatment interruptions.

**Conclusion:** Within START, we identified younger age and lower educational attainment as potential causes of ART interruption. There is a need to strengthen adherence advice and wider social support in younger people and those of lower education status.

**Keywords: ART, discontinuation, HIV, interruption, treatment**

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## Introduction

In 2015, results published from the large-scale, multi-country Strategic Timing of AntiRetroviral Treatment (START) trial showed that, among people with a $CD4^+$ cell count above 500/μl, starting treatment straight away, rather than delaying until the $CD4^+$ cell count was lower than 350 cells/μl or an AIDS disease had occurred, reduced the risk of developing serious AIDS and non-AIDS diseases [1].

People who start antiretroviral therapy (ART) early will tend to be on treatment for a longer period than those who defer treatment, and while current drugs are substantially more tolerable now than they once were, most are still not without side effects [2]. This, along with other reasons such as travel, important distracting life events, perceived and possibly real impact of treatment on quality of life, may result in treatment interruptions. This is despite the evidence from the earlier Strategies for Management of Antiretroviral Therapy trial showing the detrimental effects of treatment interruption [3].

It has been shown that certain groups are more likely to interrupt treatment than others. Although studies are differentiated by both definitions of interruption and inclusion criteria, recent studies suggest men are at higher risk of interruption than women [4–6], although some earlier studies have shown a higher risk in women [7,8]. People who inject drugs and those of younger age have also been shown to be at an increased risk of treatment interruption [7–11], as have those with low educational attainment [10].

Although risk factors associated with treatment interruptions have previously been studied, we place focus on early ART initiators in a multinational trial. Using data from the START trial, we aimed to gain insights into what factors potentially cause a raised risk of treatment interruption.

## Methods

The START trial was designed and conducted by the International Network for Strategic Initiatives in Global HIV Trials. People were eligible for the study if they were HIV positive, aged more than 18 years of age, had not yet initiated ART and had two $CD4^+$ cell counts of more than 500 cells/μl at least 2 weeks apart within 60 days before enrolment. People were randomized to either immediate initiation of ART or deferred initiation until $CD4^+$ cell count dropped to 350 cells/μl or occurrence of an AIDS defining disease or another condition that dictated the use of antiretroviral therapy (e.g. pregnancy). (For full details regarding the original study design, see the study protocol, available at NEJM.org.)

For these analyses, we defined baseline as the date of starting ART. A treatment interruption was defined as stopping all antiretroviral treatment for at least 2 weeks, regardless of the cause of interruption: that is both clinician-directed and self-reported interruptions (>75% of interruptions were self-reported) were included. Self-reported interruptions were ascertained using information from the 'Adherence to ART' questionnaires (1–203 and 1–203A) and amalgamated with the prescribed ART information. Participants were followed from baseline (the start of ART, the earliest of which was May 2009) to whichever occurred first for the following: end date of the initial phase of START (26 May 2015, based on an interim review of the study data by the study's Independent Data and Safety Monitoring Board), death, date of consent withdrawn, last known date of being alive or the date of first treatment interruption.

Kaplan–Meier analyses, stratified by randomization arm, were used to estimate the proportion of people who experienced a treatment interruption. Univariable and multivariable Cox proportional-hazards models, stratified by randomization arm were used to calculate hazard ratios and 95% confidence intervals for characteristics measured at time of start of ART that may predict treatment interruptions: age, sex/mode of acquisition, education status, region, $CD4^+$ and viral load. We also calculated hazard ratios for specific antiretroviral drugs prescribed as the initial regimen; the nucleoside reverse-transcriptase inhibitor (NRTI) backbone was categorized as tenofovir + lamivudine/emtricitabine (TDF + 3TC/FTC), abacavir (ABC) +3TC/FTC, zidovudine (ZDV) + 3TC 3TC or 'other combination' and the 'third' drug in the regimen was categorized as efavirenz (EFV), other non-nucleoside reverse-transcriptase inhibitor (NNRTI), boosted atazanavir (ATV), boosted darunavir (DRV), other boosted protease inhibitor (PI), any integrase inhibitor or 'other'.

## Results

Of the 4684 HIV positive participants who were randomized 3438 participants started ART for the first time prior to May 2015 [median time from start of ART to study end/withdrawal/death = 31.0 (interquartile range: 21.8–43.1) months]; 2286 of these participants were in the immediate arm and 1152 in the deferred arm. The median time from randomization to starting ART in the immediate arm was 0.2 (0.1–0.5) months and in the deferred arm was 18.7 (10.3–29.0) months. In total, 380 (11.1%) participants experienced at least one treatment interruption and of these, 40 participants (10.5%) did not restart treatment before the study end date. By 3 years after starting ART, 12.9% (Kaplan–Meier estimate) of people in the immediate arm and 10.5% of people in the

**Table 1. Baseline characteristics stratified by treatment interruption and randomization arm.**

| | Treatment interruption | | | |
|---|---|---|---|---|
| | Immediate, $n=2286$ | | Deferred, $n=1152$ | |
| | No | Yes | No | Yes |
| | 1993 (87.2) | 293 (12.8) | 1065 (92.4) | 87 (7.6) |
| Age | | | | |
| <35 years | 869 (84.7) | 157 (15.3) | 427 (89.5) | 50 (10.5) |
| 35–50 years | 874 (88.6) | 112 (11.4) | 464 (94.3) | 28 (5.7) |
| >50 years | 250 (91.2) | 24 (8.8) | 174 (95.1) | 9 (4.9) |
| Sex/mode of acquisition | | | | |
| IDU | 28 (75.7) | 9 (24.3) | 12 (80.0) | 3 (20.0) |
| MSM | 1138 (88.9) | 142 (11.1) | 733 (94.5) | 43 (5.5) |
| Heterosexual female | 462 (83.2) | 93 (16.8) | 173 (86.9) | 26 (13.1) |
| Heterosexual male | 265 (88.0) | 36 (12.0) | 101 (91.0) | 10 (9.0) |
| Other | 100 (88.5) | 13 (11.5) | 46 (90.2) | 5 (9.8) |
| Education | | | | |
| Less than high school | 544 (80.1) | 135 (19.9) | 203 (86.0) | 33 (14.0) |
| High school graduate | 447 (88.6) | 69 (13.4) | 216 (91.9) | 19 (8.1) |
| Completed vocational training | 189 (90.4) | 20 (9.6) | 121 (93.8) | 8 (6.2) |
| Some college/university | 344 (83.4) | 41 (10.7) | 197 (92.5) | 16 (7.5) |
| Bachelor's degree | 354 (94.4) | 21 (5.6) | 250 (97.3) | 7 (2.7) |
| Any postgraduate education | 115 (94.3) | 7 (5.7) | 78 (95.1) | 4 (4.9) |
| Region | | | | |
| Africa | 430 (87.8) | 60 (12.2) | 117 (86.0) | 19 (14.0) |
| Latin America | 483 (82.8) | 98 (17.2) | 253 (93.7) | 17 (6.3) |
| Europe and Israel | 701 (93.3) | 50 (6.7) | 465 (94.5) | 27 (5.5) |
| United States | 196 (80.3) | 48 (19.7) | 134 (87.6) | 19 (12.4) |
| Australia | 49 (87.5) | 7 (12.5) | 34 (94.4) | 2 (5.6) |
| Asia | 144 (82.8) | 30 (17.2) | 62 (95.4) | 3 (4.6) |
| NRTI backbone | | | | |
| TDF + 3TC/FTC | 1797 (88.7) | 228 (11.3) | 958 (93.0) | 72 (7.0) |
| ABC + 3TC/FTC | 61 (85.9) | 10 (14.1) | 65 (92.9) | 5 (7.1) |
| ZDV + 3TC | 133 (70.7) | 55 (29.3) | 37 (80.4) | 9 (19.6) |
| Other combination | 2 (100.0) | 0 (0.0) | 5 (83.3) | 1 (16.7) |
| Third drug | | | | |
| EFV | 1445 (87.1) | 215 (12.9) | 539 (92.9) | 41 (7.1) |
| Other NNRTI | 92 (94.9) | 5 (5.1) | 144 (92.3) | 12 (7.7) |
| ATV | 190 (83.0) | 39 (17.0) | 85 (87.6) | 12 (12.4) |
| DRV | 147 (90.2) | 16 (9.8) | 116 (92.1) | 10 (7.9) |
| Other PI | 25 (80.7) | 6 (19.3) | 24 (85.7) | 4 (14.3) |
| INSTI | 91 (89.2) | 11 (10.8) | 153 (95.0) | 8 (5.0) |
| Other | 3 (75.0) | 1 (25.0) | 5 (100.0) | 0 (0.0) |
| $CD4^+$ at start of ART cells/μl | 647 (579–757) | 666 (596–788) | 405 (319–563) | 463 (329–593) |
| Viral load at start of ART copies/ml | 14 328 (3413–46 000) | 9453 (2609–35 880) | 41 700 (12 700–120 000) | 35 100 (12 761–97 957) |

3TC, lamivudine; ABC, abacavir; ATV, boosted atazanavir; DRV, boosted darunavir; EFV, efavirenz; FTC, emtricitabine; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; TDF, tenofovir; ZDV, zidovudine.

deferred arm experienced at least one treatment interruption.

The median duration of interruption among those who restarted ART was 43 (22–93) days and 59 (30–164) days in the immediate and deferred arms, respectively. Baseline characteristics stratified by randomization arm are shown in Table 1.

In the immediate arm, lower age, IDU/heterosexual female risk groups, lower education status, higher $CD4^+$ cell count, lower viral load and receiving ZDV and 3TC as the NRTI backbone were significantly associated with treatment interruptions in univariable Cox proportional hazards model (Table 2, immediate arm, univariable analyses). Region was also significantly associated with treatment interruptions; those from Africa, Latin America, United States and Asia were at an increased risk of treatment interruption compared with those from Europe and Israel. In multivariable analyses, only age, education status, region and NRTI backbone remained significantly associated with treatment interruptions (Table 2, immediate arm, multivariable results). Similar univariable results were seen in the deferred arm, albeit with stronger associations between the factor of interest and the risk of treatment interruption (Table 2, deferred

**Table 2. Univariable and multivariable hazard ratios for treatment interruptions stratified by randomization arm.**

| | Immediate arm | | | | Deferred arm | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariable | | Multivariable | | Univariable | | Multivariable | |
| | Hazard ratios (95% CI) | *P* value | Hazard ratios (95% CI) | *P* value | Hazard ratios (95% CI) | *P* value | Hazard ratios (95% CI) | *P* value |
| Age[a] | | | | | | | | |
| <35 years | 1 | | 1 | 0.01 | 1 | 0.01 | 1 | 0.01 |
| 35–50 years | 0.74 (0.58–0.95) | 0.01 | 0.75 (0.59–0.97) | | 0.53 (0.33–0.84) | | 0.54 (0.34–0.88) | |
| >50 years | 0.58 (0.38–0.90) | | 0.52 (0.33–0.80) | | 0.49 (0.24–0.99) | | 0.43 (0.21–0.90) | |
| Sex/mode of acquisition[a] | | | | | | | | |
| IDU | 2.34 (1.19–4.59) | 0.001 | 1.63 (0.80–3.30) | 0.46 | 3.40 (1.06–10.95) | 0.001 | 3.30 (0.95–11.50) | 0.17 |
| MSM | 1 | | 1 | | 1 | | 1 | |
| Heterosexual female | 1.71 (1.31–2.22) | | 1.24 (0.88–1.74) | | 2.86 (1.75–4.66) | | 1.85 (0.98–3.49) | |
| Heterosexual male | 1.18 (0.82–1.70) | | 0.98 (0.66–1.47) | | 1.78 (0.90–3.55) | | 1.64 (0.78–3.44) | |
| Other | 1.09 (0.62–1.92) | | 0.97 (0.54–1.76) | | 1.87 (0.74–4.73) | | 1.57 (0.61–4.09) | |
| Education[a] | | | | | | | | |
| Less than high school | 1 | <0.0001 | 1 | <0.0001 | 1 | 0.0001 | 1 | 0.03 |
| High school graduate | 0.63 (0.47–0.84) | | 0.48 (0.35–0.66) | | 0.52 (0.30–0.92) | | 0.58 (0.31–1.07) | |
| Completed vocational training | 0.42 (0.27–0.68) | | 0.45 (0.27–0.76) | | 0.35 (0.16–0.77) | | 0.51 (0.22–1.16) | |
| Some college/university | 0.49 (0.34–0.69) | | 0.35 (0.24–0.52) | | 0.49 (0.27–0.88) | | 0.50 (0.25–0.98) | |
| Bachelor's degree | 0.25 (0.16–0.39) | | 0.22 (0.14–0.36) | | 0.16 (0.07–0.37) | | 0.22 (0.09–0.53) | |
| Any postgraduate education | 0.26 (0.12–0.55) | | 0.23 (0.10–0.50) | | 0.28 (0.10–0.78) | | 0.42 (0.14–1.28) | |
| Region[a] | | | | | | | | |
| Africa | 2.16 (1.48–3.15) | <0.0001 | 1.04 (0.67–1.63) | <0.0001 | 3.35 (1.86–6.05) | 0.001 | 1.26 (0.60–2.66) | 0.39 |
| Latin America | 2.97 (2.11–4.18) | | 2.70 (1.90–3.84) | | 1.38 (0.75–2.53) | | 1.23 (0.66–2.31) | |
| Europe and Israel | 1 | | 1 | | 1 | | 1 | |
| United States | 3.14 (2.11–4.67) | | 3.16 (2.09–4.77) | | 2.29 (1.27–4.12) | | 1.99 (1.06–3.73) | |
| Australia | 1.86 (0.84–4.10) | | 2.03 (0.91–4.52) | | 0.98 (0.23–4.12) | | 1.15 (0.27–4.86) | |
| Asia | 2.97 (1.89–4.68) | | 2.23 (1.37–3.65) | | 0.90 (0.27–2.97) | | 0.81 (0.24–2.75) | |
| $CD4^+$ at start of ART[a] | | | | | | | | |
| Per 50 cells higher | 1.04 (1.01–1.07) | 0.01 | 1.02 (0.99–1.05) | 0.21 | 1.04 (0.99–1.09) | 0.13 | 1.02 (0.97–1.08) | 0.35 |
| Viral load at start of ART[a] | | | | | | | | |
| Per 1 log higher | 0.83 (0.74–0.94) | 0.004 | 0.95 (0.82–1.09) | 0.45 | 0.87 (0.68–1.11) | 0.25 | 1.08 (0.83–1.40) | 0.57 |
| NRTI backbone[b] | | | | | | | | |
| TDF + 3TC/FTC | 1.24 (0.66–2.33) | <0.0001 | 1.54 (0.79–3.01) | <0.0001 | 0.97 (0.39–2.39) | 0.01 | 1.01 (0.39–2.64) | 0.35 |
| ABC + 3TC/FTC | 1 | | 1 | | 1 | | 1 | |
| ZDV + 3TC | 2.77 (2.06–3.71) | | 2.14 (1.53–3.01) | | 2.78 (1.39–5.56) | | 1.90 (0.80–4.51) | |
| Third drug[b] | | | | | | | | |
| EFV | 1 | 0.12 | 1 | 0.30 | 1 | 0.46 | 1 | 0.36 |
| Other NNRTI | 0.44 (0.18–1.06) | | 0.52 (0.21–1.29) | | 1.19 (0.62–2.26) | | 1.39 (0.66–2.93) | |
| ATV | 1.28 (0.91–1.80) | | 1.37 (0.95–1.97) | | 1.66 (0.87–3.17) | | 2.10 (1.04–4.27) | |
| DRV | 0.71 (0.43–1.18) | | 1.06 (0.61–1.83) | | 0.99 (0.49–1.97) | | 1.29 (0.58–2.88) | |
| Other PI | 1.40 (0.62–3.15) | | 1.35 (0.60–3.06) | | 1.90 (0.68–5.29) | | 0.73 (0.22–2.44) | |
| INSTI | 0.84 (0.46–1.55) | | 1.19 (0.63–2.24) | | 0.79 (0.37–1.69) | | 1.01 (0.43–2.36) | |

3TC, lamivudine; ABC, abacavir; ATV, boosted atazanavir; CI, confidence interval; DRV, boosted darunavir; EFV, efavirenz; FTC, emtricitabine; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; TDF, tenofovir; ZDV, zidovudine.

[a]Multivariable model mutually adjusted for age, sex/mode of acquisition, education, region, $CD4^+$ and viral load.

[b]Multivariable model adjusted for age, sex/mode of acquisition, education, region, $CD4^+$ and viral load.

arm, univariable results). In multivariable analyses, only age and education status were significantly associated with treatment interruptions (Table 2, deferred arm, multivariable results).

## Discussion

Using data from a diverse multinational cohort of participants in the START trial, we found that 12.9% of people who started ART in the immediate arm and 10.5% of those who started ART in the deferred arm had at least one treatment interruption after 3 years of starting ART. Treatment interruptions took place on average 5 months after starting ART and generally lasted from 3 to 15 weeks. We found that after adjusting for potential confounders, participants who started ART were more likely to experience treatment interruptions if they were of younger age and had lower education status. Region and the NRTI backbone used was significantly associated with treatment interruptions in the immediate arm but not in the deferred arm.

Our finding of a higher risk of treatment interruption (regardless of randomization arm) among those of younger age is consistent with earlier studies [7–11]. It is possible that younger people are less stable both in terms of living conditions (less likely to be in permanent housing) and socially, and this may impact on taking treatment regularly.

Level of education was also independently associated with treatment interruptions in both the immediate and deferred arms. The association between education and treatment interruptions/low adherence has been shown in other studies [10,12,13]. Education attainment is also linked to a greater ability to deal with life events due to enhanced psychosocial skills [14]. Hence, those experiencing difficult life events who have higher education attainment may be less likely to interrupt therapy than those with lower education attainment, and they may also have greater support available when such events occur. Higher education is generally seen, at least partially, as a proxy for socioeconomic status and is likely to be linked to increased health literacy and in turn better adherence to medication. We note that socioeconomic status is a potentially important unmeasured confounder in our study which prohibited exploration of the independent potentially causal roles of education and socioeconomic status.

Region was significantly associated with treatment interruption. People from the United States were over three times more likely to experience treatment interruptions than people from Europe and Israel, while those from Latin America and Asia had over double the risk of experiencing a treatment interruption. Regional differences could partially reflect differences in healthcare systems leading to different selection factors affecting who is enrolled. For example, within the United States, people from lower socioeconomic status may have been more likely to enrol in the trial to gain access to free medication.

General adherence to ART may also explain the finding between region and interruption. In a systematic review of young adults, Kim *et al.* [15] found that people from North America had the lowest average ART adherence, though this was followed by those from Europe and South America, with higher levels seen in Africa and Asia. A meta-analysis which included HIV-infected adults in North America and sub-Saharan Africa also showed low levels of adherence among people from North-America compared with sub-Saharan Africa [16]. This may be due to the epidemic being more generalized in sub-Saharan Africa and hence ART provision and adherence counselling being more widespread. In the United States, the epidemic is more focussed among certain communities, in which health care may not be fully utilized, despite the overall richer resource setting. However, it is likely that the epidemic is similarly focussed in certain communities in Europe and hence this explanation is unlikely to fully explain the association seen. Another possible explanation is that health systems within Europe place a greater emphasis on the importance of adherence and risks of interruption by delivering specific counselling to people which may not be available for a range of reasons, including financial constraints on healthcare budgets, outside of Europe. Other factors such as physician experience [17], relationship with healthcare provider [18] and mental health [19] have also been shown to be associated with the risk of treatment interruptions, whereas outside the setting of a randomized controlled trial, factors such as different healthcare policies and treatment options may also contribute to this risk.

Further, we cannot rule out the possibility of other unmeasured confounding; participants from countries in which a higher rate of treatment interruption was seen may have personal attributes (e.g. attitudes to health care and provision) which contribute to a higher risk of interruption but were not captured within the study.

People receiving ZDV + 3TC in the immediate arm had a significantly increased risk of interruption compared with those receiving other NRTI backbone regimens. A considerable proportion of people in Latin America (20%) and Africa (8%) were receiving ZDV + 3TC as their first regimen and one likely reason for discontinuation among these people is the poorer toxicity profile associated with ZDV compared with newer drugs [20]. Most of these people had enrolled onto the trial prior to the end of 2013 and the proportion being prescribed this backbone combination has since declined.

Although people interrupt treatment for a range of reasons, it is of concern that within our multinational study in which we were able to separately analyse risk factors for treatment interruptions among early initiators, selected subgroups are still more likely to interrupt treatment. Further work to confirm these findings is needed. Interrupting therapy is associated with long-term poorer outcomes [3]. Improved approaches to support young people and those with lower educational attainment to sustain their taking of antiretrovirals are required.

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## Conflicts of interest

There are no conflicts of interest.

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