Antiretroviral pill count and clinical outcomes in treatment naive patients with HIV

Jim Young[1], Colette Smith[2], Ramon Teira[3], Peter Reiss[4], Inmaculada Jarrín Vera[5], Heidi Crane[6], Jose Miro[7], Antonella d'Arminio Monforte[8], Michael Saag[9], Robert Zangerle[10], Heiner C Bucher[1,11§] and the Antiretroviral Therapy Cohort Collaboration (ART-CC)

[1] Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, Basel, Switzerland

[2] Research Department of Infection and Population Health, University College London, London, United Kingdom

[3] Unit of Infectious Diseases, Hospital Sierrallana, Torrelavega, Spain

[4] Department of Internal Medicine, Division of Infectious Diseases, Center for Infection and Immunity–Amsterdam, Academic Medical Center, The Netherlands.

[5] National Center of Epidemiology, Instituto de Salud Carlos III, Madrid, Spain

[6] Center for AIDS Research, University of Washington, Seattle, United States of America

[7] Hospital Clínic-IDIBAPS, University of Barcelona, Barcelona, Spain

[8] Clinic of Infectious Diseases and Tropical Medicine, San Paolo Hospital, University of Milan, Italy

[9] Division of Infectious Disease, Department of Medicine, University of Alabama, Birmingham, United States of America

[10] Medical University Innsbruck, Innsbruck, Austria

[11] Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Basel, Switzerland

[§] Corresponding author

Heiner Bucher, Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, CH-4031 Basel, Switzerland.

Tel: +41 61 265 3100; fax: +41 61 265 3109; e-mail: heiner.bucher@usb.ch

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Abstract

Objectives: Treatment guidelines recommend single tablet regimens for patients with HIV starting antiretroviral therapy. These regimens might be as effective and cost less if taken as separate drugs. We assessed whether the one pill once a day combination of efavirenz, emtricitabine and tenofovir reduces the risk of disease progression compared to multiple pill formulations of the same regimen.

Methods: We selected treatment naïve patients starting one, two or three pill formulations of this regimen in data from the ART Cohort Collaboration. These patients were followed until an AIDS event or death or until they modified their regimen. We analysed these data using Cox regression models; then used our models to predict the consequences of treating a future population with either one or three pills.

Results: Among 11,739 treatment naive patients starting the regimen there were 386 AIDS events and 87 deaths. Follow up often ended when patients switched to the same regimen with fewer pills. After the first month, two pills rather than one was associated with an increase in the risk of AIDS or death (hazard ratio, HR, 1.39, 95% confidence interval, CI, 1.01-1.91) but three pills rather than two did not appreciably add to that increase (HR 1.19, 95% CI 0.84-1.68). We estimate that 77 patients would need to be treated for one year with one pill rather than three pills to avoid one additional AIDS event or death.

Conclusions: This single tablet regimen is associated with a modest decrease in the risk of AIDS or death relative to multiple pill formulations.

Introduction

In developed countries, many patients with HIV start antiretroviral therapy (ART) on a single tablet once a day regimen. Such regimens are popular with patients because they are simple to take [1], and this has encouraged the pharmaceutical industry to develop single tablet regimens (STRs) using existing drugs. However the existing drugs may become available in a cheaper generic form while the STR is still under patent. Public health systems could potentially use these generics to reduce drug costs and transfer savings to prevention and detection programmes leading to better public health outcomes [2].

Treatment guidelines recommend STRs [3-5] but as yet, there is little evidence that these regimens are better than a multiple pill formulation of the same regimen. In theory STRs improve adherence to ART by reducing the pill burden of therapy leading ultimately to a lower risk of disease progression. In practice systematic reviews suggest that once daily regimens lead to better adherence than twice daily regimens but that this has little effect on virologic suppression [1,6,7]. Some studies have compared single tablet once daily regimens to alternatives with different components and these studies suggest better adherence with the STR [8]. One study suggests reducing the pill count in the same once daily regimen from three to two may improve adherence [9]. There are no data with which to assess whether reducing the number of pills in a once daily regimen lowers the risk of disease progression in HIV. As a consequence, economic evaluations of STRs have been based on projecting clinical outcomes from a mathematical simulation of HIV infection rather than on real world data [10].

In this study we assess whether the one pill combination of efavirenz, emtricitabine and tenofovir reduces the risk of AIDS or death in treatment naïve HIV-infected patients starting ART compared to two or three pill formulations of the same regimen. We aim to provide estimates from real world data for future health economic modelling. Our analysis is based on data from the ART Cohort Collaboration of observational HIV cohorts from Europe and Northern America.

Methods

Patient selection

The ART Cohort Collaboration (ART-CC) was set up to study the prognosis of HIV-1 positive ART naïve adults [11]. The 2013 update of ART-CC includes data from 20 observational cohorts in Europe and North America but not all cohorts contributed data to this study. Cohort representatives were asked to confirm that in their data, one, two and three pill formulations of the same regimen could be identified. In cohorts where that was possible, we then selected all ART naïve patients starting one of the following efavirenz based regimens: (1) the one pill formulation of efavirenz, tenofovir and emtricitabine (Atripla®); (2) the two pill formulation of efavirenz, tenofovir and emtricitabine (efavirenz plus Truvada®); (3) the three pill formulation of efavirenz, tenofovir and either lamivudine or emtricitabine, all as single tablets. In general, lamivudine or emtricitabine can be considered as interchangeable; however there could be an increased risk of mutations following virologic failure when patients receive lamivudine [12,13].

Statistical methods

Our primary outcome was the time from starting ART to a first new or recurrent AIDS event or death. Patients were included in our analyses from the time they started ART until this outcome, six months after a last visit (if lost to follow up), the end of the study (administrative censoring), or any change in regimen components or formulation (artificial censoring) – whichever came first. We used Cox regression models to analyse these data. The exposure of interest in our models was the number of pills in the regimen. Models included covariates (specified in the analysis plan) to adjust for differences between the patients starting one, two or three pill regimens. The covariates in our models were sex, injection drug use as the mostly likely mode of HIV infection and – when starting ART – age, a previous AIDS event, calendar year, log 10 HIV RNA and CD4 cell count. We represented CD4 cell count in our models as a linear spline [14] with a knot at 200 cells/μL [15]. All models were

stratified by cohort so that each cohort had its own baseline hazard function. Model parameters are reported as the estimated hazard ratio (HR) and its 95% confidence interval (CI).

We expected that if there was a difference in the risk of AIDS or death, this difference would be greater between two and one pill regimens than between three and two pill regimens. We followed a three step modelling process.

First we fit two separate proportional hazards models, one for the choice between two or one pill regimens and a second for the choice between three and two pill regimens, with each model fit to a subset of the data. With these separate models, we restricted data to those years in which clinicians were actually prescribing both regimens to their patients and we removed patients not followed for at least one month. We assumed that early events – in the first month on ART – would not be influenced by the number of pills in the regimen but would more likely reflect an unmasking of a unknown existing AIDS defining infection or a clinical worsening and reoccurrence of a known infection [16].

Second we fit a joint non-proportional hazards model to all data – including data from the first month – to make sure that a joint model could reproduce estimates seen in the two separate models. In the joint model, we estimated two hazard ratios – one for the first month on ART and one for follow up after one month – for each of two indicators of exposure: two pills versus one, and three pills versus two.

Third we used parameters from the joint model to predict the probability of an AIDS event or death in a hypothetical future population where patients would be treated with either one pill or three pills. This hypothetical future population comprised all the patients in this study subject to a common baseline hazard across all cohorts, rather than a separate hazard for each cohort, because we can only predict probabilities at event times and some smaller cohorts had no events near the times of interest (one, two and three years on ART). We then calculated the number of patients that would need to be treated with one pill rather than three over a given period to avoid one additional

AIDS event or death by averaging risk differences across the patients in this hypothetical future population [17].

All models were fit in SAS 9.4; published SAS code was used to estimate AIDS event free survival probabilities for models with time-varying hazards and to calculate numbers needed to treat to avoid one additional event [17,18].

Sensitivity analyses

We carried out a range of sensitivity analyses. The methods used for these analyses and their results are described in full in supplementary material and are only briefly noted here.

First our use of one month to separate early events from later events is somewhat arbitrary. While many immune reconstitution inflammatory syndrome (IRIS) events will be reported within weeks of starting ART [16], such events can occur up to three months after starting ART or even later [19]. We therefore also estimated hazard ratios for each exposure before and after three or six months on ART (Appendix A, Supporting Information).

Second we present results for a joint model with and without including calendar year as a covariate because of the correlation between calendar year and the number of pills in the regimen, our exposure of interest (Appendix B, Supporting Information).

Third, in our main analysis, we did not categorise continuous confounders such as age, viral load, CD4 cell count or calendar year when starting ART. We provide sensitivity analyses to check that our use of continuous confounders has not misrepresented the evidence for an association between exposure and outcome (Appendix C, Supporting Information).

Fourth we also fitted a joint model using stabilised inverse probability of censoring weights [20] to allow for differences in patients remaining on each formulation over time. These weights allow for various scenarios where certain sorts of patients are more likely to switch to other regimens or to the same regimen with fewer pills (Appendix D, Supporting Information).

Finally we also analysed a secondary outcome: time to virologic failure, a first new or recurrent AIDS event or death. For this outcome, we fitted a Cox regression model appropriate for interval censored data [21]. Virologic failure is interval censored because it is only known to have occurred at some point between one RNA measurement and the next (Appendix E, Supporting Information).

Results

Study population

Our main analysis was of 11,739 treatment naive patients starting ART with efavirenz, tenofovir and either lamivudine or emtricitabine (Figure 1). Patients starting this regimen with one pill (rather than two or three pills) were less likely to be female, to have been infected with HIV through injection drug use, to have had a previous AIDS event, and on average had a lower viral load and a higher CD4 cell count (Table 1). The median time to the primary outcome or censoring was 11 months in these patients, with 386 AIDS events and 87 deaths, but follow up often ended in artificial censoring because many patients on two or three pill regimens switched to the same regimen with fewer pills (Tables D1 to D5, Supporting Information). Unadjusted rates of AIDS events or deaths were lower in patients on one pill than in those on two or three pills – with 20, 35 and 48 such events per 1000 years of treatment for patients on one, two and three pills respectively. However, because of the high rate of events within the first month (Table F1, Supporting Information), after one month there were only 12, 26 and 31 such events per 1000 years of treatment for patients on one, two and three pills respectively.

Modelling

Clinicians were prescribing two or one pill regimens to their patients during the period 2006 to 2012 (Table B1, Supporting Information). A model fit to data from patients starting the regimen during this period – and including only patients followed for at least one month – suggests that two pills rather than one was associated with an increase in the risk of AIDS or death (HR 1.37, 95% CI 0.94 to 2.00, Table 2). During the period 2004 to 2008, clinicians were prescribing three or two pill regimens to their patients. A model fit to these data suggests that three pills rather than two did not appreciably add to that increase in risk (HR 1.19, 95% CI 0.75 to 1.88).

A Kaplan Meier plot for all our data shows how the association between the number of pills in the regimen and the risk of AIDS or death changes over time (Figure 2). In the log-minus-log plot of

AIDS event free survival against log survival time, the line for two pills crosses the line for one pill in the first few months of treatment. If a proportional hazards model were appropriate for these data, the two lines would not cross.[22] Therefore, when modelling all our data, we estimated different hazard ratios before and after one month on ART. This joint model reproduced the point estimates seen in the two separate models for associations after one month on ART between the number of pills in the regimen and the risk of AIDS or death (Table 2). However because the joint model used all the data, its estimates were more precise.

However this joint model also suggests that patients treated with a two pill regimen had a lower risk of AIDS or death in the first month on ART (HR 0.65, 95% 0.44 to 0.95) than patients treated with a one pill regimen. This was unexpected. Patients starting one pill had early AIDS events at an appreciably lower CD4 cell count than those starting two or three pills (Table F1). It is possible that this reflects changes over time in the monitoring of individuals at risk of HIV, in the treatment of opportunistic infections, or in the diagnosis of IRIS events (Appendix F, Supporting Information). We would not expect such changes in the past to apply to a future population where patients were treated with either the STR or three generic drugs.

In both separate and joint models, there was a strong correlation between the parameter estimate for calendar year and parameter estimates for the number of pills in the regimen (Table B2). Estimates for the association between calendar year and the risk of AIDS or death were imprecise with wide confidence intervals (Table 2). Fitting a simple Cox model to the short period when all three formulations were being prescribed (2006 to 2008) does suggest that our models are over-estimating the association between calendar year and the primary outcome (Appendix B, Supporting Information). Because of the strong correlation, if the association with calendar year is over-estimated, the association with exposure will be under-estimated. In economic modelling, it may be better to use estimates that over-estimate rather than under-estimate the benefits of current treatment guidelines recommending STRs so that any decision to replace a STR with generic

drugs is conservative. A joint model without calendar year as a covariate led to higher HRs for exposure parameters, as expected (Table 2).

In sensitivity analyses, estimates of the association between the number of pills and the risk of AIDS or death varied predictably when using either three or six months rather than one month to separate early events from later events, consistent with a change in HRs within the first few months on ART (Appendix A, Supporting Information). In all models, later HRs implied that after the change, two pills rather than one was associated with an increase in the risk of AIDS or death but three pills rather than two did not appreciably add to that increase. Estimates were not materially different when using categorical covariates rather than continuous covariates (Appendix C, Supporting Information); or when using inverse probability of censoring weights (Appendix D, Supporting Information). With our secondary outcome (time to virologic failure, an AIDS event or death), we were not able to reproduce estimates seen with the primary outcome unless we used three months rather than one month to separate early events from later events and fitted a model without calendar year as a covariate (Appendix E, Supporting Information). Interval censoring makes it difficult to estimate early HRs in the joint model: interval censoring implies we do not know exactly when virologic failure occurred between two RNA measurements and for most patients, the time between starting ART and the next RNA measurement was more than one month.

Number needed to treat (NNT)

If we were to treat future patients with either the STR or three generic drugs, we would expect no difference in the risk of AIDS or death during their first month on ART. We therefore set early HRs to one when predicting the probability of an AIDS event or death from our joint model. With this change made, 77 patients would need to be treated for one year with one pill rather than three to avoid one additional AIDS event or death (Table 3). If we kept early HRs as estimated, rather than setting them to one, it made little difference (NNT = 72) because these early HRs only effect the probability of events within the first month. For practical reasons, we assumed a common baseline

hazard rate for all cohorts in our hypothetical population. We can only predict probabilities at event times, and some smaller cohorts had no events near the times of interest (one, two and three years on ART). We could instead use the baseline hazard rate seen in one of the larger cohorts for our hypothetical population. The baseline hazard rate from the Athena cohort gave similar results to a common baseline hazard rate (NNT=73). However predicting from a model without calendar year as a covariate led to fewer patients needing treatment for one year with one pill rather than three to avoid one additional AIDS event or death (NNT=61) because of this model's higher HRs for exposure parameters. Preliminary calculations of NNTs for the secondary outcome suggest that the potential cost savings from using three pills rather than one could be greater than first reported (Appendix E, Supporting Information).

Discussion

Economic modelling shows that replacing patented STRs with generic drugs could led to substantial savings for health systems in the US and UK.[2,10,23] The cost of antiretrovirals is more than half the total cost of HIV heathcare [24], and recent treatment initiatives – test and treat regardless of CD4 cell count and pre-exposure prophylaxis – are likely to increase both the absolute cost of antiretrovirals and their percentage of total costs. With either initiative, generics may be needed to contain costs [25,26]. However uncertainty about the comparative effectiveness of once a day regimens formulated as one, two or three pills has added to the uncertainty of economic modelling and health economists have asked for better data [10]. We show that a one pill regimen has a lower relative risk of an AIDS event or death than a regimen with several pills for ART naive patients remaining on a first regimen of efavirenz, tenofovir and either lamivudine or emtricitabine for more than a month. This decrease in risk is mostly associated with using a one pill regimen instead of a two pill regimen, rather than using a two pill regimen instead of a three pill regimen. Using these results, we predict that 77, 60 and 48 patients would need to be treated with one pill rather than three pills for one, two and three years respectively in order to avoid one additional AIDS event or death.

The combination of efavirenz, tenofovir and emtricitabine is no longer a recommended first regimen in many developed countries [4,5,27]. However it is widely used and those successfully treated with it are likely to remain on it. Indeed those successfully treated with it are likely to be more open to switching to a multiple pill generic formulation in order to reduce the cost of their treatment [28]. The combination is now considered an alternative regimen because of concern over the tolerability of efavirenz [4,27]. So our results represent an upper limit to the benefit one might logically expect from other once a day STRs over multiple pill formulations of the same regimen. This is because the anchor drug in other STRs – dolutegravir, elvitegravir, rilpivirine – is likely to prove more tolerable than efavirenz [29-31]. Tolerability is a strong driver of adherence [32-34] and some of the improvement in adherence with a STR comes about because patients are not able to take just

part of their regimen [33-35]. Our results could be used to evaluate any premium paid for other STRs over multiple pill formulations of the same regimen by assuming that our results represent a best case scenario. Deliberate non-adherence (rather than accidental) could explain why most of the reduction in the risk of AIDS or death in this study came from using a one pill regimen rather than a two pill regimen [36]. With a one pill regimen, patients cannot take just part of their regimen; with two or three pill regimens, patients can avoid taking efavirenz while still taking the other drugs.

The combination of efavirenz, tenofovir and emtricitabine is the preferred first regimen in developing countries [37]. However our results do not easily generalise to this setting. Adherence to a regimen may well be higher in this setting [38] and access to both care and treatment are probably more important determinants of treatment success than adherence [39,40] STRs then offer additional advantages beyond improved adherence, with supply chain and stock management easier when only a single tablet is involved [41].

The strengths of this study are data collected in routine clinical practice on a large number of patients so that we were able to assess the association between the number of pills in the regimen and disease progression in patients taking the same once a day regimen. An observational study of this sort is probably the best way to evaluate the effect of STRs on disease progression. A pragmatic randomised controlled trial would be difficult: blinding is impossible so that differential dropout is likely [42] with a loss of randomisation; adherence is likely to be greater and sustained for longer in a clinical trial setting [43]; and large numbers of patients would be need to be enrolled and followed for more than a year in order to evaluate the effect on relatively rare events [44]. Well designed observational studies do not necessarily overestimate the effects of interventions compared to randomised controlled trials [45-47].

As in any observational study, our adjustment for confounding variables may be incomplete. We had difficulty adjusting for some anticipated confounding effects because of a strong correlation between calendar time, a surrogate for these unmeasured confounding effects, and the number of

pills in the regimen, our exposure of interest. In economic modelling, it may be better to use NNTs that overstate rather than understate the benefit of current treatment guidelines recommending one pill once a day regimens because medical decision makers are typically risk averse when faced with new uncertain treatment strategies [48,49]. Using a model without calendar time as a covariate, we predict that 61, 48 and 38 patients would need to be treated with one pill rather than three pills for one, two and three years respectively in order to avoid one additional AIDS event or death. These are still high NNTs compared to those reported for other pharmaceutical interventions [50]. We did not have sufficient events to estimate an association between the number of pills in the regimen and mortality alone. Our results are based on treatment naive patients and do not show what would happen if patients currently treated with one pill were then switched to three. We did not have data on adherence that could be used to assess whether the number of pills in the regimen was associated with clinical outcome through adherence.

In general results from meta analyses and individual studies show that STRs improve adherence to ART and are consistent with some slight reduction in the relative risk of virologic failure [1,6-8,42]. Studies may find no significant difference in virologic failure between STRs and multiple pill regimens, but often there are few failures and estimates are in the direction of benefit [1,42]. And, as noted above, benefit is likely to be less apparent in the setting of a randomised controlled trial.

We show that the one pill combination of efavirenz, emtricitabine and tenofovir is associated with a modest decrease in the risk of progression to AIDS or death compared to two or three pill formulations of the same regimen. This does not imply that a STR should be used rather than a multiple pill formulation of the same regimen using generic drugs. Rather we provide statistics that could be used to evaluate whether STRs are more cost-effective than other formulations. Our statistics could be used either as model inputs or to calibrate or validate models based on other data.

If undiagnosed HIV is the limiting factor in the cascade of HIV care [2], then saving money on drug costs could fund prevention and detection programmes leading to better public health outcomes.

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Table 1. Characteristics when starting antiretroviral therapy (ART) and outcomes for patients in the main analysis (n=11739).

Characteristic or outcome	Number of pills in the regimen		
	One (n=4814)	Two (n=5260)	Three (n=1665)
Female (%)	14	16	23
Age in years (median)	38	39	39
Injection drug use [1] (%)	7	7	11
Previous AIDS event (%)	11	14	24
Chronic hepatitis B (%)	7	11	15
Hepatitis C (%)	11	13	17
HIV RNA, log 10 copies/mL (median)	4.8	4.9	5.0
CD4 cell count, cells/µL (median)	300	260	190
CD4 cell count < 50 cells/µL(%)	8	9	16
Primary outcome [2]			
- AIDS disease (n)	143	155	88
- Death (n)	27	26	34
- Rate, per 1000 years of ART	20	35	46
- Rate after 1 month, per 1000 years of ART	12	26	31
Secondary outcome [3]			
- Virologic failure (n)	202	161	106
- AIDS disease (n)	140	152	86
- Death (n)	27	23	32
- Rate, per 1000 years of ART	46	67	90
- Rate after 1 month, per 1000 years of ART	38	59	74

[1] Injection drug use as the most likely mode of infection.

[2] The first occurrence of a new or recurrent AIDS event or death.

[3] The first occurrence of virologic failure, a new or recurrent AIDS event or death.

Table 2. Cox model estimates for the analysis of the primary outcome: time from starting antiretroviral therapy to a first new or recurrent AIDS event or death. The association between this outcome and two or one pill regimens or three or two pill regimens is estimated in the first month (early effect) and after one month (later effect) on antiretroviral therapy.

Hazard ratio (95% CI)		Separate models – restricted data				Joint model – all data [1]			
Covariate		Two pills versus one [2]		Three pills versus two [3]		With calendar year		Without calendar year	
Female		1.33	(0.93 to 1.85)	0.88	(0.57 to 1.31)	1.03	(0.81 to 1.29)	1.03	(0.81 to 1.30)
Age (per 10 years)		1.29	(1.14 to 1.46)	1.10	(0.94 to 1.28)	1.20	(1.10 to 1.30)	1.19	(1.09 to 1.30)
Injection drug use [4]		1.04	(0.62 to 1.65)	0.96	(0.55 to 1.58)	1.01	(0.72 to 1.38)	1.01	(0.72 to 1.39)
Previous AIDS event		1.62	(1.14 to 2.29)	2.04	(1.40 to 2.97)	1.47	(1.18 to 1.84)	1.48	(1.18 to 1.84)
HIV RNA (per log10 copies/mL)		1.52	(1.25 to 1.86)	1.16	(0.94 to 1.45)	1.38	(1.21 to 1.58)	1.38	(1.21 to 1.58)
CD4 cell count ≤ 200 (per 100 cells/μL)		0.69	(0.54 to 0.88)	0.67	(0.51 to 0.88)	0.51	(0.43 to 0.60)	0.51	(0.44 to 0.60)
CD4 cell count > 200 (per 100 cells/μL)		0.87	(0.72 to 1.02)	1.04	(0.83 to 1.24)	0.80	(0.69 to 0.92)	0.80	(0.68 to 0.91)
Calendar year (per 10 years)		0.45	(0.15 to 1.31)	0.47	(0.09 to 2.56)	0.80	(0.42 to 1.50)	-	-
Two pills versus one	Early effect	-	-	-	-	0.65	(0.44 to 0.95)	0.67	(0.46 to 0.98)
	Later effect	1.37	(0.94 to 2.00)	-	-	1.39	(1.01 to 1.91)	1.45	(1.09 to 1.95)
Three pills versus two	Early effect	-	-	-	-	1.64	(1.05 to 2.55)	1.76	(1.18 to 2.61)
	Later effect	-	-	1.19	(0.75 to 1.88)	1.19	(0.84 to 1.68)	1.27	(0.94 to 1.71)

CI, confidence interval.

[1] 473 events among the 11,739 patients in the main analysis – see Figure 1.

[2] 214 events among 8,911 patients starting either a two or one pill regimen during the period from 2006 to 2012 inclusive and followed for more than one

month.

[3] 159 events among 3,914 patients starting either a three or two pill regimen during the period from 2004 to 2008 inclusive and followed for more than one month.

[4] Injection drug use as the most likely mode of HIV infection.

Table 3. The number of patients that would need to be treated with a one pill regimen rather than a three pill regimen to avoid one additional AIDS event or death.

Number needed to treat	Years treated		
Joint model	One	Two	Three
With early HRs=1.0, common baseline hazard	77	60	48
With all HRs as estimated, common baseline hazard	72	57	46
With early HRs=1.0, baseline hazard from the Athena cohort	73	54	46
Without calendar year, early HRs=1.0, common baseline hazard	61	48	38

HR, hazard ratio.

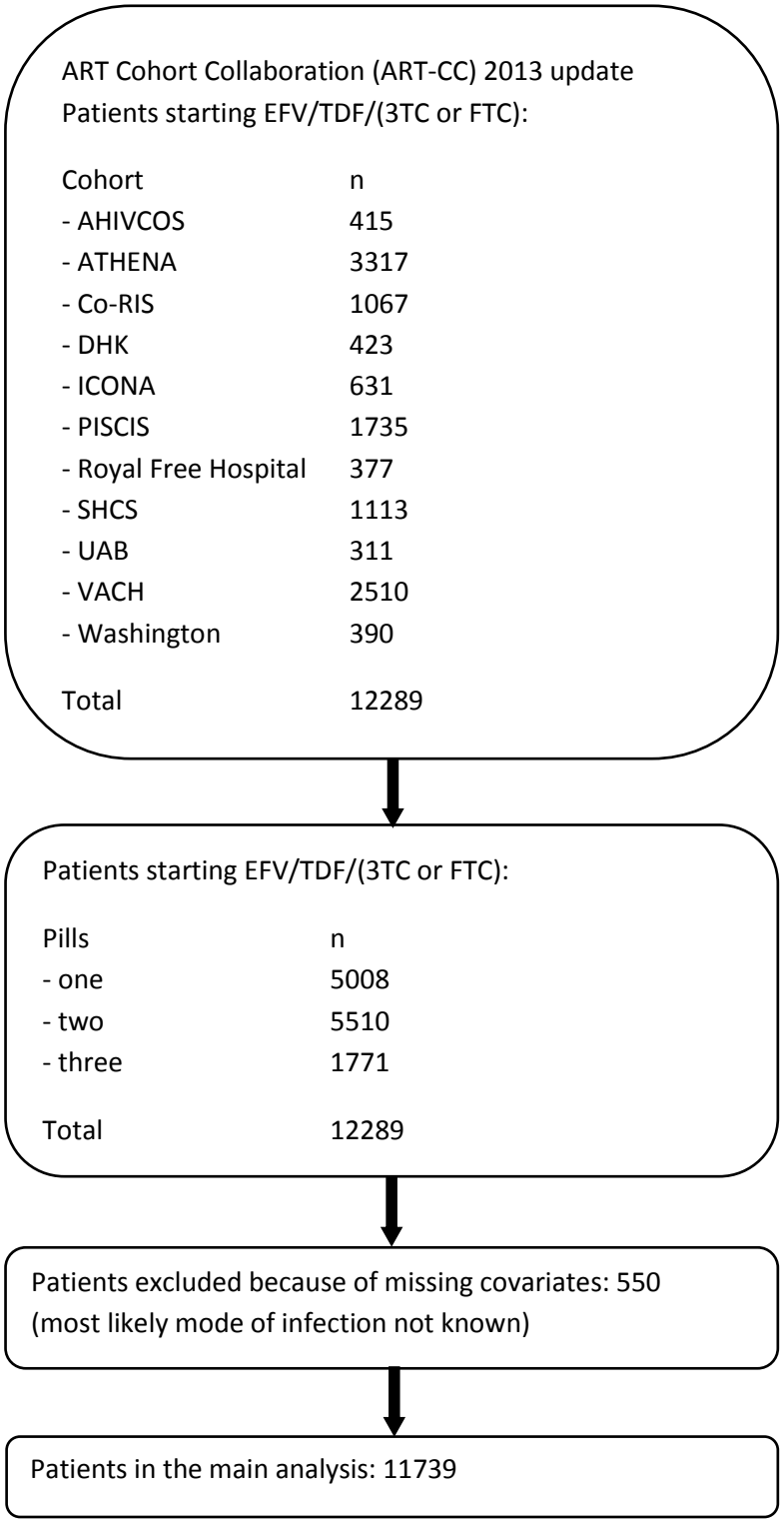
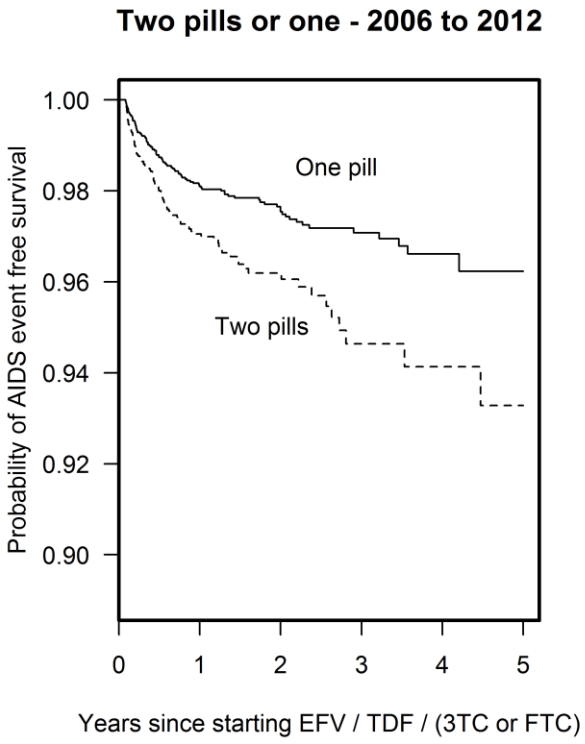
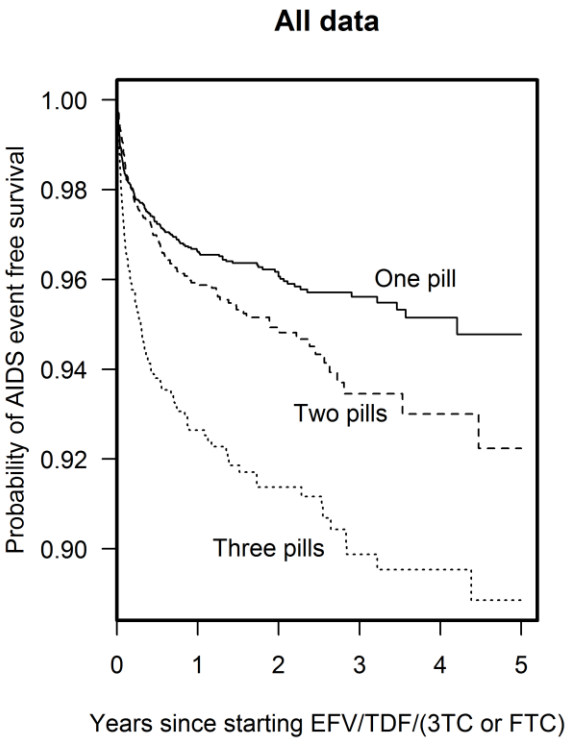
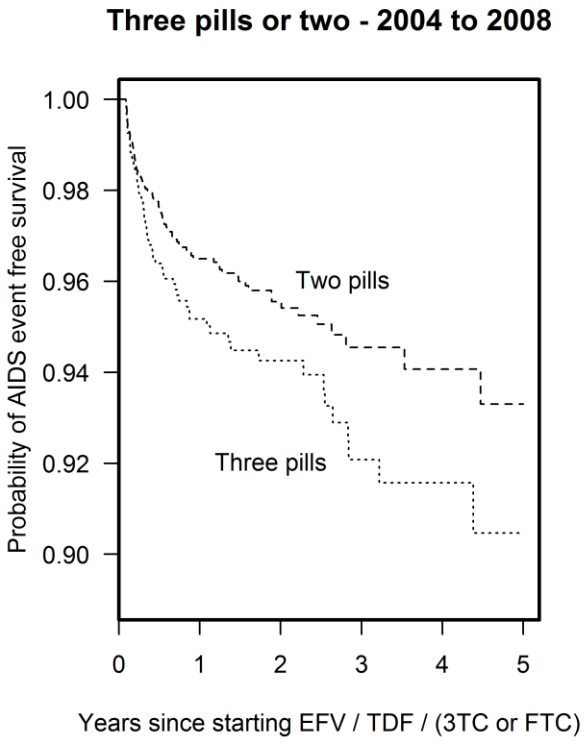


Figure 1. Patient selection for the main analysis: antiretroviral therapy naive patients starting efavirenz (EFV), tenofovir (TDF) and either lamivudine (3TC) or emtricitabine (FTC) as either one, two or three pills.


Two pills or one - 2006 to 2012
Probability of AIDS event free survival
1.00
0.98
0.96
0.94
0.92
0.90
One pill
Two pills
0
1
2
3
4
5
Years since starting EFV / TDF / (3TC or FTC)


All data
Probability of AIDS event free survival
1.00
0.98
0.96
0.94
0.92
0.90
One pill
Two pills
Three pills
0
1
2
3
4
5
Years since starting EFV/TDF/(3TC or FTC)


Three pills or two - 2004 to 2008
Probability of AIDS event free survival
1.00
0.98
0.96
0.94
0.92
0.90
Two pills
Three pills
0
1
2
3
4
5
Years since starting EFV / TDF / (3TC or FTC)

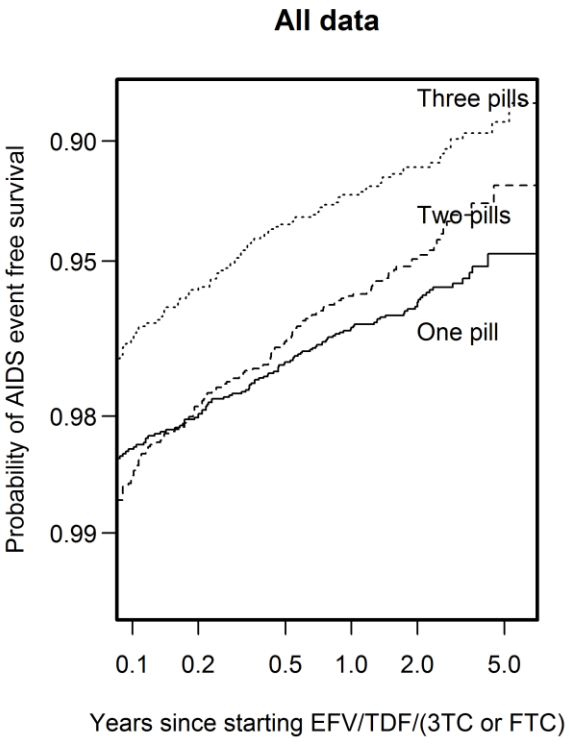

All data
Probability of AIDS event free survival
0.90
0.95
0.98
0.99
Three pills
Two pills
One pill
0.1
0.2
0.5
1.0
2.0
5.0
Years since starting EFV/TDF/(3TC or FTC)

Figure 2. The probability of AIDS event free survival over time for antiretroviral naive patients starting efavirenz (EFV), tenofovir (TDF) and either lamivudine (3TC) or emtricitabine (FTC) as either one, two or three pills. Kaplan Meier plots are shown of the probability of AIDS event free survival over time for patients starting two or one pill regimens over the period 2006 to 2012 (n=8,911); starting three or two pill regimens over the period 2004 to 2008 (n=3,914); and starting any of these three regimens at any time (n=11,739). The final plot (bottom right) is a plot of log(-log(probability of AIDS event free survival)) against log(time) for patients starting any of the three regimens at any time. The line for a two pill regimen crosses the line for a one pill regimen in the first few months of treatment.