AIDS Rev. 2008;10:236-44

CD4+ Guided Antiretroviral Treatment Interruption in HIV Infection: A Meta-Analysis

Elena Seminari[1], Annalisa De Silvestri[1], Andrea Boschi[2] and Carmine Tinelli[1]

[1]Clinical Epidemiology and Biometric Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [2]Division of Infectious Diseases, AUSL Rimini, Rimini, Italy

Abstract

The aim of this meta-analysis study was to evaluate the relative risk of death or AIDS-defining events associated to CD4+ guided treatment interruption in patients with chronic HIV infection.

A search was conducted using PubMed and Cochrane Library; key words for PubMed were: "antiretroviral therapy and interrupt*" in the full papers from January 1, 2000 up to and including December 31, 2007. To limit the publication bias, clinical trials performed on the topic of the meta-analysis were searched also on http://www.clinicaltrial.gov. Inclusion criteria of studies were: starting a CD4+ guided interruption of HAART in HIV chronically infected patients with CD4+ cell count > 350 cells/mm^3, age > 13 years old, and absence of concomitant use of immunomodulatory drugs. Using a conservative approach, to be included in the meta-analysis, studies had to have a follow up period > 100 person years to minimize the bias of a too short observation time. The studies were classified into two categories: randomized clinical trial (one arm stops therapy and other arms continues HAART) and cohort studies. For each study measures of effect (hazard ratio or incidence rate ratio) were reported, when available, uncorrected and corrected for potential confounders. Publication bias was assessed graphically through funnel plot. Pooled relative risk and pooled risk difference were calculated by use of a random effects model following the DerSimonian-Laird method. Observational studies were considered separately and the incidence of primary endpoint was evaluated in each study and the cumulative incidence was calculated.

Of the 555 full papers found, all abstracts were screened and 58 full text articles for potential inclusion were retrieved and 18 were retained (seven randomized clinical trials and 11 observational studies). In randomized clinical trials, the meta-analysis showed that the pooled relative risk of AIDS-defining event or mortality was 2.50 (95% CI: 1.87-3.34; p < 0.001); the pooled risk difference of AIDS-defining event or mortality was 0.02 (95% CI: –0.01-0.05; p = 0.168). The respective values corrected for latest CD4+ value were 1.77 (95% CI: 1.29-2.42; p < 0.001) and 0.01 (95% CI: –0.01-0.02; p = 0.37). The pooled relative risk of death was 1.8 (95% CI: 1.18-2.77; p = 0.007), and the corresponding pooled risk difference was 0.01 (95% CI: 0.001-0.012; p = 0.03). The risk of death resulted to have increased in patients that interrupted treatment; the corresponding value of risk difference was significant, although it was low (one extra death per 100 person years). Considering that a separate analysis corrected for the latest CD4+ value was not feasible for this endpoint, and that mortality rates in HIV-infected patients are inversely correlated with the CD4+ count, the value reported is extremely conservative. In cohort studies, the cumulative incidence of deaths or AIDS-defining events in the five studies with follow-up > 100 person years, was 0.77 (95% CI: 0.37-1.42 events per 100 person years), ranging in different studies from 0 to 3.2 events per 100 person years. This meta-analysis suggests that in patients undergoing a treatment interruption, there is an increased risk of developing AIDS or death, and that this risk is decreased if a relatively high CD4+ threshold is chosen to reinitiate the treatment, while the risk difference does not reach statistical significance. **(AIDS Rev. 2008;10:236-44)**

Corresponding author: Elena Seminari, e.seminari@smatteo.pv.it

Key words

HIV-infection. CD4+. Treatment interruption.

Correspondence to:
Elena Seminari
Clinical Epidemiology and Biometric Unit
Fondazione IRCCS Policlinico San Matteo
P.le Golgi 2,
I-27100 Pavia, Italy
E-mail: e.seminari@smatteo.pv.it

Introduction

The widespread use of antiretroviral therapy has reduced the morbidity and mortality among individuals infected with HIV[1], although the current antiretroviral drugs cannot eradicate infection and a lifelong antiretroviral treatment is required to control virus replication. It is frequent that patients periodically interrupt their treatments[2]; this might happen for many reasons such as drug toxicity, intercurrent illness, after pregnancy, virologic failure, and patient choice[3-5]. The use of treatment interruption has been considered as an alternative strategy to continuous suppression of the plasma viral load to treat HIV-infected patients by maintaining an adequate $CD4^+$ cell count during periods off therapy ($CD4^+$ guided treatment interruption)[6-20]. However, the threshold chosen to restart the antiretroviral therapy is controversial. A relatively high $CD4^+$ cell count threshold (400 cells/mm^3) is chosen by some scientists[10], whilst others tend to choose a lower value (250 cells/mm^3)[16,17,21]. Many of the studies that evaluated the effect of $CD4^+$ guided treatment interruption involve a small number of patients and have a short follow-up.

The aim of this meta-analysis study was to evaluate the relative risk (RR) and the risk difference (RD) of death or AIDS-defining events associated to $CD4^+$ guided treatment interruption in patients with chronic HIV infection.

Methods

A search was conducted using PubMed and Cochrane Library. The Medical Subject Headings were developed in collaboration with an experienced medical librarian. Key words anywhere in the text for PubMed were: "antiretroviral therapy and interrupt*" in the full paper from January 1, 2000 up to and including December 31, 2007. The search was limited to human studies with full manuscript published in English; abstracts presented at conferences were excluded due to lack of complete peer-reviewed information.

To limit the publication bias, clinical trials (ongoing and closed) performed on the topic of the meta-analysis were searched also on http://www.clinicaltrial.gov. On each retrieved article a manual research of references was performed. Inclusion criteria of studies were: starting a $CD4^+$ guided interruption of HAART in HIV chronically infected patients with a $CD4^+$ cell count > 350 cells/mm^3, age > 13 years old, and absence of concomitant use of immunomodulatory drugs. Using a conservative approach, to be included in the meta-analysis for primary endpoint, studies had to have a follow up period > 100 person years to minimize the bias of a too short observation time.

Abstracts of all papers were evaluated separately by Seminari and De Silvestri, and the papers that fulfilled the inclusion criteria were selected.

Published studies were evaluated by 2-3 independent readers according to the CONSORT algorithm[22] for randomized clinical trials and the STROBE statement[23] for cohort studies. Papers were independently evaluated by two authors (Seminari and De Silvestri), and in the presence of discordance in scoring, the final judgment was obtained after a discussion with a third author (Tinelli). Cohen statistics kappa was calculated to evaluate the inter-evaluator agreement. The literature search process is illustrated in figure 1.

The studies were classified into two categories: randomized clinical trials (RCT) where one arm stops therapy and other arms continues HAART, and cohort studies.

The main outcome was the occurrence of AIDS-defining events and/or mortality. Secondary outcomes were the occurrence of HIV-related, non AIDS-defining events.

Among studies conducted on the same cohort of patients, the most recent was retained for analysis.

Statistical analysis

For each study, measures of effect (hazard ratio or incidence rate ratio; HR or IRR) were reported, when available, uncorrected and corrected for potential confounders. Publication bias was assessed graphically through funnel plot. Heterogeneity was assessed through the Cochran's Q test and measured through the I^2 index proposed by Higgins and Thompson that can be interpreted as the percentage of the variability due to true heterogeneity, that is, to inter-study variability[24]. Pooled relative risk and pooled risk difference were calculated by use of a random effects model following the DerSimonian-Laird method because this model incorporates the heterogeneity between studies in the analysis.

Observational studies were considered separately and the incidence of primary endpoint was evaluated in each study and the cumulative incidence was calculated. A "p" value less than 0.05 indicated a significant difference that was unlikely to have arisen by chance and this was used as the cutoff value for significance in our study.

Reporting of this meta-analysis follows the QUORUM guidelines[26]. Since no individual and identifiable patient data were used, approval by a research ethical committee was not required. Where necessary, we contacted authors of studies for clarifications. Data were analyzed using Stata statistical software version 9.0.

Results

A total of 555 full papers were found, all abstracts were screened, and 58 full text articles for potential inclusion were retrieved and 18 were retained (seven RCT and 11 observational)[6-21,27,28]. Of the abstracts, 497 were excluded because they did not fulfill the inclusion criteria. Among the full text papers examined, some were excluded for

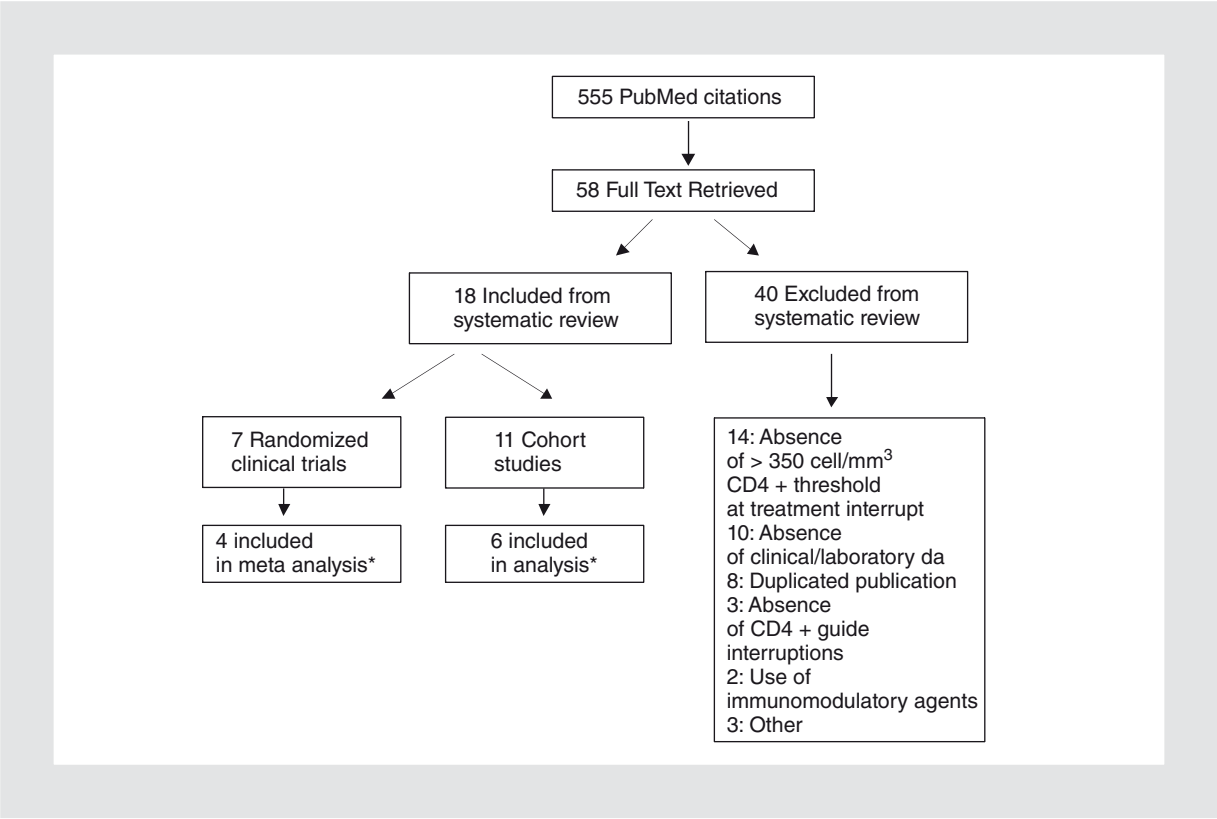

Figure 1. *Details of the literature search. *Follow-up > 100 person years.*

various reasons such as the absence of clinical/laboratory data, absence of the 350 cells/mm^3 CD4$^+$ threshold at treatment interruption, duplicated publications, use of immunomodulatory agents, and/or treatment on continuous therapy arm was different from HAART.

Studies were conducted mainly in Europe (three in Italy, four in Spain, three in France, one in the Netherlands), one was in the USA, one in Argentina, and one in Thailand; four were collaborations (one study was conducted in Cote d'Ivoire in collaboration with French Institutions, two were conducted mainly in Thailand in collaboration with the Netherlands and Australia, and one was a multicenter study in which patients were recruited from North and South America, Europe, Africa and Asia).

The 18 studies included 4,379 patients that interrupted the therapy, and 3,173 patients that continued antiretroviral therapy.

Publication bias was evaluated through funnel plot (Fig. 2), which shows that the majority of studies showing a small risk difference had a high level of imprecision, possible due to small sample size. At the top and in the bottom right of the graph there are the two studies that enrolled a greater number of patients, both showing a greater risk difference, but with a different grade of precision. We cannot exclude a publication bias involving small studies showing a high risk difference.

Randomized clinical trials

In RCT, participants on treatment interruption were compared to participants on continuous treatment. The goal of treatment interruption was to maintain the CD4$^+$ count above a particular level, which varies among the different studies, and to evaluate the safety of this approach. The characteristics of RCT are listed in table 1.

A total of 3,409 patients were enrolled in the CD4$^+$ guided treatment interruption arm, while 3,173 patients were enrolled in the continuous treatment arm.

AIDS-defining events or mortality

The incidence rate of primary endpoint was evaluable for all the studies (Table 1).

The SMART study[17] reported an increased incidence of new AIDS-defining events or death for any cause in patients in the treatment interruption arm compared to those in the continuous therapy arm; the event rate was 3.3 vs. 1.3 per 100 person years, respectively, and the corresponding HR was 2.6 (95% CI: 1.9-3.7; $p < 0.001$). After correction for both latest HIV RNA level and latest CD4$^+$ count, the corresponding HR was 1.5 (95% CI: 1.0-2.1). The HR for death from causes other than opportunistic

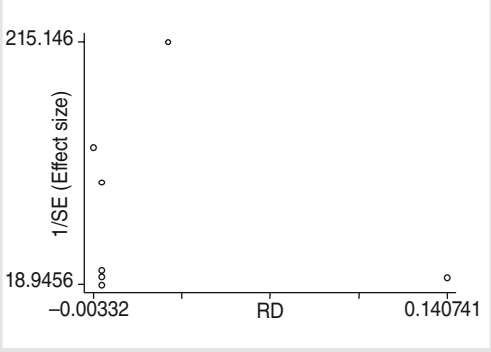

Figure 2. *Funnel plot. RD: risk difference; 1/SE: 1/standard error.*

disease was 1.8 (95% CI: 1.1-2.9), and after correction for both latest HIV RNA level and latest CD4+ count, the corresponding value was 1.2 (95% CI: 0.7-2.2). The HR for serious opportunistic disease was 6.6 (95% CI: 1.5-29.1; p = 0.01).

In the Trivacan study[21], conducted in Cote d'Ivoire, mortality was not statistically different between the continuous therapy and CD4 guided interruption groups (IRR: 0.48; 95% CI: 0.01-4.91; p = 0.57), although the overall severe morbidity (for which the following diseases were included: bacterial diseases, esophageal, oropharyngeal and vaginal candidiasis, isosporiasis) was greater in the treatment interruption arm and led to premature discontinuation of the trial (HR: 2.58; 95% CI: 1.35-4.95; p = 0.0042). In this study, the most frequent causes of severe morbidity were invasive bacterial diseases, oral candidiasis, and tuberculosis, all diseases being one of the major groups of infectious diseases in HIV-infected adults in sub-Saharan Africa (Anglaret, AIDS 2003). After correction for CD4+ updated value, the HR of severe events (death or WHO grade 3 or 4) was 2.14 (95% CI: 0.95-4.81; p = 0.066; personal communication by authors).

Absence of serious events due to HIV infection was reported in the Staccato trial[6] (two deaths, one for each arm, which were not related to HIV). However, this study was not powered to detect differences in mortality or in the incidence of AIDS-defining conditions. No new AIDS events or death were recorded in the other studies evaluated[7,9,10,15].

Among the four studies with follow-up > 100 person years included in the meta-analysis, the incidence rate of AIDS or death was 1.8 per 100 person years (95% CI: 1.5-2.0); in the treatment interruption arm, the incidence rate was 2.4 per 100 person years (95% CI: 2.0-2.7), and in the continuous treatment arm the incidence rate was 1.0 per 100 person years (95% CI: 0.8-1.3).

Table 1. Randomized clinical trials

Reference	Setting	Patients (n)	Treatment interruption (n)	Control (n)	CD4+ threshold to reinitiate therapy (cell/mm^3)	Incidence rate (per 100 person years)	Total follow-up (person years)
El-Sadr[17]	Multicenter (North and South America, Europe, Africa, Asia)	5,472	2,720	2,752	250	3.3 TI 1.3 control	3,700TI 3,700 control
Ananworanich[6]	Multicenter (Thailand, Switzerland, Australia)	430	284	146	350	0.2 TI 0.4 control	484 TI 262 control
Krolewiecki[9]	Argentina	36	20	16	350	0 TI 0 control	18 TI 15 control
Maggiolo[10]	Italy	69	46	23	400	0 TI 0 control	41 TI 21 control
Cardiello[7]	Multicenter (Netherlands, Thailand, Australia)	74	23	25	350	0 TI 0 control	21 TI 23 control
Danel[21]	Cote d'Ivoire	326	216	110	250	17.6 TI 6.7 control	341 TI 175 control
Ruiz[15]	Spain	201	100	101	350	0 TI 0 control	84 TI 186 control

TI: treatment interruption.

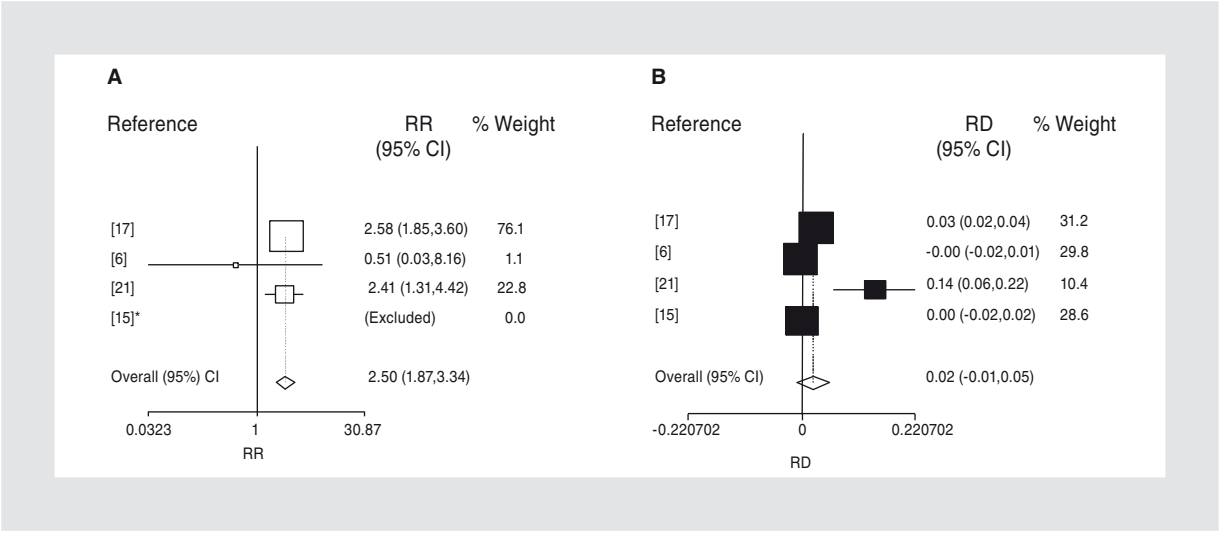

Figure 3. ***A****: Pooled relative risk (RR).* ***B****: Pooled risk difference (RD).*
**Reference [15] was automatically excluded as no events were reported.*

Meta-analysis of the studies with a follow-up of > 100 person years showed that the pooled relative risk of AIDS-defining event or mortality was 2.50 (95% CI: 1.87-3.34; p < 0.001, using DerSimonian-Laird random effects method), (Q statistics for heterogeneity = 1.31; DF = 2; p = 0.52; I^2 = 0); the pooled risk difference of AIDS-defining event or mortality was 0.02 (95% CI: –0.01-0.05; p = 0.168, DerSimonian-Laird random effects method), (Q statistics for heterogeneity = 35.11; DF = 3; p < 0.001; I^2 = 91.5%; 95% CI: 81.3-96.1%) (Fig. 3). This difference is small in size and is not statistically significant; heterogeneity was observed, possibly due to the effect of small studies or to the effect of different $CD4^+$ thresholds chosen.

The pooled relative risk risk of AIDS-defining event or mortality corrected for the latest $CD4^+$ value was 1.77 (95% CI: 1.29-2.42; p < 0.001, DerSimonian-Laird random effects method), (Q statistics for heterogeneity = 0.82; DF = 2; p = 0.66; I^2 = 0), the pooled risk difference of AIDS-defining event or mortality corrected for the latest $CD4^+$ value was 0.01 (95% CI: –0.01-0.02; p = 0.37, DerSimonian-Laird random effects), (Q statistics for heterogeneity = 10.59; DF=3; p = 0.014; I^2 = 71.7%; 95% CI: 19.5-90%) (Fig. 4).

The pooled relative risk of death of any cause was 1.8 (95% CI: 1.18-2.77; p = 0.007, DerSimonian-Laird random effects method), (Q statistics for heterogeneity = 0.82; DF = 2; p = 0.66; I^2 = 0), and the corresponding pooled risk difference was 0.01 (95% CI: 0.001-0.012; p = 0.03, DerSimonian-Laird random effects method), (Q statistics for heterogeneity = 3.09; DF = 3; p = 0.38; I^2 = 2.9%; 95% CI: 0-85.1%). A sensibility analysis was performed dividing the cause of death as AIDS or non AIDS-related. The percentage of causes of death classified as "unknown" in the SMART trial was 27.3% in the treatment interruption arm and 10% in the continuous treatment arm; in the Trivacan study two causes of death were classified as unknown. The causes of death classified as unknown were thus considered as 0, 50, or 100% AIDS-related and successively as 0, 50, or 100% non AIDS-related.

The pooled relative risk of deaths due to AIDS-related disease, considering 0% of deaths classified unknown as AIDS-related, was 1.53 (95% CI: 0.4-5.8; p = 0.5, DerSimonian-Laird random effects method), (Q statistics for heterogeneity = 0.14; DF = 1; p = 0.71; I^2 = 0), and the corresponding pooled risk difference was 0.001 (95% CI: –0.001-0.002; p = 0.6, DerSimonian-Laird random effects method), (Q statistics for heterogeneity = 0.95; DF = 3; p = 0.81; I^2 = 0); considering 50% of deaths classified unknown as being AIDS-related, the corresponding pooled relative risk and pooled risk difference were 2.4 (95% CI: 0.91-6.54; p = 0.08, DerSimonian-Laird random effects method), (Q statistics for heterogeneity = 0; DF = 1; p = 0.96; I^2 = 0), and 0.003 (95% CI: –0.0003-0.005; p = 0.08, DerSimonian-Laird random effects method), (Q statistics for heterogeneity = 0.79; DF = 3; p = 0.83; I^2 = 0); considering 100% of deaths classified unknown as AIDS-related, the corresponding pooled relative risk and pooled risk difference were 3.31 (95% CI: 1.38-7.93; p = 0.007, DerSimonian-Laird random effects method), (Q statistics for heterogeneity = 0.05; DF = 1; p = 0.81; I^2 = 0) and 0.004 (95% CI: 0.002-0.008; p = 0.01; DerSimonian-Laird random effects method), (Q statistics for heterogeneity = 2.49; DF = 3; p = 0.48; I^2 = 0).

The pooled relative risk of deaths due to non AIDS-related disease, considering 0% of deaths classified unknown as not AIDS-related, was 1.18 (95% CI: 0.50-2.81; p = 0.7, DerSimonian-Laird random effects method), (Q statistics for heterogeneity = 2.27; DF = 2; p = 0.32; I^2 = 11.9; 95% CI: 0-90.8), and the corresponding pooled risk difference was 0.003 (95% CI: –0.002-0.008; p = 0.27, DerSimonian-

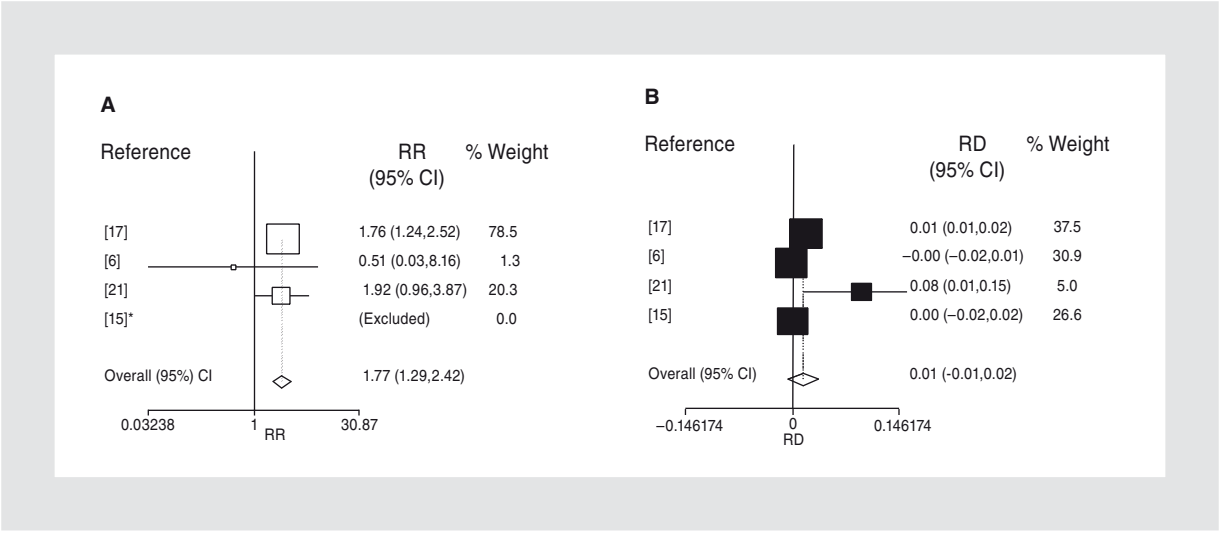

Figure 4. ***A****: Pooled relative risk (RR) adjusted for the latest CD4+ value.* ***B****: Pooled risk difference (RD) adjusted for the latest CD4+ value. *Reference [15] was automatically excluded as no events were reported.*

Laird random effects method), (Q statistics for heterogeneity = 2.21; DF = 3; p = 0.53; I^2 = 0); considering 50% of deaths classified unknown as non AIDS-related, the corresponding pooled relative risk and pooled risk difference were 1.60 (95% CI: 1.0-2.56; p = 0.05, DerSimonian-Laird random effects method), (Q statistics for heterogeneity = 1.38; DF = 2; p = 0.5; I^2 = 0) and 0.004 (95% CI: –0.001-0.09; p = 0.1, DerSimonian-Laird random effects method), (Q statistics for heterogeneity = 2.72; DF = 3; p = 0.44; I^2 = 26.5%; 95% CI: 0-92.4%); considering 100% of deaths classified unknown as non AIDS-related, the corresponding pooled relative risk and pooled risk difference were 1.8 (95% CI: 1.15-2.82; p = 0.01, DerSimonian-Laird random effects method), (Q statistics for heterogeneity = 1.14; DF = 2; p = 0.57; I^2 = 0) and 0.005 (95% CI: –0.001-0.01; p = 0.08, DerSimonian-Laird random effects method), (Q statistics for heterogeneity = 3.24; DF = 3; p = 0.35; I^2 = 7.4%; 95% CI: 0-85.8%).

Other events non AIDS-defining

A formal meta-analysis both of HIV-related, non AIDS-defining events or drug-related side effects was not performed because data relative to these outcomes were heterogeneously reported only in some of studies included in this analysis. The HIV-related events were divided into non AIDS-defining and acute antiretroviral syndrome.

Events considered as HIV-related, non AIDS-defining were fever with no focus, malaria, popular prurigo, herpes zoster[21], oral and genital candidiasis, thrombocytopenia, and neuropathy[6,10,15]. The cumulative incidence of HIV-related, non AIDS-defining events was 23.2 events per 100 person years in the treatment-interruption group (95% CI: 20.5-26.1) and 11.9 per 100 person years in the control group (95% CI: 9.4-14.9)[6,10,15,21]. The incidence of antiretroviral syndrome was 3.4 per 100 person years (95% CI: 2-5)[6,10,15].

Drug-related side effects were reported as comparable in the two arms (19.1 per 100 person years in the continuous treatment arm versus 17.3 in the treatment interruption arm[21], with a frequency of more than 2% in each group[6]) or slightly lower in the treatment interruption arm (1.5 per 100 person years in the continuous treatment arm versus 5.4 in the treatment interruption arm[15], or increased in the treatment interruption arm (65 vs. 44% of patients)[7]. The cumulative incidence of drug-related events was 13.5 events per 100 person years in treatment interruption group (95% CI: 12-16) and 15.1 in the control group (95% CI: 12.4-18.3)[6,7,9,10,15,21].

Quality assessment

Cohen's kappa was equal to 81% (95% CI: 77-85%), indicating an optimal inter-evaluator agreement. Title and abstract were correctly reported. Participants, interventions (for each group), objectives (except one)[10], and outcome (except one)[7] were clearly defined in all studies. Sample size determination was not available in two studies[7,15]. Randomization methodology was variously specified among the studies; two studies well defined all procedures[6,21], one study specified the method used for random allocation sequence, but no method is reported concerning allocation concealment and implementation[17]. The remaining studies gave random and little information on their randomization processes. Statistical methods used for the analysis were detailed in all except one case[7]. Results were reported accurately in all the studies, one

Table 2. Cohort studies

Reference	Setting	Patients (n)	CD4+ threshold to reinitiate therapy (cell/mm^3)	Incidence rate (per 100 person years)	Total follow-up (person years)
Giuntini[8]	Italy	74	350	0.8	131
Mussini[12]	Italy	139	350	0.5	212
Pogany[14]	Netherlands	46	350	0	38
Thiebaut[20]	France	57	300	0	43
Sungkanuparph[18]	Thailand	99	250	0	76
Tarwater[19]	US	105	200	0	321
Molina-Pinelo[27]	Spain	39	350	0	34
Skiest[16]	US	167	250	3.2	248
Pellegrin[13]	France	57	200	0	53
Fernandez Guerrero[28]	Spain	46	300	0	81
Mata[11]	Spain	141	350	0	392

study did not report data on patient recruitment[10], and one paper did not summarize primary and secondary endpoints[7].

Cohort studies

In cohort studies, efficacy and safety in CD4$^+$ guided treatment interruption were evaluated in uncontrolled, single-arm, concurrent studies[8,11-14,16,18,20,27,28], except for one study that used a mixed cohort, partially concurrent and partially non-current[19]. The characteristics of cohort studies are listed in table 2. A total of 970 subjects were enrolled.

AIDS-defining event or mortality

The cumulative incidence of deaths or AIDS-defining events in the five studies with follow-up > 100 person years was 0.77 (95% CI: 0.37-1.42 events per 100 person years), ranging in different studies from 0 to 3.2 events per 100 person years. In the mixed cohort study, no deaths or new AIDS-defining events were observed. The study[16] with the lowest threshold to reinitiate treatment (CD4$^+$ < 250 cells/mm^3) showed an incidence of AIDS-defining illness or mortality of 3.23 per 100 person years (95% CI: 1.39-6.36), while in the remaining studies, where the threshold to resume therapy was > 350 cells/mm^3, the incidence was lower.

The cumulative incidence of death was 0.46 per 100 person years (95% CI: 0.17-1.01). Overall, six episodes of death were registered, five were reported by Skiest, et al.[16] (classified as four non AIDS-related and one possibly AIDS-related) and one by Giuntini, et al.[8] (classified as non AIDS-related).

Other events not AIDS-defining

Events were divided in HIV-related (i.e. oral candidiasis, herpes zoster, thrombocytopenia) and antiretroviral syndrome. The cumulative incidence of HIV-related events was 3.89 per 100 person years (95% CI: 2.99-4.98), and the cumulative incidence of antiretroviral syndrome was 1.11 per 100 person years (95% CI: 0.66-1.76).

Quality assessment

Cohen's kappa was equal to 70.1% (95% CI: 65-75%), indicating a good inter-evaluator agreement. Three papers[13,16,19] gave inadequate information on the setting, locations, and relevant dates. Only one paper[12] sufficiently described efforts taken to address potential sources of bias; none described how the sample size was determined. Four papers[11,13,19,20] gave no information or inadequate information on the number of individuals at each stage (potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up and analyzed), and three studies[12,14,16] gave information about reasons for nonparticipation at each stage. All studies gave characteristics of study participants and reported follow-up lengths. Three studies[11,16,19] reported information on the number of participants with missing data; the majority of studies, except for two[14,16], gave precise esti-

mates. All studies gave good information on study design, inclusion criteria, and the source and methods of selection of participants. They clearly defined outcomes, exposures, and confounders and gave source of data and details on measurement, reporting the number of outcome events.

Discussion

A formal meta-analysis was performed for primary endpoint in RCT, where an increase in the risk of severe events (serious opportunistic disease and death) in patients who had interrupted treatment compared with patients who continued their antiretroviral therapy was observed. After correcting for the latest $CD4^+$ value, the relative risk was lower, although an increased risk remained significantly associated to treatment interruption.

The pooled risk difference or attributable risk, that is the expression of the difference in outcome between the arms that can be ascribed to the difference in treatment, was of a small size which did not reach statistical significance. In particular, two extra patients out of 100 patients followed up for a year will develop a serious adverse event if the treatment interruption group is compared with the treated group; after correction for latest $CD4^+$ value, the pooled observed risk difference was further reduced.

In cohort studies, the cumulative incidence of primary endpoint was lower than that observed in RCT. Despite the bias in cohort studies when compared with RCT (which include the absence of a control group, randomization, and of standardized methods in diagnosis), the relatively high number of patients included in the analysis and the long follow-up time made the observed data relevant.

In particular, both RCT and cohort studies highlight that the risk of AIDS defining events and/or death seems to be greater the lower the $CD4^+$ threshold chosen to reintroduce the antiretroviral treatment. Specifically, the RCT[17,21] and observational studies[16] that report the greatest incidence of opportunistic diseases or deaths are those which have chosen a lower $CD4^+$ threshold to reinitiate the treatment (< 350 cells/mm^3).

The inverse association of the absolute $CD4^+$ cell count with short-term risk (six months) of developing AIDS has been demonstrated in naive patients[29]. Although naive patients with a relatively high $CD4^+$ cell count (500-650 cells/mm^3) also show a raised risk of AIDS or death compared with patients with $CD4^+$ cell counts > 650 cells/mm^3, the absolute value of the difference is low: rate of AIDS or death 1.54 per 100 person years (95% CI: 1.22-1-86), risk of death alone 0.20 per 100 person years (95% CI: 0.10-0.34)[30].

The risk of death resulted to have increased in patients that interrupted treatment; the corresponding value of risk difference was significant, although it was low (one extra death per 100 person years). Considering that a separate analysis corrected for the latest $CD4^+$ value was not feasible for this endpoint, and that mortality rates in HIV-infected patients are inversely correlated with the $CD4^+$ count[31], the value reported is extremely conservative. A separate analysis was performed to evaluate the role of AIDS and non-AIDS causes of death, but the results were biased by the high percentage of death from unknown cause (observed mainly in the SMART trial). Therefore it was not possible to assess if the increased mortality observed was attributable to AIDS or non-AIDS causes.

To fully evaluate the aspects of treatment interruption, HIV-related, non AIDS-defining events and drug-related side effects were evaluated separately, although a formal meta-analysis was not performed due to the heterogeneous nature of reports on these topics. The HIV-related, non AIDS-defining events were increased in patients interrupting treatment (this analysis was not corrected for latest $CD4^+$). The analysis did not show a difference in term of drug-related toxicity due to antiretroviral therapy, although the data reported in papers on this issue are fragmentary. As it has been recently reported that laboratory abnormalities due to antiretroviral therapy can be associated with increased mortality[32], further studies to evaluate the long-term risk of toxicity are advocated.

This meta-analysis suggests that in patients undergoing a treatment interruption, there is an increased risk of developing AIDS or death, and that this risk is decreased if a relatively high $CD4^+$ threshold is chosen to reinitiate the treatment. The risk difference is low, though, and the clinical significance of this low risk attributable should be balanced by the potential toxic effects induced by HAART, even if only few data are available on the long-term toxicity of antiretroviral regimens, and on the impact that these adverse events might have on morbidity and mortality.

Recently, the initiation of antiretroviral therapy at a higher $CD4^+$ value (> 500 cells/mm^3) than that suggested by the guidelines has been advocated on the basis of the results of the SMART trial[33], this meaning that patients would be advised to initiate the antiretroviral therapy early in the course of HIV infection. As patients frequently interrupt their antiretroviral therapy for numerous reasons such as toxicity, poor adherence, concomitant disease, etc.[3-5,34-36], and adherence to treatment still remains an important issue for clinicians, further studies are recommended to better understand when and how to initiate, and possibly interrupt, therapies that only in few cases will last lifelong without interruptions. In planning these studies, the factors influencing the duration of treatment interruption, such as the $CD4^+$ cell count nadir[13,16,19,28], and the factors influencing the occurrence of adverse events during treatment interruptions, such as the level of $CD4^+$ and HIV RNA during treatment interruption[6,10,15], and the elements associated with worse outcome in previous patient history (i.e. AIDS-defining disease)[37] should be considered.

Acknowledgements

The authors thank Gabriella Gabutti for assistance in paper search and Funda Topuz for providing medical writing support; we are grateful to Xavier Anglaret, Delphine Gabillard from the Trivacan Study group and Giuntini Riccardo, Martinelli Canio for collaboration for meta-analysis in clarifications of data reported in the literature.

Financial support: This paper did not receive funding or financial support.

Potential conflict of interest: the authors declared no conflicts of interest.

References

1. Mocroft A, Ledergerber B, Katlama C, et al. Decline in the AIDS and death rates in the EuroSIDA study: An observational study. Lancet. 2003; 362:22-9.
2. D'arminio Monforte A, Cozzi-Lepri A, Phillips A, et al. Interruption of highly active antiretroviral therapy in HIV clinical practice: Results from the Italian cohort of antiretroviral-naive patients. J Acquir Immune Defic Syndr. 2005;38:407-16.
3. Glass T, De Geest S, Hirschel B, et al. Self-reported non-adherence to antiretroviral therapy repeatedly assessed by two questions predicts treatment failure in virologically suppressed patients. Antivir Ther. 2008;13:77-85.
4. Johnson M, Neilands T. Neuroticism, side effects, and health perceptions among HIV-infected individuals on antiretroviral medications. J Clin Psychol Med Settings. 2007;14:69-77.
5. Trotta M, Ammassari A, Murri R, et al. Self-reported sexual dysfunction is frequent among HIV-infected persons and is associated with suboptimal adherence to antiretrovirals. AIDS Patient Care STDS. 2008;22:291-9.
6. Ananworanich J, Gayet-Ageron A, Le Braz M, et al. CD4-guided scheduled treatment interruptions compared with continuous therapy for patients infected with HIV-1: Results of the staccato randomised trial. Lancet. 2006;368:459-65.
7. Cardiello P, Hassink E, Ananworanich J, et al. A prospective, randomized trial of structured treatment interruption for patients with chronic HIV type 1 infection. Clin Infect Dis. 2005;40:594-600.
8. Giuntini R, Martinelli C, Ambu S, et al. Prolonged treatment interruption in chronic HIV infection: A new strategy? AIDS. 2005;19:209-11.
9. Krolewiecki A, Zala C, Vanzulli C, et al. Safe treatment interruptions in patients with nadir CD4 counts of more than 350 cells/microL: A randomized trial. J Acquir Immune Defic Syndr. 2006;41:425-9.
10. Maggiolo F, Ripamonti D, Gregis G, Quinzan G, Callegaro A, Suter F. Effect of prolonged discontinuation of successful antiretroviral therapy on CD4 T cells: A controlled, prospective trial. AIDS. 2004;18:439-46.
11. Mata R, Viciana P, de Alarcon A, et al. Discontinuation of antiretroviral therapy in patients with chronic HIV infection: Clinical, virologic, and immunologic consequences. AIDS Patient Care STDS. 2005;19:550-62.
12. Mussini C, Bedini A, Borghi V, et al. CD4 cell-monitored treatment interruption in patients with a CD4 cell count > 500 x 106 cells/l. AIDS. 2005; 19:287-94.
13. Pellegrin I, Thiebaut R, Blanco P, et al. Can highly active antiretroviral therapy be interrupted in patients with sustained moderate HIV RNA and > 400 CD4+ cells/microl? impact on immunovirological parameters. J Med Virol. 2005;77:164-72.
14. Pogany K, van Valkengoed I, Prins J, et al. Effects of active treatment discontinuation in patients with a CD4+ T-cell nadir greater than 350 cells/mm^3: 48-week treatment interruption in early starters Netherlands study (TRIESTAN). J Acquir Immune Defic Syndr. 2007;44:395-400.
15. Ruiz L, Paredes R, Gomez G, et al. Antiretroviral therapy interruption guided by CD4 cell counts and plasma HIV-1 RNA levels in chronically HIV-1-infected patients. AIDS. 2007;21:169-78.
16. Skiest D, Su Z, Havlir D, et al. Interruption of antiretroviral treatment in HIV-infected patients with preserved immune function is associated with a low rate of clinical progression: A prospective study by AIDS clinical trials group 5170. J Infect Dis. 2007;195:1426-36.
17. Strategies for Management of Antiretroviral Therapy (SMART) Study Group, El-Sadr W, Lundgren J, et al. CD4+ count-guided interruption of antiretroviral treatment. N Engl J Med. 2006;355:2283-96.
18. Sungkanuparph S, Kiertiburanakul S, Apisarnthanarak A, Malathum K, Sathapatayavongs B. HIV-1 genotype after interruption of non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy and virological response after resumption of the same regimen. Int J STD AIDS. 2007;18:832-4.
19. Tarwater P, Parish M, Gallant JE. Prolonged treatment interruption after immunologic response to highly active antiretroviral therapy. Clin Infect Dis. 2003;37:1541-8.
20. Thiebaut R, Pellegrin I, Chene G, et al. Immunological markers after long-term treatment interruption in chronically HIV-1 infected patients with CD4 cell count above 400 x 10(6) cells/l. AIDS. 2005;19:53-61.
21. Danel C, Moh R, Minga A, et al. CD4-guided structured antiretroviral treatment interruption strategy in HIV-infected adults in West Africa (trivacan ANRS 1269 trial): A randomised trial. Lancet. 2006;367:1981-9.
22. Altman D, Schulz K, Moher D, et al. The revised CONSORT statement for reporting randomized trials: Explanation and elaboration. Ann Intern Med. 2001;134:663-94.
23. Von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. Lancet. 2007;370:1453-7.
24. Higgins J, Thompson S. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539-58.
25. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177-88.
26. Moher D, Cook D, Eastwood S, Olkin I, Rennie D, Stroup D. Improving the quality of reports of meta-analyses of randomised controlled trials: The QUOROM statement. Quality of reporting of meta-analyses. Lancet. 1999;354:1896-900.
27. Molina-Pinelo S, Vivancos J, De Felipe B, et al. Thymic volume predicts CD4 T-cell decline in HIV-infected adults under prolonged treatment interruption. J Acquir Immune Defic Syndr. 2006;42:203-6.
28. Fernandez Guerrero M, Rivas P, Molina M, Garcia R, De Gorgolas M. Long-term follow-up of asymptomatic HIV-infected patients who discontinued antiretroviral therapy. Clin Infect Dis. 2005;41:390-4.
29. Phillips A, CASCADE Collaboration. Short-term risk of AIDS according to current CD4 cell count and viral load in antiretroviral drug-naive individuals and those treated in the monotherapy era. AIDS. 2004;18:51-8.
30. Phillips A, Gazzard B, Gilson R, et al. Rate of AIDS diseases or death in HIV-infected antiretroviral therapy-naive individuals with high CD4 cell count. AIDS. 2007;21:1717-21.
31. Lewden C, May T, Rosenthal E, et al. Changes in causes of death among adults infected by HIV between 2000 and 2005: The "mortalite 2000 and 2005" surveys (ANRS EN19 and mortavic). J Acquir Immune Defic Syndr 2008;48:590-8.
32. Keiser O, Fellay J, Opravil M, et al. Adverse events to antiretrovirals in the Swiss HIV cohort study: Effect on mortality and treatment modification. Antivir Ther. 2007;12:1157-64.
33. Strategies for Management of Antiretroviral Therapy (SMART) Study Group, Lundgren J, Babiker A, et al. Inferior clinical outcome of the CD4+ cell count-guided antiretroviral treatment interruption strategy in the SMART study: Role of CD4+ cell counts and HIV RNA levels during follow-up. J Infect Dis. 2008;197:1145-55.
34. Ammassari A, Murri R, Pezzotti P, et al. Self-reported symptoms and medication side effects influence adherence to highly active antiretroviral therapy in persons with HIV infection. J Acquir Immune Defic Syndr. 2001;28:445-9.
35. Bardeguez A, Lindsey J, Shannon M, et al. Adherence to antiretrovirals among US women during and after pregnancy. J Acquir Immune Defic Syndr. 2008;48:408-17.
36. Kerr T, Palepu A, Barness G, et al. Psychosocial determinants of adherence to highly active antiretroviral therapy among injection drug users in Vancouver. Antivir Ther. 2004;9:407-14.
37. Holkmann Olsen C, Mocroft A, Kirk O, et al. Interruption of combination antiretroviral therapy and risk of clinical disease progression to AIDS or death. HIV Med. 2007;8:96-104.