Full title: Reference Curves for CD4+ T Cell Count Response to Combination of Antiretroviral Treatment in HIV-1 Infected Naïve Patients

Short title: Reference Curves for CD4 Response

The Standard Reference Distribution of CD4 Response to HAART Project Team for the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord*

A list of the affiliations of members of the Standard Reference distribution of CD4 response to HAART Group for Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) in EuroCoord precedes the Acknowledgements section.

Correspondence to Rodolphe Thiébaut, Centre Inserm U897 Université Bordeaux Segalen 146, rue Léo Saignat – Case 11 33076 Bordeaux cedex FRANCE

E-mail: rodolphe.thiebaut@isped.u-bordeaux2.fr

Alternate corresponding author : Vincent Bouteloup, CIC 1401 CHU de Bordeaux, ISPED 146, rue Léo Saignat – Case 11 33076 Bordeaux cedex FRANCE

E-mail : vincent.bouteloup@isped.u-bordeaux2.fr

* Members of the collaborations are listed in the Acknowledgements section.

Keywords: CD4 response, Longitudinal data, HIV monitoring, Antiretroviral treatment monitoring

Abstract

Objectives: The aim of this work is to provide a reference for the CD4+ T cell count (CD4) response in the early months after the initiation of a combination of antiretroviral treatment (cART) in HIV-1 infected patients.

Methods: From the Collaboration of Observational HIV Epidemiological Research Europe, all patients aged ≥ 18 years, who started cART for the first time between 1/1/2005 and 1/1/2010, with at least one available measure of CD4 and HIV-1 RNA ≤50 copies/mL at 6 months (+-/ 3 months) after cART initiation were included. Unadjusted, adjusted references curves and predictions were obtained by using quantile regressions.

Results: A total of 28,992 patients have been included. The median (interquartile range) CD4+ T cell count at treatment initiation was 249 (150; 336). The median observed CD4 at 6, 9 and 12 months were 382 (256; 515), 402 (274; 543) and 420 (293; 565). The two main factors explaining the variation of CD4 at 6 months were the AIDS stage and CD4+ T cell count at cART initiation. A CD4 increase of at least 100 cells/mL is generally required in order that patients stay 'on track' (ie. on the same percentile as when they start), with slightly higher gains required for those starting with CD4 in the higher percentiles. Predictions adjusted for factors influencing CD4 levels gave more precise individual predictions.

Conclusion: References curves help the evaluation of the immune response early after antiretroviral treatment initiation that leads to a viral control.

Introduction

The improvement of antiretroviral treatments since the mid-nineties has led to a large decrease in the incidence of severe morbidities [1] in those living with HIV with a substantial increase in life expectancy as a result [2]. For an individual starting combination antiretroviral treatment (cART) for the first time, the current goal of treatment is to ensure that the individual's viral load reaches undetectable levels as soon as possible after initiation of cART with his/her CD4+ T cell count increasing soon thereafter [3]. Hence, a good virological response to cART is usually determined to be an undetectable viral load within the first 6 months after cART initiation. A good immunological response, however, is less clearly defined. CD4 counts in the HIV-negative population usually lie within the range of 500-1500 cells/μL [4]. Among those with HIV, a higher CD4+ T cell count is associated with a lower risk of clinical progression [5, 6]; in particular, the longer an HIV-positive individual is able to attain a CD4+ T cell count >500 cells/μL the closer is his/her life expectancy to that of the general population [7]. The risk of clinical progression appears to be more strongly associated with the absolute level of CD4+ T cell count at a given time rather than the rate of increase in the CD4+ T cell count [8, 9].

Despite the difficulty in defining a good immune responder, it is important that clinicians are provided with a reference so that they are able to evaluate an individual's CD4+ T cell response in the early months after starting cART. This will allow them to make a decision about intervening in the management of the patient, through the frequency of clinical monitoring for instance. Our aim is to provide 'reference curves' for CD4+ T cell responses during the first 12 months of cART for patients with virological suppression and according to different characteristics at the start. It is hoped that these

will allow clinicians to determine how an individual's CD4 count response compares to that of other patients who started the same type of cART and under the same conditions.

Methods

Patients

COHERE is a collaboration of 39 cohorts from across Europe and is part of the EuroCoord network (www.EuroCoord.net). COHERE was established in 2005 with the aim of conducting epidemiological research on the prognosis and outcome of HIV-positive persons, which the individual contributing cohorts cannot address themselves because of sample size or heterogeneity of specific subgroups of HIV-positive persons. Local ethical committee and/or other regulatory approval were obtained as applicable according to local and/or national regulations in all participating cohorts. Each cohort submits data using the standardized HIV Collaboration Data Exchange Protocol (HICDEP)[10], including information on patient demographics, use of cART, CD4 counts, AIDS, and deaths. Further details can be found at http://www.eurocoord.net/partners/founding_networks/cohere.aspx. Data were pooled in September 2011 within COHERE in EuroCoord (www.cohere.org and www.EuroCoord.net). Twenty seven cohorts across 35 European countries provided data for the present analysis. All persons aged ≥18 years, who started cART for the first time between 1 January 2005 and 1 January 2010, with at least one available measure of CD4 count (in cells/μL) and HIV-1 RNA ≤50 copies/mL six months (+/- 3 months) after cART initiation were included. Patients were considered to have maintained viral suppression at month 6 when at least one HIV-1 RNA measure was available within 6 months after cART initiation (including the measure at month 6) and the HIV-1 RNA measure at month 6 was <50 copies/mL (previous measures could be >50 copies/mL). cART was defined as any regimen that contained at least three drugs, including a protease inhibitor, a non-nucleoside reverse transcriptase inhibitor, an entry inhibitor or an integrase inhibitor; or which contained three nucleoside reverse-transcriptase

inhibitors of which one was abacavir. Baseline was defined as the date of cART initiation. The follow-up was censored first at 9 months (i.e. 6+3 months) and then 15 (i.e. 12+3) months because we were interested in the short-term response to CD4+ T cell count.

Strategy for statistical analyses

Any estimate of the effect of a given factor on CD4+ T cell dynamics is likely to be significant in this large study because of the statistical power conferred by the size of the dataset. Therefore, factors used for stratified analyses or included in the regression model were defined a priori. Baseline factors known to be associated with CD4+ T cell change after cART initiation selected for the analyses were: CD4+ T cell count, AIDS clinical stage, age, HIV transmission group especially intravenous drug use (IDU), sex, HCV co-infection, HIV-1 RNA level, year of cART initiation and type of cART. cART regimen was classified as: ritonavir-boosted PI-based; NNRTI-based; both PI- and NNRTI-based; unboosted PI-based; or an other regimen that did not include either a PI or NNRTI. Integrase or fusion inhibitor-based regimens were too infrequently used to constitute specific subgroups and were allocated to the previously described categories. The distribution of CD4+ T cell count at 6 (12) months was then described by using the closest measurement between 3 (9) and 9 (15) months.

Quantile regression

Quantile regression was performed on repeated measurements of CD4+ T cell count available for each individual until 9 months and then until 15 months. Quantiles of specific interest were the 5^{th}, 10^{th}, 25^{th}, 50^{th} (i.e. median), 75^{th}, 90^{th} and 95^{th} percentiles. The models were adjusted for time with squared and cubic effects to allow enough flexibility to fit a nonlinear evolution of CD4 over time. A set of models (one for each

percentile of interest) was fitted without including any other covariates in the models after stratifying according to the baseline CD4+ T cell count (0-199; 200-349; 350-499; ≥500 cells/μL). These models were used to draw reference curves for the overall distribution of CD4+ T cell responses among individuals in the study. A second set of models was then fitted after additionally including adjustment for the covariates listed above; this set of models can be used to make predictions for individual responses where individual characteristics are taken into account. The models presented were fitted using PROC QUANTREG in SAS v9. 3 (SAS Institute, Cary, NC). Robustness analyses with median regression including a random intercept to take into account correlation of repeated measurements in patients yielded similar results [11] as did a non-parametric approach [12].

References curves can be generated for each individual through a web tool developed with Shiny, a web application framework for R (http://shiny.rstudio.com/).

Results

Study population (Figure 1, Table 1)

A total of 28,992 patients were included. A description of the study population is provided in Table 1. Compared to included individuals (table 1 additional material), those who were excluded were younger (median 38 vs 39 years-old), less frequently male (69 vs 73%), less frequently MSM (35 vs 43%), and more frequently started a PI/r-based cART regimen (51 vs 44%) ($p < 10^{-4}$ for all comparisons). The difference in baseline CD4 level at cART initiation was marginal (Wilcoxon rank sum test p=0.066). The median (interquartile range IQR) number of CD4+ T cell measures per patient available was 3 (2; 4).

Global picture of the quantiles of CD4+ T cell changes (Figure 2 and 3)

The median (IQR) observed CD4+ T cell count at treatment initiation was 249 (150; 336) cells/µL. The median observed CD4+ T cell counts at 6, 9 and 12 months were 382 (256; 515), 402 (274; 543) and 420 (293; 565). Box plots of the CD4+ T cell response at month 6 according to various baseline characteristics are presented in Figure 2. The two main factors explaining the variation of CD4+ T cell count at 6 months were the AIDS stage at cART initiation and, as expected, the baseline CD4+ T cell count (figure 1, supplementary material). A similar picture was seen at 12 months (figure 2, supplementary material).

Figure 3 shows the predicted percentiles of CD4+ T cell count from cART initiation for the full population. The figure shows that a CD4+ T cell count increase of at least 100 cells/mL is generally required in order that patients stay 'on track' (ie. on the same percentile as when they start), with slightly higher gains required to stay on track for those starting with CD4+ T cell counts in the higher percentiles (table 2, supplementary

material). For example, the median line demonstrates that patients who started cART at the median level of 251 cells/μL needed to have a CD4+ T cell count of 367 cells/μL at 6 months after cART initiation to remain on the median line. The gain required to stay on track was somewhat larger for those initiating cART at higher percentiles of the CD4+ T cell distribution. For instance, a patient starting cART with a CD4+ T cell count of 500 cells/μL (roughly equating to the 90th percentile) would need to have attained a CD4+ T cell count of 650 cells/μL by 6 months in order to remain on the same percentile line.

As examples, the trajectories of two specific patients have been depicted in Figure 3. The first one (purple line) depicts an individual, female, 30 years old, who started cART (Lopinavir/r +Zidovudine/Lamivudine) with a CD4 count of 390 cells/μL representing the 82th percentile of baseline values. Her CD4+ T cell count had increased to only 438 cells/μL over the first 7.9 months. This increase was modest but it was more obvious when looking at the position in regards of the population: a drop from the 82th percentile to the 61th percentile. In the second example (green line), cART (Efavirenz +Rilpivirine +Tenofovir/Emtricabine) was started at 112 CD4+ T cells/μL (the 18th percentile); by 7.3 months, this individual's CD4+ T cell count had reached 161 cells/μL, representing the 12th percentile which could be considered as a bad response. This figure illustrates how this type of representation could help clinicians when evaluating the CD4+ T cell count change after cART initiation.

Factors associated with CD4+ T cell count (Table 2)

Factors associated with CD4+ T cell count level were evaluated for each percentile of interest using quantile regression. For instance, women had a 25th percentile that was

14 cells/μL higher than men and this difference was consistent over the other percentiles (14 cells/μL and 11 cells/μL for the 50th and 75th percentiles, respectively). But the impact of some baseline characteristics varied according to the percentile. AIDS clinical stage had a stronger impact for individuals with CD4+ T cell counts around the 25th (-111 cells/μL) and 50th percentiles (-115 cells/μL) whereas the type of cART regimen had a greater impact for those with counts around the highest (75th and more) percentiles. For instance, those starting a regimen including both a PI and a NNRTI presented 103 cells/μL more at 6 months compared to patients who started a regimen including only boosted PI in addition to NRTIs.

Our predictions were then further refined using the measured baseline characteristics through a multivariable quantile regression. Examples are provided for two previously presented patients in Figure 4. The first patient who started with 390 cells/μL at the 82th percentile (solid purple line, left part) is classified as starting on the 44th percentile after adjustment for sex, age, transmission risk group, clinical stage, HIV RNA and cART regimen at baseline percentile (dotted purple line, left part). He had an attained CD4+ T cell count of 438 cells/μL at 7.9 months after cART initiation which corresponds to the 61th percentile from crude analysis (solid purple line, right part). However, taking the individual's characteristics into account, the patient's attained CD4+ T cell count is found to lie on only the 22th percentile after adjustment (dotted purple line, right part). Therefore, this increase of only 48 cells/μL means that, in relative terms, the patient has switched from the 44th percentile to the 22th percentile; this is clearly a poor response. The other patient (solid and dotted green lines) presented with a not so bad response as he started at the 62th adjusted percentile with 112 CD4+ T cells/μL and dropped to the

30th adjusted percentile with 161 CD4+ T cells/μL at 7 months as compared to crude percentiles that were 18th at baseline and 12th at 7 months.

Discussion

The CD4+ T cell reference curves presented here provide an indication of how the immunological response of an individual patient may compare to that of a large sample of HIV patients who have achieved viral control with potent antiretroviral therapy. These reference curves can be easily drawn through the online tool we developed, available at http://194.167.116.100/COHERE/.

The definition of immune non-response is highly variable in the literature [13-16]. One obvious explanation for the variability is that the latest absolute level of the CD4+ T cell count is more associated with clinical prognosis than the slope of CD4+ T cell increase [9]. Hence, there is no obvious threshold for a *good* immune response other than having the highest possible CD4+ T cell count. This is why we therefore propose that individual trajectories are referred to the distribution among the whole population, rather than whether the absolute count is above or below an arbitrary threshold value.

Following our reference curve, an immune non-responder may be defined as a person who, despite cART, was not able to maintain an immune response that allowed her/him to remain on the same percentile curve as at the start of cART. In the figures, we provide quartiles and extreme percentiles. Although, there is no evidence for the additional value of immune interventions [17] or changing cART regimens in such a situation, research on boosting the immune response is ongoing [18]. In addition, as long as the observed increase of a given patient means that s/he remains on the same percentile and provided that viral replication is controlled, there may be an argument for scheduling fewer visits in the subsequent months. With the availability of more potent antiretroviral drugs with fewer side effects, and a possible overall benefit of starting

antiretroviral therapy as early as possible [19], patients will tend to start cART at higher CD4+ T cell levels. Thus, a patient starting at 200 cells/μL could be at the 30th percentile in 2004 but at the 20th percentile in 2014 whereas attainment of a count of 300 cells/μL at 6 months may place him/her on the 30th percentile in 2004 but only the 20th in 2014. Therefore, these reference curves need to be regularly updated to remain relevant.

We restricted the analysis to the first nine months after cART initiation to retain homogeneity among the treatment regimens that were being used (physicians are unlikely to change regimens in the first months for non-toxicity reasons) [20]. Furthermore, the increase of CD4+ T cell over the first months is more pronounced than at later times, partly due to the redistribution of T cells [21]. On the other hand, it is likely that adherence is at its highest in the first nine months, and thus our reference curves are likely to identify those with suboptimal CD4 responses despite relatively good adherence to therapy. The extension of our findings to longer durations of cART exposure is under consideration. The results presented in this work were coming from statistical analyses that are not accounting for the correlation of repeated measures performed for each patient. Although the method proposed by Geraci and Bottai (LQMM R Package) based on random effects yields similar results for median, we found inconsistent results for the other percentiles. However, we assume that the use of a correlation matrix would have a very slight impact in our estimations considering the high number of patients as compared as a limited number of observations by patients.

Despite these limitations, this work has demonstrated the advantages of having a large sample size with a good representation of the HIV population; this may be difficult to achieve in a single study/cohort. For instance, CD4+ T cell dynamics depend on the

baseline level. In those starting cART with low CD4+ T cell counts, full immune restoration might be expected to be slow because of the profound immune suppression that has led to tissue damage in the thymus and lymph nodes [22, 23]. However, immune responses are also regulated by homeostatic mechanisms that might result in a ceiling effect, such that those initiating cART with higher CD4+ T cell counts might experience less pronounced responses than those starting with lower counts [24]. Hence looking at the literature, one can find studies where the CD4+ T cell increase was more pronounced in those with higher baseline values [9, 25-28], whereas in other studies the CD4+ T cell increase was larger in those starting cART with lower CD4+ T cell values [29-32]. These differences could be due to the differences between study populations and thus point to the need for large datasets supported by collaborations like COHERE to derive reference curves.

In conclusion, we propose reference curves for the CD4+T cell count that may be an additional tool for the clinician when evaluating responses to cART. A web tool is available at http://194.167.116.100/COHERE/.

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The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) group

Steering Committee - Contributing Cohorts: Robert Zangerle (AHIVCOS),Giota Touloumi (AMACS), Josiane Warszawski (ANRS CO1 EPF/ANRS CO11 OBSERVATOIRE EPF), Laurence Meyer (ANRS CO2 SEROCO), François Dabis (ANRS CO3 AQUITAINE), Murielle Mary Krause (FHDH-ANRS CO4), Jade Ghosn (ANRS CO6 PRIMO), Catherine Leport (ANRS CO8 COPILOTE), Linda Wittkop (ANRS CO13 HEPAVIH), Peter Reiss (ATHENA), Ferdinand Wit (ATHENA), Maria Prins (CASCADE), Heiner Bucher (CASCADE), Caroline Sabin (CHIC), Diana Gibb (CHIPS), Gerd Fätkenheuer (Cologne-Bonn), Julia Del Amo (CoRIS), Niels Obel (Danish HIV Cohort), Claire Thorne (ECS), Amanda Mocroft (EuroSIDA), Ole Kirk (EuroSIDA), Christoph Stephan (Frankfurt), Santiago Pérez-Hoyos (GEMES-Haemo), Osamah Hamouda (German ClinSurv), Barbara Bartmeyer (German ClinSurv), Nikoloz Chkhartishvili (Georgian National HIV/AIDS), Antoni Noguera-Julian (CORISPE-cat), Andrea Antinori (ICC), Antonella d'Arminio Monforte (ICONA), Norbert Brockmeyer (KOMPNET), Luis Prieto (Madrid PMTCT Cohort), Pablo Rojo Conejo (CORISPES-Madrid), Antoni Soriano-Arandes (NENEXP), Manuel Battegay (SHCS), Andri Rauch (SHCS), Cristina Mussini (Modena Cohort), Pat Tookey (NSHPC), Jordi Casabona (PISCIS), Jose M. Miro (PISCIS), Antonella Castagna (San Raffaele), Deborah_Konopnick (St. Pierre Cohort), Tessa Goetghebuer (St Pierre Paediatric Cohort), Anders Sönnerborg (Swedish InfCare), Carlo Torti

(Italian Master Cohort), Ramon Teira (VACH), Myriam Garrido (VACH). David Haerry (European AIDS Treatment Group)

Executive Committee: Stéphane de Wit (Chair, St. Pierre University Hospital), Jose M. Miro (PISCIS), Dominique Costagliola (FHDH-ANRS CO4), Antonella d'Arminio-Monforte (ICONA), Antonella Castagna (San Raffaele), Julia del Amo (CoRIS), Amanda Mocroft (EuroSida), Dorthe Raben (Head, Copenhagen Regional Coordinating Centre), Geneviève Chêne (Head, Bordeaux Regional Coordinating Centre). Paediatric Cohort Representatives: Ali Judd, Pablo Rojo Conejo.

Regional Coordinating Centres: Bordeaux RCC: Diana Barger, Céline Colin, Christine Schwimmer, Monique Termote, Linda Wittkop; Copenhagen RCC: Maria Campbell, Nina Friis-Møller, Jesper Kjaer, Dorthe Raben, Rikke Salbøl Brandt.

Project Leads and Statisticians: Juan Berenguer, Julia Bohlius, Vincent Bouteloup, Heiner Bucher, Alessandro Cozzi-Lepri, François Dabis, Antonella d'Arminio Monforte, Mary-Anne Davies, Julia del Amo, Maria Dorrucci, David Dunn, Matthias Egger, Hansjakob Furrer, Marguerite Guiguet, Sophie Grabar, Ali Judd, Ole Kirk, Olivier Lambotte, Valériane Leroy, Sara Lodi, Sophie Matheron, Laurence Meyer, Jose M. Miro, Amanda Mocroft, Susana Monge, Fumiyo Nakagawa, Roger Paredes, Andrew Phillips, Massimo Puoti, Michael Schomaker, Colette Smit, Jonathan Sterne, Rodolphe Thiebaut, Claire Thorne, Carlo Torti, , Marc van der Valk, Linda Wittkop, Natasha Wyss.

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Standard Reference distribution of CD4 response to HAART Project Team

Vincent Bouteloup (Statistician, Bordeaux University Hospital, France), Caroline Sabin (CHIC, University College London, London, UK), Amanda Mocroft (EuroSIDA, Dept Infection and Population Health, University College London, London, UK), Luuk Gras (ATHENA, Stichting HIV Monitoring, Amsterdam, the Netherlands), Nikos Pantazis (AMACS, Dpt. of Hygiene, Epidemiology & Medical Statistics Athens University Medical School, Greece), Vincent Le Moing (APROCO-COPILOTE, Montpellier University, France), Antonella d'Arminio Monforte (ICONA, Infectious Diseases, University of Milan, Italy), Murielle Mary-Krause (FHDH-ANRS CO4, INSERM, UMR_S 1136, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Paris, France, and Sorbonne Universités, UPMC Univ Paris 06, UMR_S 1136, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Paris, France), Bernardino Roca (VACH, Hospital General of Castellon, Spain), Jose M. Miro (PISCIS, Hospital Clinic Universitari, Barcelona, Spain), Manuel Battegay (SHCS, Division of Infectious Diseases and Hospital Epidemiology, Department of Clinical Research, University Hospital of Basel, Switzerland), Norbert Brockmeyer (KOMPNET, Department of Dermatology, Venerology and Allergology, St. Josef Hospital, Ruhr-Universität Bochum, Germany), Juan Berenguer (CoRIS, Hospital General Universitario Gregorio Marañón Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Spain), Philippe Morlat (AQUITAINE, Univ. Bordeaux, ISPED, Centre INSERM U897-Epidemiologie-Biostatistiques, Bordeaux, France and Service de Médecine Interne et Maladies Infectieuses, Hôpital Saint-André, Bordeaux, France), Niels Obel (Danish HIV Cohort, Department of Infectious Diseases, Copenhagen University Hospital, Copenhagen, Denmark), Stéphane De Wit (St Pierre Cohort, The Brussels Saint Pierre Cohort, Belgium), Gerd Fätkenheuer (Cologne-Bonn, Department of Internal Medicine, University

of Cologne and German Centre for Infection Research (DZIF), Cologne, Germany), Robert Zangerle (AHIVCOS, Medical University Innsbruck, Innsbruck, Austria), Jade Ghosn (PRIMO, APHP, Unité Fonctionnelle de Thérapeutique en Immuno-Infectiologie, Centre Hospitalier Universitaire Hôtel Dieu, Paris, France and Université Paris Descartes, EA 7327, Faculté de Médecine Site Necker, Sorbonne Paris Cité, Paris, France), Santiago Pérez-Hoyos (GEMES-Haemo, Vall d'Hebrón Institut de Recerca (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain), Maria Campbell (RCC Copenhagen), Maria Prins (CASCADE, Department of Internal Medicine, Division of Infectious Diseases, Center for Infection and Immunity Amsterdam (CINIMA), Academic Medical Center), Geneviève Chêne (RCC Bordeaux, University of Bordeaux, ISPED, Centre INSERM U897- Epidémiologie Statistique, Bordeaux, France), Laurence Meyer (SEROCO, INSERM, U1018, Epidemiology of HIV and STI, CESP; University Paris-Sud , Le Kremlin-Bicêtre, France Department of Public Health and Epidemiology, Bicêtre Hospital, AP-HP, Le Kremlin Bicêtre, France), Maria Dorrucci (CASCADE, Department of Infectious, Parasitic and Immune-mediated Diseases, Istituto Superiore di Sanità, Rome, Italy), Carlo Torti (MASTER, Division of Infectious and Tropical Diseases, University and Ospedali Civili of Brescia, Brescia, Italy), Rodolphe Thiébaut (Project lead, University of Bordeaux, ISPED, Centre INSERM U897-Epidémiologie Statistique, Bordeaux, France)

Conflicts of interest

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