TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

An alternative approach to estimate age-related mortality of kidney transplant recipients compared to the general population: results in favor of old-to-old transplantations

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Keywords
aging, clinical epidemiology, kidney transplantation, mortality, relative survival.

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Conflict of interest
The authors have declared no conflict of interest.

Received: 31 May 2013
Revision requested: 21 July 2013
Accepted: 10 November 2013
Published online: 20 December 2013

doi:10.1111/tri.12241

Summary

Compared to dialysis, kidney transplantation appears to be the best treatment for chronic kidney failure, even for older aged patients. Nevertheless, the individual benefit of transplanting elderly patients has to be balanced against the corresponding increase in the number of patients awaiting grafts. We analyzed the excess mortality related to kidney transplant recipients by taking into account the expected mortality of the general population (additive regression model for relative survival). We applied this method to a cohort of patients who received a first deceased-donor kidney transplant between 1998 and 2009 in France (DIVAT, $n = 3641$). Overall 10-year mortality was 13%. As expected, recipient age was the main risk factor associated with overall mortality. In contrast, recipient age was no longer significantly associated with the excess of mortality related to kidney transplant status by subtracting the expected mortality of the general population. Delayed graft function (DGF), pretransplantation immunization, and past history of diabetes appeared as the main risk factors of this higher mortality rate. Our results constitute a strong argument in favor of kidney transplantation, regardless of the patient's age. Preventing DGF may be more effective for decreasing the risk of death specifically attributable to the disease.

Introduction

In United States, the proportion of candidates on the active kidney transplant waiting list over the age of 65 years has increased during the past decade from 10 to 18% [1]. In France, a similar progressive increase has been observed, with 2.5% of patients over the age of 65 years registered on waiting list in 1996–1999, 5.2% in 2000–2003, 8.4% in 2004–2007 and 12.4% in 2008–2011. Since recipient age represents the main risk factor for post-transplantation mortality [2–7], the current increase in recipient age at transplantation time over the past decades should consequently be associated with an increased mortality after transplantation. Unexpectedly,

post-transplantation mortality has remained steady and may even be decreasing [8]. Possible hypotheses to explain this contrasted epidemiologic observation may be (i) the specific reduction in mortality related to the transplantation (for instance a lower incidence of acute rejection episodes, a better cytomegalovirus (CMV) prophylaxis or an improvement of immunosuppressive therapy management), (ii) a more stringent screening of old recipients limiting the access to the waiting list to low cardiovascular risk patients for instance, and/or (iii) small excess in mortality owing to the transplantation of older recipients. This third point is of primary importance in transplant clinical management since the individual benefit of transplanting elderly patients has to be balanced against the corresponding increase in patients on transplant waiting lists.

Several studies have evaluated this individual benefit. Transplantation appears to be the best treatment for end-stage renal disease compared to dialysis [9], even for older-aged patients [10,11]. While the long-term life expectancy of transplant recipients with a functioning graft is longer compared to patients under dialysis, it is conceivable that the mortality rate observed in kidney transplant recipients might be comparable to one observed in the general population. If this is true, this will constitute an additional argument in favor of transplantation, regardless of the age of patients in end-stage renal disease.

In this study, we proposed such an analysis by using an additive relative survival model. To the best of our knowledge, this is the first time this has been performed for a transplant cohort. This method allows a comparison of transplant recipient mortality rates against mortality rates of the general population. Three thousand six hundred and forty-one adult kidney transplant recipients, belonging to a French prospective cohort, have been studied.

Patients and methods

Study population

Inclusion criteria were recipients over 18 years of age who had received a first deceased-donor kidney transplant between January 1998 and December 2009 in the DIVAT network (www.divat.fr, Donneés Informatisées et VAlidées en Transplantation). This network consists of six French transplant centers. The "Comité National Informatique et Liberté" approved the data collection (N°891735) and written information was given to participants. This study of relative survival in kidney transplant recipients has been reviewed by the local ethics comity. We included 3641 patients with no missing data for the following variables that are historically identified as risk factors in kidney transplantation: donor age and gender, recipient age and gender, initial nephropathy of the recipient, HLA-A-B-DR mismatches, cold ischemia time, and past history of malignancy, hypertension, and diabetes. The other variables included in the analysis were the following: dialysis duration before the surgery, body mass index (BMI), last donor serum creatinine, past history of vascular disease, cerebrovascular cause of donor death, delayed graft function (DGF, defined as the need for post-transplantation dialysis), historic peak of panel-reactive antibodies (PRA, detectable or undetectable), and recipient serological status for CMV, Epstein Barr Virus (EBV) and hepatitis C virus (HCV).

Statistical analysis

Overall mortality

Time to patient death was calculated from the date of transplantation to the date of death with a functioning graft, regardless of the cause. Censoring occurred when a patient was either alive with a functioning kidney transplant at the last follow-up or was returned to dialysis. Patient survival was determined using the Kaplan–Meier estimator [12]. Risk factors were studied by the corresponding hazard ratio (HR) using the Cox's proportional hazard model [13]. Models were not stratified for centers because the analyses demonstrated homogeneity of survival between centers after adjustment for covariates. Significant variables in the univariate analysis ($P < 0.20$) were further analyzed by a multivariate model to determine those acting independently (descending procedure, $P < 0.05$). The proportional hazards assumption was tested using the weighted residuals [14].

The mortality rate related to kidney transplant recipients

Excess mortality related to kidney transplantation was assessed by subtracting the expected mortality of the general population from mortality observed post-transplantation. Expected mortality was computed from the lifetime tables proposed by the human mortality database (www.mortality.org). For each recipient, this subtraction was performed according to gender, age and year of transplantation. Risk factors were evaluated by the corresponding HR using the additive model as proposed by Esteve *et al.* [15]. More formally, for a recipient born in the year, who was a year old at transplantation, of sex s and with other characteristics z, his/her observed hazard of mortality, noticed by $\lambda_o(t|a,s,y,z)$, can be divided into two subhazards:

$$\lambda_o(t|a,s,y,z) = \lambda_e(t|a,s,y) + \lambda_r(d|a,s,z)$$

where $\lambda_e(t|a,s,y)$ is the expected mortality of a comparable individual in the general population, that is, with a similar profile $\{a,s,y\}$ (obtained from lifetime table) and $\lambda_r(d|a,s,z)$ is the excess mortality related to the disease, which may possibly depend on $\{a,s,z\}$. This excess hazard respects the proportional hazard assumption and the corresponding

regression coefficients represent the effects of covariates $\{a,s,z\}$ specifically associated with the mortality related to the transplantation. Typically, in the present study, the regression coefficients associated with the recipient age at transplantation are especially interesting in order to evaluate whether age-related post-transplant mortality can be considered greater than that of the general population. The covariate selection procedure was similar to the previous one described for the analysis of the overall mortality. The proportionality of hazards was also verified [16].

Software

All statistical analyses were performed using *R* 2.12.0 [17]. The additive relative survival model was performed using the *relsurv* package [18,19]. More precisely, the model was estimated from the expectation-maximization algorithm.

Results

Description of the cohort

The pretransplant clinical parameters are described in Table 1. The mean age at transplantation was 50.4 years (range: 18–84). We observed a notable aging of recipients according to the period with a mean increasing from 45.0 years (range: 19–67) in 1998 to 51.8 (range: 19–81) in 2009. Altogether, 24.9% of recipients were over 60 years at the time of transplantation and ranged from 11.0% in 1998 to 31.3% in 2009. The proportion of male recipients was 62.2% and showed no significant change over the study. The mean follow-up duration was 4.5 years (range: 0–12.8). Among the 3641 recipients, 231 deaths were observed.

Table 1. Characteristics of the kidney transplant recipients and donors at the time of transplantation in the DIVAT cohort (n = 3641). The column "missing" presents the number of missing values for each parameter.

	Missing	Mean (SD)
Recipient age (years)	0	50.4 (13.4)
Dialysis duration before surgery (years)	254	3.4 (3.0)
Body Mass Index (kg/m²)	48	24.2 (4.4)
Number of HLA mismatches (A + B + DR)	0	3.4 (1.2)
Cold ischemia time (h)	0	21.2 (8.3)
Donor age (years)	0	48.8 (16.0)
Last donor serum creatinine (μmol/L)	50	96.4 (58.4)
	Missing	**Percentage**
Male recipient	0	62.2
Malignancy history	0	6.6
Vascular disease history	0	11.5
Diabetes history	0	11.2
Hypertension history	0	78.9
Potentially recurrent causal nephropathy	5	31.2
Positive recipient CMV serology	18	58.7
Positive recipient EBV serology	80	96.2
Positive recipient HCV serology	12	3.9
Presence of delayed graft function	120	35.9
Male donor	0	60.3
Cerebrovascular cause of donor death	16	54.3
Detectable peak of panel-reactive antibody	526	22.4

All-cause mortality

Overall 10-year mortality, that is, the probability of dying within the first 10 years post-transplantation regardless of the cause of death, was 12.9% [CI 95% = (10.7, 15.0)]. As illustrated in Fig. 1, mortality seemed to be stable since 1998.

Univariate results are shown in Table 2. Risk factors with P-value <0.20 were further analyzed in Cox's multivariate model. The final model is presented in Table 3. As expected, the recipient age was the main risk factor of the all-cause mortality after transplantation. The relationship was not linear. Indeed, there is no significant difference in mortality rates between patients aged of 35 or less at transplantation compared to recipients aged between 36 and 50 years of age (HR = 0.9, P = 0.7784). In contrast, patients aged between 51 and 60 years old had a 2.3-fold higher risk of dying after transplantation than patients less than 35 years old (P = 0.0005). This hazard ratio increased to 3.4 for patients older than 60 years compared with recipients younger than 35 at the time of the transplantation (P = 0.0001). This analysis also demonstrated that male recipients had a 1.8-fold higher risk of dying compared to females (P = 0.0007). The other significant risk factors for transplant recipients were the history of diabetes

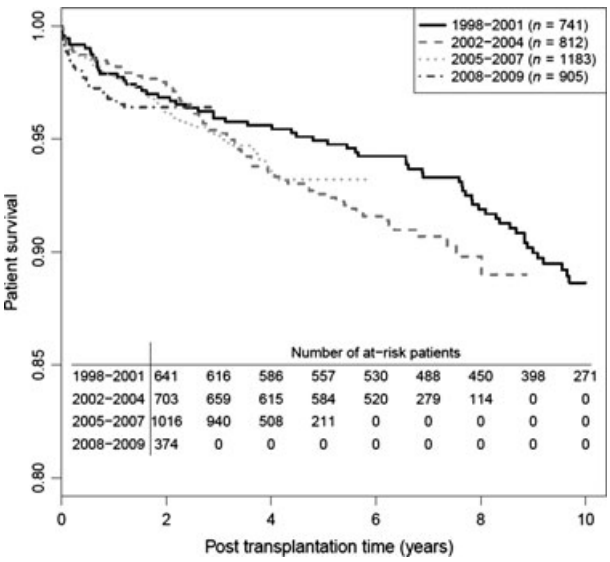

Figure 1 Overall patient survival estimated by using the Kaplan–Meier estimator according to the period of transplantation and the time post-transplantation (n = 3641).

Table 2. Univariate analysis of patient survival. Overall mortality was analyzed using the Cox model. Mortality related specifically to kidney transplant status was analyzed using the Esteve model.

	Hazard Ratio (CI 95%)	
	Overall mortality	Excess mortality
Recipient age (ref: 18–35 years)		
36–50 years	1.1 (0.6–1.9)	1.0 (0.4–2.5)
51–60 years	2.5 (1.5–4.1)	2.3 (1.1–5.0)
>60 years	4.8 (3.0–7.7)	4.1 (2.0–8.7)
Body Mass Index (ref: [13–18] kg/m²)		
18–25 kg/m²	1.2 (0.6–2.4)	0.7 (0.3–2.0)
26–30 kg/m²	1.5 (0.8–3.0)	1.0 (0.3–2.7)
>30 kg/m²	2.0 (1.0–4.3)	2.1 (0.7–6.0)
Donor age (ref: 0–25 years)		
25–40 years	0.9 (0.5–1.7)	0.8 (0.3–2.2)
40–60 years	1.6 (1.0–2.7)	1.3 (0.6–3.0)
>60 years	3.5 (2.1–5.8)	3.5 (1.6–7.6)
Number of HLA A+B+DR mismatches (ref: 0–3)		
3–4 mismatches	1.1 (0.8–1.6)	0.9 (0.5–1.6)
5–6 mismatches	1.2 (0.8–1.9)	1.0 (0.5–2.1)
Cold ischemia time (ref: 0–12 h)		
12–24 h	1.1 (0.7–1.8)	0.8 (0.4–1.8)
24–36 h	1.1 (0.7–1.9)	1.0 (0.5–2.4)
36–58 h	1.3 (0.7–2.5)	1.4 (0.5–3.7)
Last donor serum creatinine (ref: 8–60 μmol/l)		
61–100 μmol/l	1.0 (0.7–1.5)	1.0 (0.5–1.9)
101–180 μmol/l	1.0 (0.7–1.5)	0.8 (0.4–1.7)
>181 μmol/l	1.0 (0.6–1.9)	0.9 (0.3–2.7)
Dialysis duration before surgery (<1 vs. >1 year)	2.1 (1.3–3.2)	2.6 (1.3–3.2)
Recipient gender (Male versus Female)	1.6 (1.2–2.2)	1.3 (0.8–2.1)
Malignancy history (Yes versus No)	1.5 (0.9–2.3)	1.7 (0.8–3.7)
Vascular history (Yes versus No)	2.2 (1.6–3.0)	3.1 (1.9–5.1)
Diabetic history (Yes versus No)	2.6 (1.9–3.5)	3.7 (2.3–6.0)
Hypertension history	1.2 (0.9–1.7)	1.4 (0.7–2.6)
Potentially recurrent causal nephropathy	0.8 (0.6–1.0)	0.8 (0.6–1.0)
Donor gender (Male versus Female)	0.9 (0.7–1.1)	0.8 (0.5–1.3)
Vascular donor death (Yes versus No)	1.8 (1.3–2.3)	1.8 (1.1–2.8)
Recipient CMV serology (Positive versus Negative)	1.4 (1.0–1.9)	1.3 (0.8–2.1)
Recipient EBV serology (Positive versus Negative)	0.7 (0.4–1.3)	0.6 (0.2–1.5)
Recipient HCV serology (Positive versus Negative)	1.2 (0.7–2.3)	1.5 (0.5–4.1)
Delayed graft function (Yes versus No)	2.0 (1.5–2.6)	2.5 (1.5–4.2)
Detectable peak of PRA (Yes versus No)	1.3 (0.9–1.7)	1.8 (1.1–2.9)

(HR = 1.7, $P = 0.0027$), the delayed graft function (HR = 1.7, $P = 0.0005$), and the detectable historic peak of PRA (HR = 1.6, $P = 0.0099$).

Excess mortality related to the kidney transplant status

Esteve regression modeling allows the appraisal of the excess of mortality related to the kidney transplant status, since the expected mortality of the general population provided by the life table is removed regarding age, gender and birth date of each recipient. Regarding the results of the final multivariate model (Table 3, $n = 2995$ patients), we observed that recipient age was not significantly associated with the mortality excess related to the kidney transplant status. In other words, age-related post-transplant mortality was not significantly greater than that of the general population. For instance, despite patients older than 50 having a twofold higher risk of dying from a cause related to their transplant status compared to patients younger than 35, this trend was not statistically significant ($P > 0.05$).

The most significant risk factors correlating to the excess of mortality related to the kidney transplant status were the history of diabetes at the time of transplantation (HR = 2.0, $P = 0.0139$), the cerebrovascular cause of donor death (HR = 1.7, $P = 0.0416$), the delayed graft function (HR = 2.1, $P = 0.0019$), and the detectable historic peak of PRA (HR = 2.3, $P = 0.0007$). In other words, the excess risk of mortality related to the transplantation status is approximately increased by twofold if patients had a history of diabetes, if they presented a DGF after the transplantation, or if a historic PRA level was detectable.

Interaction between the donor and recipient ages

As previously described [20–22], the relationship between the recipient age and post-transplantation mortality may vary according to the donor age. We therefore tested such interaction between recipient and donor ages, and the results are presented in the Table 4. Even if interaction was not significant ($P > 0.05$), one can notice that the correlation between the recipient age and the all-cause mortality is principally verified for graft from deceased donors younger than 60 years of age. For older donors, the recipient age did not appear as a significant risk factor of death. In contrast, for both donor groups, we observed that recipient age was not significantly associated with the mortality excess related to the kidney transplant status.

Discussion

As already published in other literature, we have observed a continuing increase in transplant recipient age in our cohort over the last decades. Despite this observation, patient survival rates have remained stable. This epidemiologic observation tends to suggest that transplantation of elderly patients is not associated with excess mortality rates. To better evaluate the relationship between age and post-transplantation mortality, we present in this study the results of an original approach in transplantation: the relative survival model described by Esteve *et al.* [15]. The principle of this analysis is to remove the expected

Table 3. Multivariate analysis of patient survival. Overall mortality was analyzed using the Cox model. Mortality related specifically to kidney transplant status was analyzed using the Esteve model (n = 2995, 646 observations deleted as a result of missing values).

	Overall mortality			Excess mortality		
	HR	CI 95%	*P*-value	HR	CI 95%	*P*-value
Recipient age (ref: 18–35)						
36–50 years	0.9	0.5–1.8	0.7784	0.8	0.3–2.0	0.6478
51–60 years	2.3	1.3–4.0	0.0005	1.9	0.9–4.0	0.1209
61–85 years	3.4	1.9–6.1	0.0001	2.1	0.9–4.7	0.0785
Recipient gender (Male versus Female)	1.8	1.3–2.5	0.0007	1.6	1.0–2.7	0.0579
Diabetes history (Yes versus No)	1.7	1.2–2.5	0.0027	2.0	1.1–3.4	0.0139
Cerebrovascular donor death (Yes versus No)	1.3	1.0–1.9	0.0691	1.7	1.0–2.9	0.0416
Delayed graft function (Yes versus No)	1.7	1.3–2.3	0.0005	2.1	1.3–3.4	0.0019
Detectable peak of PRA (Yes versus No)	1.6	1.1–2.2	0.0099	2.3	1.4–3.6	0.0007

Table 4. Relationship between recipient age and patient survival according to donor age. Overall mortality was analyzed using the Cox model. Mortality related specifically to kidney transplant status was analyzed using the Esteve model (n = 2995, 646 observations deleted as a result of missing values).

	Overall mortality*			Excess mortality†		
	HR	CI 95%	*P*-value	HR	CI 95%	*P*-value
Donor age < 60 years						
36–50 years vs. 18–35 years	0.9	0.4–2.0	0.8642	0.5	0.2–1.6	0.2671
51–60 years vs. 18–35 years	2.6	1.4–5.0	0.0028	1.9	0.8–4.5	0.1191
61–85 years vs. 18–35 years	3.9	1.9–7.7	0.0002	2.0	0.7–5.8	0.2068
Donor age > 60 years						
36–50 years vs. 18–35 years	0.7	0.2–3.4	0.7254	1.0	0.2–6.1	0.9991
51–60 years vs. 18–35 years	0.8	0.2–2.9	0.7464	0.8	0.2–4.5	0.8247
61–85 years vs. 18–35 years	1.2	0.4–3.8	0.7828	0.8	0.2–3.9	0.7859

*The results were adjusted for recipient gender (HR = 1.8, CI 95% = 1.3–2.6), diabetes history (HR = 1.7, CI 95% = 1.2–2.6), cerebrovascular cause of donor death (HR = 1.3, CI 95% = 0.9–1.8), delayed graft function (HR = 1.7, CI 95% = 1.2–2.3), detectable peak of PRA (HR = 1.6, CI 95% = 1.2–2.3).

†The results were adjusted for recipient gender (HR = 1.7, CI 95% = 1.0–2.9), diabetes history (HR = 1.9, CI 95% = 1.1–3.3), cerebrovascular cause of donor death (HR = 1.7, CI 95% = 1.0–2.9), delayed graft function (HR = 2.0, CI 95% = 1.3–3.2), detectable peak of PRA (HR = 2.4, CI 95% = 1.5–3.9).

mortality of the general population by age, gender, and calendar year. We demonstrated that recipient age, which was reported as being a key for predicting the overall mortality in our results and those of other studies [2,3], was no longer a significant risk factor of the excess mortality related to kidney transplant status. This result was robust regardless of donor age, that is, organ quality. In other words, age-related post-transplant mortality was not significantly greater than that of the general population. This result constitutes an additional argument in favor of transplantation, regardless of the age of patients in terminal renal insufficiency. Importantly, given the advanced age at transplantation of older recipients, the life years gained by transplanting younger patients remains a priority. As we also described the absence of significant association between advanced recipient age and the risk of death among transplantations from donors older than 60 years, this also justifies the current increase in old-to-old transplantations.

The history of diabetes, the cerebrovascular donor death, the historic peak of PRA, and the DGF were significant risk factors for excess mortality for kidney transplant recipients compared to the general population. Because diabetes prevalence is lower in the general population than in the kidney transplant population, the corresponding hazard ratio may be overestimated. In contrast, because DGF and PRA are specific characteristics of transplant recipients, this result has to be considered. More precisely, patients with DGF had a 2.1-fold higher risk of dying because of their transplant status than patients without DGF ($P = 0.0032$). Patients with detectable historic peak of PRA had a 2.3-fold higher risk of dying because of their transplant status than patients with undetectable PRA ($P = 0.0007$). One can notice that for both models, the dialysis duration before the

surgery was not significantly associated with the post-transplantation mortality, in contrast to studies performed on North American kidney recipients [7,23]. Nevertheless, our results fit with prior observational studies already published on European kidney transplantation cohorts [3].

As usual, in parallel to the advantages of using the relative survival model in kidney transplantation, several limitations exist. The first difficulty is the required sample size. In fact, because only transplant-related deaths are indirectly taken into account and because of the inherent statistical properties of the relative survival model, the standard deviations of the HRs were larger than their respective estimations obtained from the traditional Cox's model. The lower statistical power of relative survival models may explain why fewer factors were significant, even though HR values were higher. Today, there is no solution to compute the required sample size for relative survival analysis. However, the results are based on 2995 patients, a sample size higher than many applications already published and based on this relative survival model [24–26]. The second difficulty results from the insufficient number of factors included in the lifetime tables (age, gender, and calendar year). Comorbidities such as diabetes or cardiovascular disease are probably more frequent in transplanted patients compared with the general population. In retrospect, it may have been more accurate to remove this comorbidity-related mortality. Our study illustrates the need for more complete and precise lifetime tables in the general population, including comorbidities such as diabetes or cardiovascular disease. Unfortunately, these tables are currently unavailable. The same comments could be made regarding the analysis of excess mortality after cancer; nevertheless, the relative survival approach has been widely applied to cancer registries and has improved the understanding of cancer-related mortality.

Finally, it is important to underline the possible selection bias of the healthier patients among those awaiting a transplant. This selection may be associated with a lower post-transplantation mortality compared to a (fictive) nonselected population of kidney transplant candidates. Therefore, our principal finding that recipient age did not constitute a significant risk factor of the excess mortality related to kidney transplant status may be partially due to this selection bias. This apparent limitation can be alternatively interpreted. Indeed, one can conclude that such a selection of recipients, especially elderly ones, is currently accurate for avoiding a significant excess of mortality related to their disease. Therefore, it constitutes an additional argument in favor of transplantation regardless of the age of end-stage renal disease patients, but always respecting the current recipient and donor selection rules which guarantee such good prognosis.

In conclusion, we applied the relative survival approach for the first time in transplantation. Even though we observed a trend, our study cannot demonstrate a significant excess of mortality after transplantation related to aging compared with the general population. This result constitutes an additional argument in favor of transplantation, regardless of the age of patients in terminal renal insufficiency. Moreover, rather than excluding elderly patients as candidate transplant recipients, preventing DGF may be more effective for decreasing the risk of death specifically related to the kidney transplant recipients.

Authorship

YF, AA and MG: designed study and wrote the manuscript. YF and VR: performed the analyses. KTL: was responsible of the data management. MK, ML, CL, HK, LR, NK, GM, VG, EM and FB: collected data. ML, JPD and JPS: served as scientific advisors.

Funding

The Roche Laboratory supports the collection of the data in the DIVAT cohort. This work was also supported by the RTRS "The Fondation de Co-operation Scientifique – CENTAURE" and by a grant from the French Ministry of Health (PHRC, PROG/11/85, 2011).

Acknowledgements

We thank the clinical research assistants (S. Le Floch, C. Scellier, V. Eschbach, P. Przednowed, V. Godel, K. Zurbonsen, X. Longy, C. Dagot, F. M'Raiagh). We also thank the Roche Laboratory for its support concerning the collection of the data in the DIVAT cohort.

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