Practical recommendations on long-term management of modifiable risks in kidney and liver transplant recipients – COMMIT Guidance

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University of Leuven, Belgium

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What are the key challenges we still face?

Patient and graft survival continue to decline 1 year post-transplantation

* 1-year and cumulative 5- and 10-year age-adjusted kidney graft survival rates calculated for 2005-2008 by period analysis;
† Survival probabilities were adjusted for age, gender and cause of end-stage renal disease (data shown in figure for period 2004-2008)
Reduced QOL after kidney transplantation vs general population

Similar QoL to age- and gender-matched population

- Physical functioning
  - Female patients: 63
  - Female age-matched population: 74
  - Male patients: 81
  - Male age-matched population: 84

- Emotional state
  - Female patients: 64
  - Female age-matched population: 76
  - Male patients: 68
  - Male age-matched population: 74

- Mental health
  - Female patients: 59
  - Female age-matched population: 65
  - Male patients: 57
  - Male age-matched population: 69

Significantly different QoL to age- and gender-matched population

- Lower psychophysical energy levels
  - Female patients: 47
  - Female age-matched population: 52
  - Male patients: 67
  - Male age-matched population: 60

- Reduced social activities
  - Female patients: 42
  - Female age-matched population: 71
  - Male patients: 47
  - Male age-matched population: 78

- Greater perception of pain
  - Female patients: 22
  - Female age-matched population: 18
  - Male patients: 59
  - Male age-matched population: 74

- Worsening general health perception
  - Female patients: 40
  - Female age-matched population: 49
  - Male patients: 27
  - Male age-matched population: 62

QoL, quality of life.

Reduced survival and QOL after liver transplantation vs general population

- QOL and survival in liver transplant recipients are lower than those seen in the age- and sex-matched general population\(^1\)

![Graph showing life expectancy and years lost](image)

After liver transplant HRQoL improves and remains stable; however, this does not reach the level of the general population\(^2\)

HRQoL, health-related quality of life.

The reduction in long-term graft and patient survival, in comparison with the general population, is determined by many factors some of which can be modified by allograft recipients and clinicians.
What is COMMIT?

The Consensus On Managing Modifiable risk In Transplantation (COMMIT) clinician group was formed in 2015 to provide expert practical guidance for the long-term identification and management of modifiable risk factors in kidney and liver transplantation.

What is the aim of COMMIT?

To recognise and implement simple and small changes that focus on the preventable causes of graft loss and premature death.

Who are the COMMIT group?

20 leading kidney and liver transplant specialists from ten countries across Europe
What are the objectives of the COMMIT guidance document?

- To provide **specific, practical recommendations** focussing on the management of modifiable risk in those kidney and liver transplant patients who have survived the first post-operative year

<table>
<thead>
<tr>
<th>Target audience</th>
<th>Recommendations</th>
<th>Checklist</th>
</tr>
</thead>
</table>
| • Healthcare professionals, including:  
  • Transplant and non-transplant clinicians  
  • Nurses and pharmacists  
  • Junior professionals working in transplant units | • Intended to complement local guidelines | • Systematic and efficient way to implement screening and management of modifiable risk in a clinical setting |
How was the guidance document created?

- Authors were separated into organ-specific groups and then further divided into seven workstreams for each organ.
- Workstreams were responsible for research, evidence grading and writing of specific sections of the document and for crafting recommendations.
- All members of the COMMIT programme reviewed and provided feedback on all sections of the guidance report.
How did we develop the guidance and checklist?

Over the period of approximately 1 year, authors met through a series of face-to-face and virtual meetings.

Submission to Transplantation in October 2016
Modifiable risk factors identified as priorities

- Non-adherence
- Under-immunosuppression/over-minimisation of immunosuppression
- Donor-specific antibodies (DSAs)
- Early ischaemic injury and DGF (kidney)/EAD and non-anastomotic biliary strictures (liver)

- Intra-patient variability in immunosuppressive exposure
- Adverse effects related to immunosuppression
- Cardiovascular and metabolic complications

DGF, delayed graft function; EAD, early allograft dysfunction
What is the structure of the COMMIT guidance document?

<table>
<thead>
<tr>
<th>Overall introduction of the report</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Problem to be addressed</strong></td>
</tr>
<tr>
<td>• Detailed overview of the problem to be addressed, highlighting the impact of the risk factor on patient and graft survival post-transplantation</td>
</tr>
<tr>
<td><strong>Key recent publications and reviews</strong></td>
</tr>
<tr>
<td>• Evaluate key evidence that supports recommendations and statements using the latest key literature</td>
</tr>
<tr>
<td><strong>Practical recommendation</strong></td>
</tr>
<tr>
<td>• Provide practical recommendations from available evidence and clinical experience</td>
</tr>
<tr>
<td><strong>Checklist</strong></td>
</tr>
<tr>
<td>• Checklist that provides guidance on what clinicians should be doing in terms of managing the risk factors and following-up patients</td>
</tr>
</tbody>
</table>
How were evidence and recommendations graded?

- Practical recommendation statements achieving 100% agreement among all authors (20) were included in the final guidance document.

- Evidence supporting each recommendation was evaluated and graded according to the Oxford Centre for Evidence-Based Medicine (OCEBM) system\(^1\)
  - Hierarchy of the likely best evidence
  - Helps clinicians in conducting their own appraisal of the evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Systematic review of randomised trials</td>
</tr>
<tr>
<td>2</td>
<td>Individual randomised trial/cross-sectional study/observational study</td>
</tr>
<tr>
<td>3</td>
<td>Non-randomised study/cohort study</td>
</tr>
<tr>
<td>4</td>
<td>Case-series/case-control studies</td>
</tr>
<tr>
<td>5</td>
<td>Mechanism-based reasoning</td>
</tr>
</tbody>
</table>

Hot off the press!

Tools for change...

COMMIT guidance document
and clinical checklist

Both peer reviewed by 10 external reviewers and the editorial board

Link: http://journals.lww.com/transplantjournal/toc/2017/04002

Focussing on the modifiable risk factors for graft loss
Causes of late graft loss in kidney transplant recipients

Causes of late graft loss in liver transplant recipients


HBV, hepatitis B virus; HCV, hepatitis C virus.
Major modifiable risk factors for graft loss

- Non-adherence
- Intra-patient variability in immunosuppressive exposure
- Under-immunosuppression/over-minimisation of immunosuppression
- Donor-specific antibodies (DSAs)
- Early ischaemic injury and DGF/EAD and non-anastomotic biliary strictures
- Adverse effects due to immunosuppression
- Cardiovascular and metabolic complications

DGF, delayed graft function; EAD, early allograft dysfunction
The first part of this presentation will focus on key recommendations for:

- Under-immunosuppression
- *de novo* Donor Specific Antibodies (DSAs)
- Non-adherence
Under-immunosuppression and DSAs
Under-immunosuppression can lead to DSA formation

Development of DSAs

- Acute AMR
- Chronic AMR
- Vascular AMR
- Possible TCMR
- Kidney graft survival

* CNI-free immunosuppressive protocol (under-immunosuppression).

AMR, antibody-mediated rejection; CI, Confidence interval; DSA, donor-specific antibodies; HR, hazard ratio.

Immunological status and risk of under-immunosuppression

- Patients should be stratified according to their immunological risk factors\(^1\)

Take into account both the risks and the benefits to each individual patient when determining their immunosuppressive regimen and optimal trough levels.\(^2\)

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**Complete the chart with the following information:**

- Previous transfusion
- Previous transplant
- Previous pregnancy
- Age
- HLA-DR mismatch
- PRA >0% (HLA antibodies)
- Pre-formed HLA-DSA
- Black ethnicity

**Notes:**

- DSA, donor-specific antibodies; HLA-DR, human leukocyte antigen – antigen D related; PRA, panel reactive antibody
Low tacrolimus trough levels are associated with risk of graft failure

- Renal transplant patients maintained on tacrolimus trough levels <5ng/mL* have a significantly higher risk of graft failure due to alloimmunity\(^1\)

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**Aim for tacrolimus target trough levels of 5 to 10 ng/mL in the first year after transplantation.**\(^2\)

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*versus >5ng/mL, year 1 post-transplant; tac, tacrolimus
CNI minimisation strategies may decrease BPAR

The ELITE-Symphony study: Low-dose* CNI is advantageous vs standard-dose CNI and CNI-free regimens, in terms of acute rejection and renal function1,2

<table>
<thead>
<tr>
<th>End point</th>
<th>Standard-dose cyclosporine</th>
<th>Low-dose cyclosporine</th>
<th>Low-dose tacrolimus</th>
<th>Low-dose sirolimus</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean calculated GFR (mL/min)</td>
<td>57.0±25.1</td>
<td>59.4±25.1</td>
<td>65.4±27.0</td>
<td>56.7±26.9</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>BPAR at 12 months (%)</td>
<td>30.1</td>
<td>27.2</td>
<td>15.4</td>
<td>40.2</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Allograft survival (%)</td>
<td>91.9</td>
<td>94.3</td>
<td>96.4</td>
<td>91.7</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* Actual levels in the low-dose arm were at the top of the target range (approximately 7ng/mL, rather than 3–7ng/mL; † p value for comparison with tacrolimus).

CNI, calcineurin inhibitor; ELITE, Efficacy Limiting Toxicity Elimination; BPAR, biopsy proven acute rejection.


Discourage minimisation without a convincing reason, due to increased risk of TCMR and AMR. CNI reduction, avoidance or late conversion should be carefully evaluated in each patient.3
CNI withdrawal can increase the risk of developing DSAs, and lead to graft loss\textsuperscript{1,2}

- CNI-free, mTORi-based immunosuppression leads to an increased risk of \textit{de novo} DSA development and BPAR\textsuperscript{2}

\begin{center}
\begin{tikzpicture}
\begin{axis}[
    width=\textwidth,
    height=0.5\textwidth,
    ybar,
    ymajorgrids=true,
    bar width=10pt,
    legend style={at={(0.5,-0.20)},anchor=north,legend columns=-1},
    ylabel={Incidence at 3–12 months post-kidney transplant (%)},
    symbolic x coords={De novo DSA, BPAR},
    xtick=data,
    ymin=0, ymax=30,
    x tick label style={rotate=45,anchor=east},
]

% CNI-free regimen (n=96)
\addplot[fill=gray!50] coordinates {(De novo DSA, 27.2) (BPAR, 25)};
\addlegendentry{CNI-free regimen (n=96)}

% CNI regimen (n=98)
\addplot[fill=orange!50] coordinates {(De novo DSA, 4.9) (BPAR, 5)};
\addlegendentry{CNI regimen (n=98)}

\end{axis}
\end{tikzpicture}
\end{center}

The risk of low immunosuppression/low-CNI regimens should be balanced with the potential benefit to the patient.\textsuperscript{3}

\* Chi square test. BPAR, biopsy-proven acute rejection; CNI, calcineurin inhibitor; DSA, donor-specific antibody; mTORi, mammalian target of rapamycin inhibitor

HLA mismatches are associated with DSA development

- An increased number of HLA mismatches, particularly HLA-DRβ1, are associated with the occurrence of DSAs\(^1\)

<table>
<thead>
<tr>
<th>HLA mismatches at baseline(^1)</th>
<th>De novo DSA (n=47)</th>
<th>No de novo DSA (n=268)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total HLA mismatches</td>
<td>3.28±0.9</td>
<td>2.84±1.6</td>
<td>0.009</td>
</tr>
<tr>
<td>HLA-DRβ1</td>
<td>1.15±0.5</td>
<td>0.87±0.7</td>
<td>0.005</td>
</tr>
</tbody>
</table>

- Although kidney allocation algorithms aim to reduce HLA mismatches, complete matching is not often feasible and the benefits of donor/recipient HLA matching have to be balanced against other issues, such as waiting time

DSA, donor-specific antibody; HLA, human leukocyte antigen.
Under-immunosuppression after liver transplantation
Patients with an increased need for immunosuppression

- Some liver transplant recipients may have an increased need for immunosuppression

Autoimmune liver disease
Re-transplanted for rejection\(^1\)
Grafted for HCV\(^2,3\)
Variation in drug levels

Take into account both the risks and the benefits to each individual patient when determining their immunosuppressive regimen and optimal trough levels.\(^4\)

HCV, hepatitis C virus.
Under-immunosuppression can lead to graft loss

- Under-immunosuppression can be linked to increased histological ACR, increased graft loss early post-transplant\(^1\) and increased likelihood of alloimmune response\(^2\)–\(^4\)

**Avoid under-immunosuppression (tacrolimus trough levels <6 ng/mL in the absence of induction agents, other immunosuppressive agents or mTORi)\(^5\)**

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ACR, acute cellular rejection; mTORi, mammalian target of rapamycin inhibitors.

Choice of immunosuppressive regimen can influence under-immunosuppression

- Lower dose prolonged-release tacrolimus as part of combination therapy* versus high dose tac was associated with a significant renal function benefit ($p=0.001$) and a lower incidence of biopsy-confirmed acute rejections (BCAR) ($p=0.016$)


*initially 5–15 ng/mL, then 4–12ng/mL after 3 months), and 5–15ng/mL until Day 42 then 5–12ng/mL, combined with MMF and basiliximab ; †initial dose 0.2mg/kg/day; ‡initial dose 0.175mg/kg/day. BCAR, biopsy-confirmed acute rejection; MMF, mycophenolate mofetil ; TAC, tacrolimus.

n=857
Immunosuppression withdrawal

- Complete immunosuppression withdrawal is feasible in ≈ 20% of selected liver transplant recipients\(^1\)
- In an immunosuppressive withdrawal study of 102 liver transplant recipients, 57 developed acute rejection, and 41 successfully discontinued over approximately 6.5 months (ITT population)\(^2\)

Withdrawal of immunosuppression should be confined to a research environment under strict clinical and histopathological surveillance protocols.\(^3\)

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DSAs and Non-adherence
Non-adherence is an independent risk factor for poor clinical outcomes\textsuperscript{1–3}

- It negatively impacts on graft and patient survival after liver transplantation\textsuperscript{4}
- It may contribute to graft loss in approximately 36\% of kidney transplant recipients\textsuperscript{4}

Non-adherence to an immunosuppressive regimen should be assessed as the ‘five vital sign’\textsuperscript{5}.

\textsuperscript{\textit{DSA}, donor-specific antibodies.}
\textsuperscript{a, Number of studies of each transplant type that examined each area of non-adherence; b, Significant differences (p<0.05) in rates of non-adherence were found between different types of organ transplants, based on meta-analysis}
Risk factor for the development of *de novo* DSAs

- *De novo* DSAs are associated with higher rates of graft failure in kidney transplantation\(^1\)

ABMR, antibody-mediated rejection; DSA, donor-specific antibodies.

Patient stratification by risk of DSA development

- Patients can be stratified post-transplantation based on risk of DSA development:¹

<table>
<thead>
<tr>
<th>Risk level</th>
<th>Risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk patients</td>
<td>Pre-existing DSAs</td>
</tr>
<tr>
<td>Intermediate-risk patients</td>
<td>History of DSAs but negative for DSAs at transplantation</td>
</tr>
<tr>
<td>Low-risk patients</td>
<td>Non-sensitised and receiving a first kidney transplant</td>
</tr>
</tbody>
</table>

Perform risk stratification and adjust the frequency of DSA monitoring according to the risk level.²

DSA, donor-specific antibody.
Antibody-mediated rejection after liver transplantation

- Preformed antibody (DSA)
  - Hyperacute AMR
    - Extremely rare
  - Acute AMR
    - Rare, difficult to diagnose histological definition in progress (Banff)

- De novo or persistent DSA
  - Chronic liver graft injury
    - Chronic AMR
    - Possible
    - Not yet defined

Prevalence of DSA 10 years after LT in patients presenting with unexplained liver tests abnormalities and/or unexplained fibrosis

95.5% in G0 (n=22)

51% in Control groups (n=69)

P <0.001
Median MFI according to study groups

- **G0 (n=21)**: MFI = 9916
- **Control groups DSA+ (n=35)**: MFI = 3443

P < 0.001

**Note:**
- DSA, donor-specific antibody
- MFI, mean fluorescent intensity
Screening for DSAs

- Routine screening for DSAs is not universally available nor implemented in all centres
- Improvements in tools to detect anti-HLA antibodies have led to single-antigen bead technology for detection of DSAs

COMMIT

Routine screening for DSAs is not available or implemented in all centres. Firm conclusions with regard to the effect on outcomes cannot be drawn in the absence of any proven therapy.

DSA, donor-specific antibody.
The COMMIT Checklist: De novo DSAs

5. **DE NOVO DONOR-SPECIFIC ANTIBODIES (DSAs)**

The role of DSAs is not fully understood but it is worth considering, especially:

- Before considering minimising immunosuppression
- ✓ With unexpected/unexplained graft dysfunction
- ✓ With any type of rejection (clinical, subclinical, chronic)
- ✓ In all patients at 1, 5 and 10 years post-transplant

**DSAs can be monitored through specific assays (e.g. single-antibody bead assay).**

Non-adherence leads to high intra-patient variability

- High IPV leads to poor transplant outcomes in kidney transplant patients\(^1,^2\)

- Consistent immunosuppressive therapy is critical in the early post-transplant period, when there is increased risk for graft rejection

Treatment-related factors can affect adherence

- Higher complexity and longer duration of the drug regimen
- Number of prescribed pills
- Taste and size of the pill

**Probability of non-adherence in reference to drug intake timing**

<table>
<thead>
<tr>
<th>Dosing Frequency</th>
<th>Likelihood of Adherence (odds ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ONCE DAILY</td>
<td>2.35 (95% CI*, 1.01 to 5.45)</td>
</tr>
<tr>
<td>TWICE DAILY</td>
<td>1.00</td>
</tr>
<tr>
<td>3-4X/DAY</td>
<td>.43 (95% CI, 0.22 to 0.86)</td>
</tr>
</tbody>
</table>

* CI = Confidence interval

ADMIRAD, Adherence Measurement in Stable Renal Transplant Patients Following Conversion From Prograf to Advagraf; BID, twice daily; QD, once daily; tac, tacrolimus

Simplified medication regimens can improve adherence

ADMIRAD Study: Tacrolimus BID vs tacrolimus prolonged release QD

- BID dosing (n=74)
- QD dosing (n=145)

p=0.0009

Simplified medication regimens, such as fixed-dose, once daily medications should be administered to improve adherence.\(^2\)

BID, twice daily; QD, once daily; tac, tacrolimus

Pre-transplant non-adherence to medication predicts poor adherence post-transplant\textsuperscript{1,2}

Prediction of post-transplant non-adherence by pre-transplant non-adherence in heart, liver, lung and kidney transplant patients\textsuperscript{1}

Establish a “baseline” evaluation of medication adherence; assess the patient’s previous ability to adhere to therapeutic regimens.\textsuperscript{3}

Sociodemographic factors impact adherence

- Higher in non-white patients, who have poorer social support and socioeconomic status, have low levels of education/illiterate, are unemployed, or have unstable living conditions\(^1\)
- Kidney transplant recipients aged 19–24 years are less likely to be adherent than patients aged 24–44 years\(^2\)
- Young adult and elderly patient groups may benefit from targeted education, medication schedules, clear prescription instructions, reminder cues, simplified drug regimens, and pre-filled pill boxes\(^3\)

Patient-level interventions need to focus primarily on behavioural change techniques. Simplified medication regimens, such as fixed-dose, once daily medications should be administered to improve adherence.\(^4\)

Poor motivation and forgetfulness can lead to non-adherence

- Adherence is significantly higher for patients using notifications and customised reminders, compared to those not using these aids


Identify patient barriers to adherence and develop a personalized action plan with specific solutions,(electronic)reminder systems, education and psychological behavioral support.

n=120 kidney patients
Healthcare systems can impact adherence

- Lack of adherence assessment as part of regular transplant follow-up¹
- Lack of adherence support as part of transplant follow-up¹
- Lack of coverage of immunosuppressive drugs¹
- Healthcare professionals not trained in behavioural assessment and interventions, or adequate communication style¹

Managing non-adherence

Identification

- Expressing difficulty with adhering to medication
- Non-response to treatment/clinical outcomes
- Pre-transplant non-adherence: non-adherence to dialysis in kidney transplantation
- Regular cancellation or appointments rescheduling

Non-adherent patient

Observing pill intake, pill counts, prescription refills, electronic monitoring

Management

- Drug intake monitoring using new digital technology
- Collaborative assessment from mental health specialists and nursing staff
- Determining drug concentration and by-products in the blood
- Validated self-reporting questionnaires

Discussion

Discuss non-adherence openly and non-judgmentally with the patient. Use different combined methods to identify adherence (e.g. questionnaires)

References:
Counselling and interventions can improve adherence

- An intervention course can increase adherence by 16% over 6 months

The second part of this presentation will review key recommendations for:

- Variability of immunosuppressive regimen
- Adverse effects related to over-immunosuppression
- Cardiovascular complications after kidney and liver transplantation
Variability of immunosuppressive regimen
IPV and the narrow therapeutic index

- High variability in immunosuppressive drug exposure can lead to clinically harmful events:

  1. Regular assessment of the serum trough concentrations is mandatory even in patients who are stable in the long term and are taking a constant dosage.  

Figures on this slide are illustrative
IPV and prognosis in kidney transplantation

- Tacrolimus IPV is a well recognised prognostic factor in kidney transplantation\(^1\)
- Patients with significant tacrolimus IPV are at an increased risk of rejection, graft loss and death\(^2\)

<table>
<thead>
<tr>
<th>TacSD threshold</th>
<th>Hazard ratio (95% CI) for primary composite end point(^a)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1.5 vs. ≤ 1.5</td>
<td>1.33 (0.75, 2.37)</td>
<td>0.33</td>
</tr>
<tr>
<td>&gt; 2 vs. ≤ 2</td>
<td>1.50 (0.89, 2.54)</td>
<td>0.13</td>
</tr>
<tr>
<td>&gt; 2.5 vs. ≤ 2.5</td>
<td>1.84 (1.04, 3.25)</td>
<td>0.04</td>
</tr>
<tr>
<td>&gt; 3 vs. ≤ 3</td>
<td>2.56 (1.42, 4.62)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

\(^a\)Primary composite end point (total graft loss, late acute rejection and transplant glomerulopathy) by TacSD threshold\(^1\)

**IPV, intra-patient variability**

Estimated hazard ratios

IPV, intra-patient variability
Time-dependent variability in tacrolimus trough blood levels is a risk factor for late kidney transplant failure

Ruth Sapir-Pichhadze, Yao Wang, Olusegun Famure, Yanhong Li and S. Joseph Kim

Division of Nephrology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada; Division of Nephrology and the Kidney Transplant Program, Toronto General Hospital, University Health Network, Toronto, Ontario, Canada; Division of Nephrology and the Renal Transplant Program, St Michael's Hospital, Toronto, Ontario, Canada and Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada


Tacrolimus trough-level variability predicts long-term allograft survival following kidney transplantation

John A. O'Regan, Mark Canney, Dervla M. Connaughton, Patrick O'Kelly, Yvonne Williams, Geraldine Collier, Declan G. deFreitas, Conall M. O'Seaghdha and Peter J. Conlon

High Inpatient Tacrolimus Variability Is Associated With Worse Outcomes in Renal Transplantation Using a Low-Dose Tacrolimus Immunosuppressive Regime


High IPV of tacrolimus predicts accelerated progression of chronic histological lesions in renal recipients


**Figure 2:** Change in chronicity score between month 3 and year 2, by intrapatient variability (IPV) tertile.

- **Low:** Change in chronicity score
  - p = 0.880

- **Middle:** Change in chronicity score
  - p = 0.023

- **High:** Change in chronicity score

IPV, intra-patient variability

IPV and risk of graft rejection in liver transplantation

- Variability was significantly higher in patients with biopsy-confirmed rejection vs those without (p=0.003)\textsuperscript{1}

Incidence of graft rejection in liver transplant patients by MLVI

![Bar graph showing incidence of graft rejection by MLVI values](https://via.placeholder.com/150)

- Low risk
- High risk

Adapted from Supelana et al, 2014.

* Mean trough concentrations within the first 15 days after liver transplantation; † reference value. MLVI, Medication Level Variability Index

Intra-patient variability

CV, coefficient of variation; SD, standard deviation

Variability calculator

Variability calculator
Coefficient of Variation (CV%) in tacrolimus trough levels

Easy to use

Retrospective tacrolimus levels

Visualises patient within-variability against accepted CV%

CV, coefficient of variation
## Determinants of tacrolimus IPV

<table>
<thead>
<tr>
<th>Factors&lt;sup&gt;1-5&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Highly modifiable</strong></td>
</tr>
<tr>
<td>• Food (dietary fat content, grapefruit juice, pomelo)</td>
</tr>
<tr>
<td>• Drug–drug interactions: antifungals, antivirals, other immunosuppressants, and other drugs</td>
</tr>
<tr>
<td>• Herbal products</td>
</tr>
<tr>
<td>• Uncontrolled generic substitution</td>
</tr>
<tr>
<td><strong>Slightly modifiable</strong></td>
</tr>
<tr>
<td>• Non-adherence</td>
</tr>
<tr>
<td>• Gastrointestinal events (diarrhoea)</td>
</tr>
<tr>
<td>• Any clinical situation motivating liver graft dysfunction</td>
</tr>
<tr>
<td>• Low serum proteins (hypoalbuminemia)</td>
</tr>
<tr>
<td>• Anaemia</td>
</tr>
<tr>
<td><strong>Non-modifiable</strong></td>
</tr>
<tr>
<td>• Pharmacogenetics</td>
</tr>
<tr>
<td>• Circadian rhythm of tacrolimus exposure</td>
</tr>
</tbody>
</table>

Improved adherence in renal recipients with tacrolimus QD compared with tacrolimus BID

- Randomised controlled trial using electronic monitoring

![Persistence Curves of Patients in the TAC QD and TAC BID Groups]


BID, twice-daily; QD, once-daily
Tacrolimus variability may occur when converting to generic formulations\(^1\)
- Insufficient evidence to provide reassurance that, in transplanted patients, generics are therapeutically equivalent to innovator immunosuppressants
- Safety concerns given the clinical consequences linked to both overexposure and underexposure
- However, there are no data to firmly suggest that generics are not equivalent and therefore unsafe\(^2\)

ESOT recommendations include situations where prescribing generics is deemed appropriate (i.e., cost conservative markets)\(^3\)

**Substitution to generic tacrolimus formulations should be attempted only in stable patients and under close monitoring of trough concentrations.**\(^4\)

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ESOT, European Society for Organ Transplantation
Converting from twice-daily to prolonged-release tacrolimus reduces IPV

Mean within-patient variability in tacrolimus trough levels reduced from 14.0% to 8.5% (p<0.05) after conversion

![Graph showing comparison between twice daily and prolonged release tacrolimus](image)

Converting from twice-daily to prolonged-release tacrolimus reduces IPV

Tacrolimus trough levels before and after conversion from tacrolimus BID to tacrolimus QD. Boxes represent the 25% quartile, median value and 75% quartile of range; vertical lines represent ranges

Adherence should be discussed with patients in whom tacrolimus trough concentrations change more than expected, despite a stable dose.\textsuperscript{1}

Avoiding significant variability early after liver transplant, is strongly recommended.\textsuperscript{1}

In patients with documented high levels of variability receiving tacrolimus BID, conversion to tacrolimus QD may be helpful.\textsuperscript{1}

Adverse effects related to over-immunosuppression
Over-immunosuppression is linked to adverse effects in both kidney and liver transplantation

- Over-immunosuppression is associated with a range of adverse effects that can lead to poor patient and graft survival:¹–⁴

**Class-related and drug-specific adverse effects¹–³**

- Renal impairment
- CV risk
- Metabolic complications
- Malignancies

**Increased risk of infections¹,⁴**

- Fungal
- Bacterial
- Viral

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Risk stratification, preventative measures and early detection of adverse events are vital for graft and patient survival.⁵

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CV, cardiovascular.
Viral infections due to over-immunosuppression are common in the first months after transplantation\(^1\)

Common virus infections include CMV, Polyomavirus, EBV, HHV-6, HHV-8, VZV\(^1\)

Higher rates of infection with ATG induction therapy,\(^1\) or cyclosporine-based regimens\(^2\)

Lower rates of CMV infection with mTORi based regimens\(^2\)

Liver transplant recipients are commonly chronically infected with HBV or HCV\(^3,4\)

CMV impacts on liver transplant outcomes\(^5\)

Vaccination is generally less effective during immunosuppression\(^6\)

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ATG, anti-thymocyte globulin; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV, Human herpes viruses; VZV, Varicella-zoster virus; HBV, hepatitis B virus; HCV, hepatitis C virus

Increased risk of bacterial and fungal infections

- There is a well established link between over-immunosuppression and bacterial infection

- Invasive fungal infections are linked with high morbidity and mortality after liver transplantation

- Infection rates can be reduced by:
  - Modifying immunosuppression
  - Using antifungal or antibacterial prophylaxis

- Pre-transplant screening for fungal colonisation may help determine if targeted pre-transplant or post-transplant antifungal prophylaxis is required in liver transplant patients.

TB, tuberculosis; CMV, cytomegalovirus
Routine screening and vaccination should be conducted for pneumococcal and influenza viruses.¹

Prophylaxis for *Pneumocystis jirovecii* infection and CMV infection should be given to patients following kidney transplantation.¹
Increased risk of renal impairment

- Post-liver transplant, CNIs are associated with a risk of renal impairment\(^1\)

Risk of impaired renal function may be managed by:

- **Choice of immunosuppressive regimen\(^1\)**
- **Early post-operative dose reduction of tac\(^1\)**
- **Conversion from immediate-release to prolonged-release tac\(^2\)**

Regularly monitor post-1 year transplantation for evidence of unwanted side effects of immunosuppression, including renal impairment.\(^4\)

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**eGFR**; estimated glomerular filtration rate; MDRD4; the four variable of modification of diet in renal disease; MMF, mycophenolate mofetil

Early high exposure to CNIs is associated with graft loss

• Patients with early high exposure to tacrolimus (trough levels >10ng/mL)* have an increased risk of graft loss after liver transplantation

<table>
<thead>
<tr>
<th>Mean tacrolimus trough concentrations*</th>
<th>n</th>
<th>RR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7 ng/ml</td>
<td>166</td>
<td>2.32 (1.28–4.16)</td>
<td>0.006</td>
</tr>
<tr>
<td>7–10 ng/ml</td>
<td>171</td>
<td>1†</td>
<td>–</td>
</tr>
<tr>
<td>10–15 ng/ml</td>
<td>128</td>
<td>2.17 (1.16–4.03)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

* Mean trough concentrations within the first 15 days after liver transplantation; † reference value.
Risk of recurrent HCC

- High levels of cyclosporine (>300ng/mL) and tac (>10ng/mL) have been associated with an increased risk of HCC recurrence\(^1\)
- The role of mTORi in reducing recurrent cancer post-transplant is unknown\(^2\)

Screening for malignancies

- Risk of cancer is increased after kidney transplant\(^1\)

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Standardised incidence ratio (SIR)(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaposi’s sarcoma</td>
<td>17.1</td>
</tr>
<tr>
<td>Non-melanoma skin cancer</td>
<td>16.6</td>
</tr>
<tr>
<td>Cancer of the lip</td>
<td>65.5</td>
</tr>
</tbody>
</table>

- Tumour screening programmes are not validated in the liver transplant setting\(^1\)

- Surveillance options include:
  - Annual skin examinations (all patients)\(^2\)
  - Yearly colonoscopy (PSC and IBD patients)\(^3\)
  - Low-dose CT screening for lung cancer (high-risk patients with smoking history)\(^4\)

Prevention and screening for cancer should follow the same recommendations as for the general population. Liver transplant patients should be screened annually for malignancies.\(^5\)

CT, computed tomography; IBD, irritable bowel disease; PSC, primary sclerosing cholangitis.

Management of cancer patients

- Decreasing immunosuppression in kidney transplant patients with cancer is common practice but is associated with an increased risk of graft rejection\(^1\)

- Switching to mTORi can reduce the risk of cancer compared with a control group,\(^*\) but has been associated with an increased risk of death\(^2\)

**Immunosuppression reduction in patients with cancer should be balanced, taking into consideration the prognosis of cancer, the type of anti-neoplastic therapy and the risk of rejection.\(^3\)**

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\(^1\) Gutierrez-Dalmau et al. Drugs 2007; 67 (8): 1167-1198

\(^2\) Knoll GA et al. BMJ. 2014;349:g6679

Cardiovascular complications after kidney and liver transplantation
Manage risk factors for cardiovascular disease according to current established treatment guidelines. Because specific guidelines for kidney and liver transplant recipients are lacking, guidelines for the general population should be followed.¹

Patient lifestyle factors

- Post-transplant obesity and related complications are common in liver transplantation\(^1\)
- Positive lifestyle changes may improve patient outcomes\(^2\)

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Educate patients on the benefits of lifestyle modification and provide support in achieving these goals.\(^3\)

AF, atrial fibrillation; CHF, congestive heart failure; CVEs, cardiovascular events; IHD, ischaemic heart disease.

Pre-transplant risk factors for post-transplant CVD

- Pre-transplant risk factors for post-transplant CVD include:  
  - Atrial fibrillation, prolonged QTc interval \(^2,^3\)
  - Pre-transplant diastolic dysfunction \(^4\)
  - Severe pre-operative coronary artery disease \(^5\)
  - Prior history of CVD (independent risk factor) \(^6\)
  - Pre-operative renal impairment and decreased kidney function assessed by eGFR (independent predictor of CV risk) \(^3,^7\)

- Pre-existing conditions that are also risk factors for CVD:
  - AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; CVD, cardiovascular disease; CVE, cardiovascular event; eGFR, estimated glomerular filtration rate.

Screen high-risk patients pre-operatively to establish risk factors for CVE. \(^8\)

Impact of cyclosporine on CVEs

- Switching from cyclosporine to tacrolimus has been associated with a reduction in LDL-cholesterol\textsuperscript{1}
- Belatacept-based regimens have been associated with lower BP levels and improved lipid profiles versus cyclosporine regimens\textsuperscript{2}

Impact of tacrolimus on CVEs

- Patients treated with tacrolimus may have lower risk of post-transplant CVD compared to other immunosuppressants\(^1\)
- A steroid-free regimen with tac + MMF has been associated with reduction of CV risk 1-year post-transplant\(^2\)

Multivariate analysis of the association between immunosuppressive regimens in liver transplant recipients without prior CVD\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus vs cyclosporine</td>
<td>0.72</td>
<td>0.535</td>
</tr>
<tr>
<td>Tacrolimus versus other*</td>
<td>0.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cyclosporine vs other*</td>
<td>0.33</td>
<td>0.060</td>
</tr>
</tbody>
</table>

* Defined as no tacrolimus or cyclosporine

CAD, coronary artery disease; CI, confidence interval; CNIs, calineurin inhibitors; CVD, cardiovascular disease; MMF, mycophenolate mofetil; tac. tacrolimus

Development of metabolic syndrome linked to mTORi

- Some immunosuppressive regimens have been associated with metabolic syndrome in liver transplant recipients \(^1,^2\)

- Switching from CNI to mTORi is linked with:
  - Hypertension\(^1\)
  - Dyslipidaemia\(^1\)
  - Weight gain\(^2\)

CNI-based immunosuppression is preferred over mTORi in patients at risk of developing dyslipidaemia.\(^3\)

**Development of diabetes**

**In renal transplant patients:**

- The incidence of NODAT is higher with tacrolimus vs cyclosporine (25% vs 9.5%; p<0.001)\(^1\)

- Incidence rises with increase in prednisolone dose\(^2\)

- NODAT and type 2 diabetes are associated with:\(^2\)
  - Poorer long-term survival
  - Increased CV risk

**In liver transplant patients:**

Risk factors for NODAT include:\(^2\)

- Older age
- Obesity
- Haemochromatosis
- Pre-transplant impaired glucose tolerance
- Alcohol-related disease
- Autoimmune hepatitis
- CNI use
- Glucocorticoids
- HCV

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CYP, cytochrome P450; CKD, chronic kidney disease; CNI, calcineurin inhibitor; CVE, cardiovascular event; DDP-4, dipeptidyl peptidase-4; GFR, glomerular filtration rate; HCV, hepatitis C virus; NODAT, new-onset diabetes after transplantation; tac, tacrolimus.

Development of dyslipidaemia

- KDIGO 2013 guidelines suggest statins for all kidney transplant recipients\(^1\)
- Reductions in LDL-cholesterol are associated with a reduced risk of CV endpoints\(^2\)
- Liver transplant is associated with increased rates of hyperlipidaemia\(^3\)
- The impact of hyperlipidaemia on post-liver transplant survival has not been studied in depth\(^3\)

KDIGO 2013 guidelines suggest all kidney transplant recipients are treated with a statin.\(^4\)

For liver transplant patients, target LDL cholesterol level is dependent on the patient’s cardiac risk level; the target of 3.4 mmol/L (130 mg/dL) Reduce for those with increasing risk.\(^4\)

CNI, calcineurin inhibitor; CV, cardiovascular; KDIGO, Kidney Disease Improving Global Outcomes; LDL, low-density lipoprotein; SD, standard deviation.
Development of hypertension

- KDIGO guidelines recommend a BP target of 130/80mmHg;\(^1\) however, evidence for specific BP targets is still lacking.\(^2\)

Liver transplant is associated with increased rates of hypertension.\(^4\)

- Hypertensive patients have \(\approx 2\)-fold higher risk of experiencing a post-transplant CVE.\(^5\)

Control of systolic BP may be associated with improved graft, patient and CVD-free survival.\(^3\)

Target BP should be 130/80 mmHg.\(^6\)

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BP, blood pressure; CNI, calcineurin inhibitor; CTS, The Collaborative Transplant Study; CVD, cardiovascular disease; CVE, cardiovascular event; KDIGO, Kidney Disease Improving Global Outcomes.

Liver and kidney transplantation is a great success but recipients still have a reduced quality and quantity of life, compared with a normal, age- and gender-matched population.

We believe that the risk of premature graft failure and patient death can be reduced by small improvements in follow-up.

COMMIT was formed of senior clinicians across Europe to produce guidance to help health care professionals improve management of allograft recipients.
Tools for change…

COMMIT guidance document
(Validated by external peer review)

Clinical checklist
(Developed to help implement the guidance)