**Transplant Recipient Adherence Monitoring and Management (TRAMM) Tool**

**Project Goal**
To create a tool for transplant professionals that summarizes strategies to optimize adherence monitoring and management within their post-transplant clinical practice.

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**NONADHERENCE MANAGEMENT**

- General Principles for Managing Nonadherence
- General Steps to Consider When Developing a Management Plan
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  - Patient Education
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  - Medication Simplification and Organization Tools
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  - Self-action Plan
  - Family/Caregiver Involvement
- Multidisciplinary Team Involvement in Nonadherence Management
- Develop a Plan with the Patient
- Establish a Follow-up Plan

Thank you for using the TRAMM Tool. Please scan the QR code below to provide feedback so we can improve this tool. Alternatively you can use this hyperlink: [TRAMM Tool Feedback](#)
I. ADHERENCE MONITORING: Strategies

- Identify a monitoring strategy that:
  - Fits your program’s goals related to adherence monitoring
  - Is able to be implemented and become part of your standard workflow
  - Fits one of the following categories
    - **Proactive**: Monitoring for nonadherence as part of standard of care follow-up
    - **Reactive**: Addition of nonadherence monitoring to your follow-up process once an issue is identified
    - **Hybrid**: A combination of both proactive and reactive with the use of each type varying according to the time post-transplant and/or patient population and program-specific needs

<table>
<thead>
<tr>
<th>Proactive Monitoring</th>
<th>Reactive Monitoring</th>
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<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td></td>
</tr>
<tr>
<td>Real time monitoring</td>
<td>Allows for a patient-specific (or subpopulation-specific) method to address nonadherence</td>
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<tr>
<td>Identifies issues before they result in a problem</td>
<td>Able to assess correlation of intervention with adherence issue/problem (assess if beneficial?)</td>
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<tr>
<td>Includes adherence monitoring as standard practice</td>
<td>Less time consuming as includes only one or a subset of patients</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td></td>
</tr>
<tr>
<td>May take more time initially to get setup and standardize into normal workflow</td>
<td>Includes only subset of patients</td>
</tr>
<tr>
<td>Lacks gold standard</td>
<td>Lacks gold standard</td>
</tr>
<tr>
<td>Difficult to know what type of metric(s) to utilize and at what time points</td>
<td>Maybe too little, too late (damage already done)</td>
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<tr>
<td></td>
<td>May be limited to “severe” nonadherence (e.g. missing labs and appointment)</td>
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II. ADHERENCE MONITORING: Key Considerations

<table>
<thead>
<tr>
<th>Key Considerations</th>
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<tbody>
<tr>
<td><strong>Who/How?</strong></td>
</tr>
<tr>
<td>• How will you identify non-adherent patients?</td>
</tr>
<tr>
<td>o How will you define nonadherence?</td>
</tr>
<tr>
<td>o How will you define when nonadherence requires an intervention (or adherence pathway)?</td>
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<tr>
<td>• What kind of personnel can you dedicate to this? In addition, would support from other disciplines be needed to implement this? If so, which ones?</td>
</tr>
<tr>
<td>o Consider partnering with care extenders such as home health care agencies and pharmacies</td>
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<tr>
<td>o Do you have IT support to build and disseminate reports and/or questionnaires (if deemed necessary)?</td>
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<tr>
<td>o Will it require team education/training? If so, how much would be needed and what type of education/training would you expect?</td>
</tr>
<tr>
<td>• Are there associated costs? If so, what are the costs?</td>
</tr>
<tr>
<td>• How important is tool validity? How important is sensitivity/specificity?</td>
</tr>
<tr>
<td><strong>What?</strong></td>
</tr>
<tr>
<td>• What resources are available?</td>
</tr>
<tr>
<td>• Does your adherence monitoring strategy involve patients using adherence tools?</td>
</tr>
<tr>
<td>o If so, will patient be able to use it? Will they require education regarding use? Will there be tech support readily available? Are there fees associated?</td>
</tr>
<tr>
<td><strong>Where?</strong></td>
</tr>
<tr>
<td>• Is adherence monitoring feasible to conduct within your clinic practice (e.g. in-person, telemedicine, remote)?</td>
</tr>
<tr>
<td><strong>When?</strong></td>
</tr>
<tr>
<td>• Do you utilize a proactive or reactive approach?</td>
</tr>
<tr>
<td>• What timeframe will you use to assess nonadherence?</td>
</tr>
<tr>
<td><strong>Why?</strong></td>
</tr>
<tr>
<td>• Why are you monitoring adherence?</td>
</tr>
<tr>
<td>• Does this align with your practice setting and programmatic goals?</td>
</tr>
<tr>
<td>• Will this help to address the identified issue/problem?</td>
</tr>
</tbody>
</table>

- **Define population**
  - **Total population**
    - All patients within your clinical practice
  - **Subpopulation**
    - Subset of patients proactively identified as potentially at risk for nonadherence
    - Subset of patients retrospectively identified as having issues with nonadherence
Examples

- Patients with an allograft rejection within 1 year post transplant due to not taking medications as prescribed
- Expanding adherence education for your pediatric patients to include adherence education that includes electronic delivery (e.g. videos, phone apps)
- Flag patients with potential risk factors for nonadherence
  - Job, insurance, or social support change or loss
  - High medication cost (e.g. medication cost meets a specific threshold)
  - Cultural language barriers, low health literacy, physical or cognitive impairments

Define monitoring time point(s)

- At every assessment time point
  - Adherence monitoring occurs as part of your standard of care at each assessment time point for all recipients or a subpopulation of recipients

- At some pre-specified assessment time points
  - Adherence monitoring occurs as part of your standard of care at certain assessment time points for all recipients (defined according to your standard operating process) or a subpopulation of recipients (defined per subpopulation, identified issue etc.)

Examples

- Adherence assessment conducted as part of the standard pharmacist assessment for all transplant patients
- Adherence assessment conducted on day of allograft biopsy, and monthly thereafter x 6 for those who have experienced allograft rejection
- Adherence assessment conducted within 30 days of notification, then every 3 months x 2 for those patients identified as having a change in employment/medical insurance
- Adherence assessment conducted within 1 week of identification of pattern of clinic no show/cancellations and determine next steps based on assessment

In summary, multiple factors must be considered when defining population and monitoring time points including:

- Adherence monitoring goals within your practice
- Which population(s)
- Feasibility
- What type of tools you are using (refer to subsequent sections)
### III. ADHERENCE MONITORING: Tools

- In this section, an overview of 6 different types of monitoring tools is provided
- For each tool: definitions, quantification strategies, keys for clinical practice implementation, available tools/references and clinical pearls are summarized

<table>
<thead>
<tr>
<th>Adherence Monitoring Tool Summary</th>
<th>Definition</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
</table>
| **Self-Report**                  | Questions directly investigate medication adherence or other variables via patient response | • Inexpensive  
• Customizable to your workflow | • Burdensome for patients  
• Time consuming for transplant team  
• Subjective |
| **Pill Count**                   | Objective measure to count the actual number of dosage units (e.g. pill, tablet) the patient has not taken at a specified time point | • Inexpensive  
• Simple  
• Objective | • Calculation relies on medication dispense date  
• Unable to generate information related to medication taking patterns/behaviors |
| **Lab and Appointment Visit Frequency** | Comparison of the number of actual lab and appointment visits completed to the expected number of visits to be completed in a defined time period | • Inexpensive  
• Objective  
• Data in EHR | • EHR data may lack accuracy and be difficult to automate  
• Difficult to standardize definitions |
| **Immunosuppressant Levels**     | Degree of adherence is defined according to the IS drug level measured and method of quantification | • Objective  
• No data collection needed  
• Data in EHR | • Complex calculations  
• Multiple factors may influence calculation  
• Potentially expensive |
| **Refill Records**               | Review of medication refill history to estimate the percent of time the patient had enough medication to take as prescribed | • Inexpensive  
• Objective  
• Time consuming if data not in EHR | • Provides no data on how medication is ingested  
• Multiple factors may influence calculation |
| **Biomarker Monitoring**         | Serial assessment of biomarkers such as donor-specific antibody, donor-derived cell free DNA, and gene expression profiling for detection of rejection potentially related to non-adherence | • Objective  
• Noninvasive monitoring | • No specific data currently to support adherence monitoring  
• Potentially expensive  
• Some affected by blood transfusions  
• May require specific testing locations  
• Intra- and inter-lab variability  
• May involve third party |
• **Common Implementation Pearls:**
  o Select tool(s) that fit within your standard practice to prevent delays or disruptions
  o Develop a monitoring process (timing and frequency)
    ▪ Serial monitoring and longitudinal assessments are preferred
    ▪ Monitoring should fit your workflow if possible
  o Establish threshold to define a patient as non-adherent
    ▪ There are no gold standard thresholds for any of the available tools
    ▪ Patients who meet the established threshold trigger a specific intervention or pathway
  o Develop a data collection process
    ▪ Reports with automated distribution or shared dashboards are preferred
      • Utilize your EHR
      • Create a dashboard/report to calculate desired metric and report when a patient meets the pre-defined nonadherence threshold
      • Implementing an electronic option allows for results that can be compiled and shared in real-time
  o Investigate available options. If what you need isn’t available reach out and discuss with your IT department
    ▪ Consider including transplant leadership to demonstrate support for your initiative
  o Develop a data review process with multidisciplinary team (pharmacist, provider, nurse) to allow for optimal team member support and participation
    ▪ Ensure process is in place and responsibilities are defined
      • If not an automated report or dashboard, who collects or inputs the data, and how is it collected?
      • Who reviews the data?
      • Who implements the intervention?
    ▪ Establish a frequency to review data
    ▪ Develop a process for notifying a defined pool of team members for patients meeting the established threshold
      • Create a message pool within EHR
      • Enter results within a shared data repository
      • Use care alerts within the EHR
        o Automated notification through EHR
  o Create a clinical pathway
    ▪ Use results to guide patient discussion about non-adherent behaviors
    ▪ Educate staff on selected tools and workflow, and educate patients on expectations if indicated based on the tool
- **Self-Report**
  - **Define**
    - Method to obtain information from patients about their specific attitudes, feelings and beliefs about something (e.g. medication adherence)
    - Contains specific, open-ended questions aimed to allow patients to describe their behaviors related to medication adherence (e.g. how many doses have you missed in the past week?)
    - Questions directly investigate medication adherence (e.g. did you miss any doses) or other variables associated with adherence (e.g. taking medication is a burden)
    - Usually completed by patient themselves but could alternatively have team member review/ask/discuss with patient
  - **Quantify**
    - Method assesses initiation, implementation, and persistence
    - Degree of nonadherence is defined by the tool used
    - The threshold of nonadherence that triggers intervention defined by the transplant program

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**Examples**

- Patients that report missing any medications since last pharmacy assessment will trigger an adherence pathway

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- **How to implement:**
  - *Should be customized to your workflow without causing delays or disruptions and consider:*
    - **Timing**
      - During in-person clinic visit; while waiting in the lobby or once in their exam room
      - During telemedicine visit
      - At an alternate time than the clinic visit (e.g. before the visit, after the visit or at set post-transplant time periods which may or may not coincide with the standard clinic visit)
    - **Frequency**
      - Select according to what would fit best within your standard practice if possible (rather than revising your practice to include questionnaire)
      - Longitudinal assessments preferred
      - Consider monthly or quarterly to provide a continuous link between the transplant program and patient
      - This will allow identification of cognitive, psychological, regimen, medical, social, or economic related problems that can impact adherence over time and possibly lead to late rejection(s)
• **Options for distribution**
  o Paper, Electronic, Verbal

**Examples**

- Email or text link
- Use existing tools within EHR with IT support (e.g. as part of eCheck-In for visit)
- Electronic survey tool completed with tablet, computer or smartphone
  o REDCap or another electronic survey tool
    - Consider shared REDCap library of survey instruments
      ▪ [https://redcap.vanderbilt.edu/consortium/library/search.php](https://redcap.vanderbilt.edu/consortium/library/search.php)
  o Survey Monkey
  o Qualtrics

• **Establish adherence threshold**
  o Patients who meet the established threshold trigger a specific intervention or pathway

• **Data collection and review**
  o Develop a data collection process. Reports with automated distribution or shared dashboards are preferred. Utilize your EHR.
    ▪ Investigate available options. If what you need isn’t available reach out and discuss with your IT department (consider including transplant leadership to demonstrate support for your initiative)
    ▪ Create a dashboard/report to calculate desired metric and report when a patient meets the pre-defined nonadherence threshold
  o Develop a data review process with multidisciplinary team (pharmacist, provider, nurse) to allow for optimal team member support and participation
    ▪ Ensure process is in place and responsibilities are defined
      • If not an automated report or dashboard, who collects or inputs the data, and how is it collected?
      • Who reviews the data?
      • Who implements the intervention?
    ▪ Establish a frequency to review data
    ▪ Develop a process for notifying a defined pool of team members for patients meeting the established threshold
      • Create a message pool within EHR
      • Enter results within a shared data repository
      • Use care alerts within the EHR
      • Automated notification through HER
**Examples**

- Enter results within a shared data repository that all team members can access (e.g. flowsheet, EHR synopsis)
- Use care alerts via EHR sent by transplant nurse coordinator or pharmacist if adherence related issue identified

**Create a clinical pathway**
- Use results to guide patient discussion about non-adherent behaviors

**Available Tools and References**
- Basel assessment of adherence to immunosuppressive medication scale (BAASIS) questionnaire
- Imunosuppressant therapy adherence instrument (ITAS)
- Imunosuppressant therapy adherence barrier instrument (ITBS)
- Identification of medication adherence barriers questionnaire (IMAB Q10)
- Patient-Reported Outcomes Measurement Information System (PROMIS) Medication Adherence Scale (PMAS)
- Simplified medication adherence questionnaire (SMAQ)

**Clinical and Monitoring Pearls**
- Consider internal/external validity of tool
- Method typically underreports medication nonadherence

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TRAMM Tool - Created by Transplant Pharmacy Adherence Consortium (TPAC). October 2023
Contributors: Nohely Castro, Paige Dunton, Kayla Evans, James Fleming, Haley Gutstein, Jennifer Iuppa, Tiffany Kaiser, Karen Khalil, Mary Leick, Abbie Leino, Holly Mansell, Jeong Park, TrisAnn Rendulic, Christina Ruggia-Check, Rahul Samudralwar, Tricia Suarez, David Taber, Kimi Ueda
• **Pill Count**
  
  o **Define**
  
  - Objective measure to count the actual number of dosage units (e.g. pill, tablet) the patient has not taken at a specified time point (e.g. clinic visit)
  - The amount of dosage units remaining is then compared to the amount of dosage units prescribed to determine degree of medication taking adherence
  - Can be used for variety of types of medicine formulations (e.g. tablets, capsules, liquids) but not feasible for nondiscrete or prn dosing
  - Usually completed by member of the transplant team through a visual inspection of the patients pillbox and/or pill bottles. May also be done via records review from patient’s electronic pillbox and/or bottle cap data
  
  o **Quantify**
  
  - Approach will vary according to program specific definitions, protocols and standards of practice
  
<table>
<thead>
<tr>
<th>Example</th>
</tr>
</thead>
</table>
  | Pill count = \[
  \frac{\text{Number of dosage units dispensed} - \text{number of dosage units remained}}{\text{Prescribed number of dosage units per day} \times \text{number of days between 2 timepoints}} \times 100
  \] |

  - Time points being compared will vary (e.g. clinic visits, phone calls) and should be selected in accordance with your clinical practice
  - Calculation based on the medication dispense date; therefore unable to consider early refills and having surplus medication
  - Pill count percentage calculated can be used as measure of medication taking adherence with adherence threshold defined according to your clinical practice (there is no standard value or goal)
  - The threshold of nonadherence that triggers intervention defined by the transplant program

<table>
<thead>
<tr>
<th>Example</th>
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</thead>
<tbody>
<tr>
<td>Patients with pill count &lt; 90% will trigger an adherence pathway</td>
</tr>
</tbody>
</table>

  o **How to implement:**

  - *Should be customized to your workflow without causing delays or disruptions; should consider the following:*
  
  - **Timing**
    - During the in-person clinic visit; while waiting in the lobby or once in their exam room
    - During the telemedicine video visit
    - At an alternate time than the clinic visit (e.g. before the visit, after the visit or at set post-transplant time periods which may or may not coincide with the standard clinic visit)
- **Frequency**
  - Select according to what would fit best within your standard practice if possible
  - Longitudinal assessments preferred
  - Consider monthly initially and then increase to quarterly or semi-annually

- **Establish adherence threshold**
  - Patients who meet the established threshold trigger a specific intervention or pathway

- **Data collection and review**
  - Develop a data collection process.
  - Develop a data review process with multidisciplinary team (pharmacist, provider, nurse) to allow for optimal team member support and participation
    - Ensure process is in place and responsibilities are defined
      - If not an automated report or dashboard, who collects or inputs the data, and how is it collected?
      - Who reviews the data?
      - Who implements the intervention?
  - Develop a process for notifying a defined pool of team members for patients meeting the established threshold
    - Create a message pool within EHR
    - Enter results within a shared data repository
  - Use care alerts within the EHR

<table>
<thead>
<tr>
<th>Examples</th>
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<tbody>
<tr>
<td>- Enter results within a shared data repository that all team members can access (e.g. flowsheet, EHR synopsis)</td>
</tr>
<tr>
<td>- Use care alerts via EHR sent by transplant nurse coordinator or pharmacist if adherence related issue identified</td>
</tr>
</tbody>
</table>

- **Create a clinical pathway**
  - Use results to guide patient discussion about non-adherent behaviors

- **Available Tools and References**
  - MEMS: Medication Event Monitoring System: may be helpful for assessing real behaviors regarding taking medications, but may be expensive and impractical for regimens with lots of meds
  - Pillbox check

- **Clinical and Monitoring Pearls**
  - Unable to factor in non-discrete or PRN dosing and early refills
  - Lacks accuracy as relies on medication dispense date
  - Patient may forget to bring all medicines or alter unused portion
  - Method typically underreports medication nonadherence
• **Lab and Appointment Visit Completion Frequency**
  
  **Define**
  
  - **Laboratory visit**: What does this mean for your program?
    - Which lab locations are included (only internal labs or both internal and external lab locations)?
    - Which labs are included (all or just those ordered by transplant program)?
    - How frequently do lab visits occur? Does frequency vary over time post-transplant?
    - Are patients required to attend all lab visits to be adherent?
  
  - **Appointment visit**: What does this mean for your program?
    - Which appointments are included (all or just those related to transplant)?
    - Are appointments at any location or just specific locations included?
    - How frequently do appointments occur? Does it vary over time post-transplant?
    - Are patients required to attend all appointment visits to be adherent?
  
  - **Rescheduled, missed or no-show visits**
    - How does your program define and monitor? What threshold indicates issue with adherence?

  **Quantify**
  
  - Approach will vary according to program specific definitions, protocols and standards of practice.

  **Examples**

<table>
<thead>
<tr>
<th>Visit completion rate:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compare <strong>ACTUAL number of visits</strong> completed to <strong>EXPECTED number of visits</strong> to be completed within a defined time period</td>
</tr>
<tr>
<td>Quantify the number of no-show visits</td>
</tr>
<tr>
<td>The number of visits can be calculated separately or combined (lab visits, appointment visits or combined as labs plus appointment visits)</td>
</tr>
</tbody>
</table>

  **How to implement:**
  
  - *Should be customized to your workflow without causing delays or disruptions; should consider the following:*
  
  - **Develop a monitoring process (timing and frequency)**
  
  - **Establish adherence threshold**
    - Must define expected lab and appointment visit frequency during post-transplant follow up period as well as the expected completion frequency

  - **Education**
    - Provide education on lab and appointment visit completion frequency expectations to patients and transplant team
    - Provide education on the process for monitoring and tracking lab and appointment visit completion frequency to allow for standardization

  - **Establish adherence threshold**
• Patients who meet the established threshold trigger a specific intervention or pathway
• Establish a threshold to define when a patient is nonadherent in terms of lab and appointment visit completion frequency
  o Thresholds can be established for separate events (labs or appointments) or combined

### Data collection and review
• Develop a data collection process. Reports with automated distribution or shared dashboards are preferred. Utilize your EHR.
  o Investigate available options. If what you need isn’t available reach out and discuss with your IT department (consider including transplant leadership to demonstrate support for your initiative)
  o Create a dashboard/report to calculate desired metric and report when a patient meets the pre-defined nonadherence threshold
• Develop a data review process with multidisciplinary team (pharmacist, provider, nurse) to allow for optimal team member support and participation
  o Ensure process is in place and responsibilities are defined
    ▪ If not an automated report or dashboard, who collects or inputs the data, and how is it collected?
    ▪ Who reviews the data?
    ▪ Who implements the intervention?
  o Establish a frequency to review data
  o Develop a process for notifying a defined pool of team members for patients meeting the established threshold
    ▪ Create a message pool within EHR
    ▪ Enter results within a shared data repository
    ▪ Use care alerts within the EHR
• Automated notification through EHR or lab provider. If external lab results are part of the visit completion rates defined by your program need to ensure these results are entered (e.g. manually or auto-populate) within the EHR.
• Investigate options with laboratory providers

### Create a clinical pathway
• Use results to guide patient discussion about non-adherent behaviors

### Available Tools and References
• **Impact of healthcare appointment nonadherence on graft outcomes in kidney recipients**
• **Nonadherence to appointments strong predictor of medication nonadherence and outcomes in kidney transplant recipients** (may require institutional access or purchase)
• **Adherence to laboratory testing in pediatric liver transplant recipients**
• **Nonadherence to post transplant care: prevalence, risk factors and outcomes in adolescent liver transplant recipients**

• **Clinical and Monitoring Pearls**
  - Monitoring for nonadherence to lab and appointment visits should be completed on a routine basis through normal workflow procedures via automation or visual assessment
  - Patients that surpass the predetermined program-specific threshold should trigger a pathway (set standard of practice for teams action/follow up for those meeting the nonadherence threshold)
  - Provide lab and appointment completion frequency education to patients and team members to ensure process is standardized and completion frequency can be assessed
• **Immunosuppressant (IS) Levels**
  
  **Define/Quantify**
  
  - In addition to being used as a measure of drug exposure and toxicity, routine IS drug level monitoring has been utilized in the setting of assessing medication nonadherence.
  - Degree of adherence is defined according to the IS drug level measured and method of quantification.
  - Threshold to establish nonadherence for each IS may differ and may vary according to various factors (e.g., drug formulation, lab methodology, specific transplant program).
  - Most evidence for this approach uses tacrolimus, but theoretically this type of IS monitoring can be done with any others as well (e.g., cyclosporine, sirolimus, everolimus).
  - Options for tacrolimus drug levels as a measure of medication adherence:

<table>
<thead>
<tr>
<th>Quantification</th>
<th>Description</th>
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</table>
| Intrapatient variability (IPV)  | • IPV is the fluctuation in tacrolimus trough concentrations within an individual over a period of time during which the tacrolimus dose is stable.  
  • Usually calculated via standard deviation or coefficient of variation  
    - Standard deviation (SD) measures extent of deviation amongst a group of tacrolimus levels  
    - Coefficient of variation (CV) = SD/mean trough concentration x 100 |
| Undetectable trough concentration | • Blood levels that are too low to be detected by laboratory tests          |
| Time in therapeutic range (TTR) | • Percentage of time the patient’s tacrolimus level was within the target range |
| Dried blood spot (DBS)          | • DBS is when a few drops of blood are applied to an absorbent paper and analyzed for tacrolimus  
  • This can be done at home in between lab draw visits  
  • Qualitative or quantitative                                    |

  o **Quantify**
  
  - Methods vary
  - Examples for tacrolimus are listed in the table above
  
  - Determine which time points to obtain tacrolimus levels for IPV calculations
    - Consider waiting at least 3-6 months post-transplant or when on a stable dose
    - Clinical utility after 1-2 years post-transplant is not well established
  - Determine the quantity and frequency of tacrolimus levels
    - At least 3 levels
    - At least 1 level per month
Examples

- Highly variable drug is defined as one exhibiting a within subject CV > 30% (Midah KK, 2005)
- Tacrolimus CV 15.2% in a highly adherent patient population (Leino AD, 2019)
- Tacrolimus CV > 25-40% will trigger an adherence pathway for the patient (per center specific data)

- Existing literature suggests the threshold associated with risk of poor clinical outcomes (including nonadherence) may depend on organ group, time post-transplant, race
- Limited evidence directly evaluating an IPV threshold and adherence status

Data collection and review

- Develop a data collection process
- Reports with automated distribution or shared dashboards are preferred.
- Utilize your EHR
  - Investigate available options
  - If what you need isn’t available reach out and discuss with your IT department (consider including transplant leadership to demonstrate support for your initiative)
  - Create a dashboard/report to calculate desired metric and report when a patient meets the pre-defined nonadherence threshold
- Develop a data review process with multidisciplinary team (pharmacist, provider, nurse) to allow for optimal team member support and participation
- Ensure process is in place and responsibilities are defined
  - If not an automated report or dashboard, who collects or inputs the data, and how is it collected?
  - Who reviews the data?
  - Who implements the intervention?
- Establish a frequency to review data
- Develop a process for notifying a defined pool of team members for patients meeting the established threshold
  - Create a message pool within EHR
  - Enter results within a shared data repository
  - Use care alerts within the EHR
  - Automated notification through EHR or lab provider
- Need to “clean up” included levels used for quantification
  - Define parameters (# or period to include, drawn between 7-11a, outpatient only, etc.)
  - Ensure levels are accurate and were drawn correctly
  - Discard outlier levels
- Most literature includes a static calculation at 1 year with all levels from 3 or 6 months to 12 months
- Assessment should consider other factors that may impact IS drug levels (e.g. drug interactions, food effects, diarrheal illness, laboratory assay, nonadherence)

- **Create clinical pathway**
  - Use results to guide patient discussion about non-adherent behaviors

- **Available Tools and References**
  - [Etiologies and Outcomes Associated with Tacrolimus Levels Out of a Typical Range That Lead to High Variability in Kidney Transplant Recipients](#) (may require institutional access or purchase)
  - [A comprehensive review of the impact of tacrolimus intrapatient variability on clinical outcomes in kidney transplantation](#)
  - [Intrapatient Variability of Tacrolimus Exposure in Solid Organ Transplantation: A Novel Marker for Clinical Outcome](#)
  - [Tacrolimus intrapatient variability in solid organ transplantation: A multi-organ perspective](#)

- **Clinical and Monitoring Pearls**
  - Nonadherence monitoring via IS levels should be done on a routine basis, include a standardized calculation, occur within the normal workflow and via automation (if possible)
  - Should include team collaboration and working with EHR analysts
• **Refill Records**
  
  o **Define**
    - Review of medication refill history to estimate the percent of time the patient had enough medication to take as prescribed
    - Can detect initiation and persistence
    - May be unable to detect some patterns of nonadherence such as late or missed doses
    - Data could suggest different outcomes (e.g. 7 day drug holiday vs 14 missed doses over a year)
  
  o **Quantify**
    - Multiple calculations are available
    - The most common are medication possession ratio (MPR) and proportion of days covered (PDC)

<table>
<thead>
<tr>
<th>Calculation</th>
<th>MPR</th>
<th>PDC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\frac{\text{Days supply for all fills in period}}{\text{Number of days in period}} \times 100%$</td>
<td>$\frac{\text{Number of days covered during period}}{\text{Number of days in period}} \times 100$</td>
</tr>
</tbody>
</table>
| Considerations | • Often overestimates adherence, more likely to be affected by early refills | • Addresses stockpiling and early refills by moving forward additional supply to the next period
• Better equipped to accurately estimate adherence when considering all drugs in a regimen together
• PDC is preferred by the Pharmacy Quality Alliance and used for the calculation of Medicare Star Ratings

• **How to implement:**
  
  - Should be customized to your workflow without causing delays or disruptions; should consider the following:
    - **Develop a monitoring process (timing and frequency)**
      - Align with patient appointment
      - At an alternate time than the clinic visit (e.g. quarterly)
      - Select according to what would fit best within your standard practice if possible
      - Longitudinal assessments preferred
  
  - **Establish adherence threshold**
    - Patients who meet the established threshold trigger a specific intervention or pathway
    - No transplant specific threshold/cutoff
    - Most literature identifies 10-20% of patients as nonadherent based on refill records typically using an 80% threshold (range 80-95%)
• However, the average PDC or MPR among transplant recipients is reported to be >90%
• Setting a higher threshold may be warranted

**Data collection and review**

- Develop a data collection process. Reports with automated distribution or shared dashboards are preferred. Utilize your EHR.
  - Investigate available options. If what you need isn’t available reach out and discuss with your IT department (consider including transplant leadership to demonstrate support for your initiative)
  - Create a dashboard/report to calculate desired metric and report when a patient meets the pre-defined nonadherence threshold
- Develop a data review process with multidisciplinary team (pharmacist, provider, nurse) to allow for optimal team member support and participation
  - Ensure process is in place and responsibilities are defined
    - If not an automated report or dashboard, who collects or inputs the data, and how is it collected?
    - Who reviews the data?
    - Who implements the intervention?
- Establish a frequency to review data
- Develop a process for notifying a defined pool of team members for patients meeting the established threshold
  - Create a message pool within EHR
  - Enter results within a shared data repository
  - Use care alerts within the EHR
  - Automated notification through EHR

**Available Tools and References**

### Examples

<table>
<thead>
<tr>
<th>• Auto-calculated by EHR (e.g. Epic from SureScripts data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No/limited data on accuracy</td>
</tr>
<tr>
<td>• Likely depends on location and local pharmacy inclusion in SureScripts</td>
</tr>
<tr>
<td>• Missing data leads to lots of false positives (likely if a patient uses multiple pharmacies or switches to a pharmacy not included in the claims database)</td>
</tr>
<tr>
<td>- Can be reduced by establishing inclusion criteria such as at least 1 fill within 30 days of the start period, at least 1 fill within 100-360 days, and at least 3 fills during the study period</td>
</tr>
<tr>
<td>• Collaboration with specialty pharmacy</td>
</tr>
<tr>
<td>• Not all patients can use a specified pharmacy</td>
</tr>
</tbody>
</table>
  - Likely not feasible if must contact each patient’s pharmacy individually |
  - Most likely requires access to a large pharmacy claims database such as SureScripts or Symphony |
• References
  o Medication adherence and graft survival among kidney transplant recipients
  o Medication adherence and graft survival among heart transplant recipients
  o Long-term Immunosuppression Adherence After Kidney Transplant and Relationship to Allograft Histology
  o A retrospective analysis of immunosuppression compliance, dose reduction and discontinuation in kidney transplant recipients
  o Immunosuppressant therapy adherence and graft failure among pediatric renal transplant recipients
  o Estimating time-varying drug adherence using electronic records: extending the proportion of days covered (PDC) method
  o Refill-Based Medication Use Quality Measures in Kidney Transplant Recipients: Examination of Proportion of Days Covered and Medication Possession Ratio

• Clinical and Monitoring Pearls
  • Multiple factors may influence calculation
    o Frequent or prolonged hospitalizations
    o Accuracy of pharmacy prescriptions (e.g., are tacrolimus dose changes always sent to the pharmacy, stockpiling for a trip)
    o Be aware of patients who use auto-refills (may reduce usefulness)
    o Limited data on the best evaluation period (denominator of equations)
      ▪ Reports frequently use 30 or 360/365 days
      ▪ Time varying extensions of PDC have been proposed
    o Unclear if entire regimen combined, all drugs separately, or the drug least likely to have frequent dose adjustments should be used
    o Consider nuances of multiple pharmacy sources (mail order, VA, specialty, retail, etc.)
• **Biomarker Monitoring**
  
  *Note: There is no data to recommend the use of biomarker monitoring as an adherence-monitoring tool. The authors decided to include this section as data may suggest the use of biomarker monitoring as a tool for early signs of rejection, which may or may not be related to adherence.*

  - **Define/Quantify**
    - **Donor Specific Antibody (DSA):** appearance of new or significantly increased levels of DSA
      - Nonadherence has become a strong predictor of de novo DSA (Sellares 2011, Wiebe 2012, Wiebe 2015)
      - Caution: If using DSA as a measure of nonadherence, transplant team needs to avoid diagnosing/treating AMR based solely on DSA
      - A close relationship with HLA lab/director may be necessary to successfully implement this tool
        - Limitations: variable cutoffs for DSA (measured in MFI or mean fluorescent intensity), highly sensitized patients may have positive DSA despite adherence
    - **Donor-derived cell free DNA (dd-cfDNA):** DNA of donor origin in the blood of a transplant recipient increases when injury to allograft
      - Measures proportion of donor-derived cfDNA to recipient derived cfDNA
      - More sensitive to AMR than ACR → possible marker of nonadherence
      - No studies on association with nonadherence
      - Limitations: nonspecific marker, cost, potential for false negatives (short half life may lead to normal levels in noncompliant patients as there may not be constant injury), and most of the available evidence relates to use to rule out rejection not for chronic surveillance
    - **Gene Expression Profiling (GEP):** Panel of genes identified as having a role in allograft rejection
      - Most useful as negative predictor of acute cellular rejection
        - No studies on association with nonadherence
      - Limited literature on new tools, cell-free DNA and gene expression (Kataria 2021, Maldonado 2021)

  - **How to implement:**
    - **Develop a monitoring process (timing and frequency)**
      - Select according to what would fit best within your standard practice if possible (rather than revising your practice to include questionnaire)
      - Longitudinal assessments preferred
      - Try to include as add on monitoring with other transplant follow-up labs
    - **Program protocols/guidelines**
      - Must define within your program in what situations biomarker monitoring should be utilized
    - **Establish adherence threshold**
• Patients who meet the established threshold trigger a specific intervention or pathway
• **DSA:** MFI cutoff for level of positivity
  o No standard threshold established (MFI varies per laboratory and possibly within the same laboratory over time)
• **dd-cfDNA:** variable practices dependent on organ type
  o Measured at least 2 weeks post-transplant
  o No standard for frequency
  o No standard for monitoring for surveillance (data all in diagnostic performance, not prognostic for nonadherence or other outcomes)
• **GEP:** variable practices dependent on organ type
  o No commercially available test currently validated before 90 days post-transplant
  o Meaning of multiple values or patterns unknown
  o Turnaround time varies per test manufacturer
  o Refer to specific commercial products for detailed information including limitations
  o All data in diagnostic performance, not prognostic for nonadherence or other outcomes

- **Data collection and review**
  • Develop a data collection process. Reports with automated distribution or shared dashboards are preferred. Utilize your EHR.
    o Investigate available options
      ▪ If what you need isn’t available reach out and discuss with your IT department (consider including transplant leadership to demonstrate support for your initiative)
    o Create a dashboard/report to calculate desired metric and report when a patient meets the pre-defined nonadherence threshold
  • Develop a data review process with multidisciplinary team (pharmacist, provider, nurse) to allow for optimal team member support and participation
    o Ensure process is in place and responsibilities are defined
      ▪ If not an automated report or dashboard, who collects or inputs the data, and how is it collected?
      ▪ Who reviews the data?
      ▪ Who implements the intervention?
    o Establish a frequency to review data
    o Develop a process for notifying a defined pool of team members for patients meeting the established threshold
      ▪ Create a message pool within EHR
      ▪ Enter results within a shared data repository
      ▪ Use care alerts within the EHR
      ▪ Automated notification through EHR or lab provider

- **Create a clinical pathway**
  • Use results to guide patient discussion about non-adherent behaviors
• At this time there is insufficient data to warrant utilizing biomarker results to guide immunosuppression dose adjustments

**Available Tools and References**

• **Donor-derived Cell-free DNA in Solid-organ Transplant Diagnostics: Indications, Limitations, and Future Directions**

• **Understanding the Causes of Kidney Transplant Failure: The Dominant Role of Antibody-Mediated Rejection and Nonadherence**

• **Evolution and Clinical Pathologic Correlations of De Novo Donor-Specific HLA Antibody Post Kidney Transplant**

• **The Synergistic Effect of Class II HLA Epitope-Mismatch and Nonadherence on Acute Rejection and Graft Survival**

• **Advances in personalized medicine and noninvasive diagnostics in solid organ transplantation**

**Clinical and Monitoring Pearls**

• May involve third party (e.g. HLA lab) and results unable to be reported within the EHR

• Consider logistics required to complete biomarker monitoring
  - Testing locations (e.g. test may only be able to be performed at specific lab locations, health systems versus external labs), patients geographical distance and transportation capabilities

• Evaluation of cost-benefit should be conducted at each center (e.g. protocol biopsies, repeat biopsies compared to surveillance test)
  - All tests are covered by Medicare and most commercial insurances; should review payer benefits related to allowed frequency of testing

• **DSA**
  - No standard MFI threshold established

• **MFI** varies per laboratory and possibly within the same laboratory over time

• **dd-cfDNA**
  - Not applicable for pregnant patients, identical twins, multi-organ or repeat transplants or history of BMT
  - Not be used within 30 days of blood transfusions
  - Turnaround time is 3-6 days

• **GEP**
  - TruGraf to be used in stable renal function (serum creatinine< 2.3, <20% increase compared to previous values)
  - Neither test validated before 90 days (Trugraf) and 6 months (Allomap)
  - Turnaround time varies per test manufacturer (e.g. 2 days (Allomap) or 3 days (Trugraf))
NONADHERENCE MANAGEMENT

- **General principles for managing nonadherence**
  - Cause(s) and risk factors of nonadherence are complex and multifactorial (Neuberger 2017)
  - Consider patient-centered and tailored approach with multimodal interventions

<table>
<thead>
<tr>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>- <strong>The MAESTRO-Tx trial</strong> (Dobbels, et al. 2017)</td>
</tr>
<tr>
<td>- <strong>TAKE-IT</strong> (Foster, et al. 2018)</td>
</tr>
</tbody>
</table>

- Consider a multidisciplinary approach with team and patient
- Ensure shared-decision making with patients in identifying barriers and interventions
- Degree of adherence can fluctuate over time, as can the barriers to adherence
  - Regular monitoring is recommended
  - Adapt strategies as needed

- **General steps to consider when developing a management plan**

<table>
<thead>
<tr>
<th>Nonadherence identification</th>
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<tbody>
<tr>
<td>Self-report</td>
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</table>

1. **Identify the cause(s) of nonadherence**
   - Use motivational interviewing
   - Active Listening

2. **Identify the tools that would be most appropriate for the patient**
   - Patient Education
   - Simplify/Organize Meds
   - Technology
   - Self-action plan
   - Involve Family/Caregiver

3. **Include multidisciplinary team in management based on identified causes**
   - Transplant Team (e.g. pharmacist, social worker, financial counselor, APP, nurse, physician, psychologist, dietitian)
   - Medical Teams (e.g. cardiology, endocrinology, primary care)
   - Other (e.g. pharmacy technician, home health aide)

4. **Meet with the patient to establish the plan (in-person, telephone or video visit)**
   - Shared decision-making is key

5. **Follow-up**
   - Develop a plan for how frequent follow-up will be conducted
Once nonadherence is identified, identify cause(s)
  ▪ Motivational interviewing is an effective strategy
  ▪ Key Principles
    o Express empathy using open-ended questions and reflective listening
    o Explore ambivalence towards a behavior to identify personal motivations
    o Highlight discrepancies between personal motivations and current behavior
    o Present reasons for behavior change from the individual’s point-of-view
    o Roll with resistance by reflecting or rephrasing arguments against change
    o Support self-efficacy by highlighting genuine strengths
  ▪ Resources
    • Motivational Interviewing Pocket Guide
    • Motivational Interviewing Best Practices Training Guide
    • Home Study ACPE Activity (may require membership or fees to access)
  o Identify tools that would most appropriately address the patient’s cause(s) for nonadherence
  ▪ Patient Education
    • Most will benefit from patient education (or re-education)
    • Information on the importance of adherence
      o Pre-transplant
        ▪ Adherence is an important criterion for transplant listing
        ▪ Adherence to medications is one way, but also consider adherence to dialysis, pretransplant clinic appointments, etc.
        ▪ If a patient is determined not eligible due to nonadherence, set a timeframe needed to show commitment to become active again. May consider implementing some type of adherence contract/agreement
      o Post-transplant
        ▪ Nonadherence has been associated with poor outcomes such as antibody-mediated rejection and death-censored allograft failure (Sellas J, 2012)
    • Information on medications
      o Provide clear, verbal and written medication instructions and medication schedules at an appropriate level for the patient’s health literacy
        https://www.ahrq.gov/health-literacy/improve/pharmacy/tools.html
        ▪ Consider patient-specific factors (e.g., age, health literacy) to determine an effective mode of education
      ▪ AST Resources:
        • Medicines to keep new organ healthy
        • Transplant fact or fiction video on side effects
        • Transplant medicines: what are they and why needed for life
• **Solid Organ Transplantation: An Educational Miniseries for Patients** (describes kidney transplant process in 6 videos; video 5 = medications)

• ITNS Educational Brochures
  o While knowledge about adherence is important, interventions that only target knowledge are likely inadequate and require a multidimensional approach

• *Consider barrier-specific strategies when picking adherence tools*

<table>
<thead>
<tr>
<th>Barrier-specific Strategies</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Cognitive impairment, forgetfulness, and interruption with daily routine</td>
<td>Involves family and adequate support for medication management, consider a simplified regimen (e.g. once-daily dosing, monotherapy) encourage counselling/behavioral intervention (e.g. reminders, alarms, use of pillbox, motivational interview)</td>
</tr>
<tr>
<td>Language barriers</td>
<td>Ensure teaching tools in native language, use teach back method, use a translator, establish effective communication plans for longitudinal care</td>
</tr>
<tr>
<td>Low health literacy</td>
<td>Involves family and adequate social support for medication management, use a pillbox with a visual aid (e.g. numbering system)</td>
</tr>
<tr>
<td>Age</td>
<td>Different learning strategies for pediatrics vs. adults, vulnerable populations: transition to adult, elderly, peer group mentorship or support groups may be helpful, especially for pediatric populations</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>Consider at least 16 font print on prescription labels, braille labels, blister cards</td>
</tr>
</tbody>
</table>

**Medication simplification and organization tools**

• Consider advantages and disadvantages of tools such as: organizational packaging, regimen modification, reminder devices (*Chisholm-Burns MA, 2012; Table 1*; may require institutional access or purchase)

• Select according to what is most appropriate for the specific patient

**Technology**

• Consider the patient population (e.g. young adults vs elderly) when choosing the most appropriate technology

• Reminder systems (e.g., phone alarms, text messages, electronic pillbox)
  o EMR online portal (e.g., MyChart)
  o MedActionPlan PRO
  o Apps; suggest transplant specific apps (Medisafe, Transplant Hero, AlloCare Transplant Health)
    • Link to data supporting use for adherence
Examples

- **Pharmacist-led mobile health intervention and transplant medication safety: a randomized controlled trial**
- **Significant hospitalization cost savings to the payer with a pharmacist-led mobile health intervention to improve medication safety in kidney transplant recipients**
- **Impact of a pharmacist-led, mHealth-based intervention on tacrolimus trough variability in kidney transplant recipients: a report from the TRANSAFE Rx randomized controlled trial**

- Evolving patient care technologies
  - Current applications
    - Data is largely patient self-reported (manual logging med doses consumed, vitals, and other values)
    - Patients able to grant application access to care partner
    - Connect with affiliated mail order pharmacies to facilitate refills
  - Future state
    - EHR integration: able to seamlessly import patient medication list from patient portal/EHR
    - Bluetooth or connected devices (pillbox, blood pressure cuffs, glucometers) to automate data reporting
    - Integrated clinician dashboards (clinicians able to correct medication list, view population health data, alerts)

- **Self-action Plan**
  - Patient specific written agreements aimed to address issues involving adherence (may include adherence/behavior contract)

Example

- **Chisholm-Burns MA, et al. J Am Pharm Assoc 2012;52:816-822** (Figure 1: Example of a behavioral contract; may require institutional access or purchase)

- **Family/Caregiver Involvement**
  - Include multidisciplinary team in management of nonadherence based on identified cause(s)
    - Financial counselors when finances have been associated with nonadherence (e.g. low income, unemployment, lack of or change in insurance coverage)
    - Social workers to help with assistance to overcome logistical barriers (e.g. transportation, childcare, health literacy, other social determinants of health that may limit access to care)
    - Transplant providers and APPs (Advanced Practice Providers) can help with motivational interviewing, additional education, and emphasis on the importance of adherence
    - Therapists, psychologists and/or psychiatrists can be helpful in the setting of depression, anxiety, or mood disorder affecting adherence
  - Develop a plan with the patient
    - A shared plan with the patient is essential for success

TRAMM Tool - Created by Transplant Pharmacy Adherence Consortium (TPAC). October 2023
Contributors: Nohely Castro, Paige Dunton, Kayla Evans, James Fleming, Haley Gutstein, Jennifer Iuppa, Tiffany Kaiser, Karen Khalil, Mary Leick, Abbie Leino, Holly Mansell, Jeong Park, TrisAnn Rendulic, Christina Ruggia-Check, Rahul Samudralwar, Tricia Suarez, David Taber, Kimi Ueda
- Plan should include defined goals for the patient that can be assessed over time
  - **Establish a follow-up plan**
    - Should include review of how patient is progressing toward pre-defined goals of the shared plan
    - Frequency of follow-up may vary and will depend on patients’ progress (important to remember that adherence can vary over time)
    - Once these goals have been achieved, determine whether continued follow-up is necessary
References


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https://power2save.org/transplant-fact-or-fiction/

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