ARCHITECT Tacrolimus

REF 1L77-25

en

Tacrolimus
1L77
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B1L770

Revised September 2015.

Package insert instructions must be carefully followed. Reliability of assay results cannot be guaranteed if there are any deviations from the instructions in this package insert.

NAME

ARCHITECT Tacrolimus

INTENDED USE

The ARCHITECT Tacrolimus assay is a chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of tacrolimus in human whole blood on the ARCHITECT iSystem.

The ARCHITECT Tacrolimus assay is to be used as an aid in the management of liver and kidney allograft patients receiving tacrolimus therapy.[1, 2]

SUMMARY AND EXPLANATION OF THE TEST

Tacrolimus is an immunosuppressive drug discovered in 1984 by the Fujisawa Pharmaceutical Co., Ltd. It has been shown to be effective for the treatment of organ rejection following transplantation. The results of clinical trials with liver[3] and kidney[4, 5] have been published. Clinical studies are continuing for a variety of indications.

Tacrolimus binds to a family of proteins termed FK506 (tacrolimus) binding proteins (FKBPs).[6, 7] The formation of a larger pentameric complex comprised of FKBP, tacrolimus, calmodulin and calcineurins A and B results in the inhibition of the phosphatase activity of calcineurin.[8] The action of transcription factors requiring dephosphorylation for transport to the cell nucleus are thus inhibited leading to blockage of T-cell proliferation and function.

Tacrolimus may be administered IV or orally. Absorption from the gastrointestinal tract is variable and irregular.[9] Pharmacokinetic studies with tacrolimus have shown that there are large inter- and intra-individual differences in its kinetics in organ transplant patients.[10, 11]

Pharmacokinetic studies have also indicated that whole blood rather than plasma may serve as the more appropriate medium to describe the pharmacokinetic characteristics of tacrolimus. Tacrolimus is bound to proteins, mainly albumin and α-1-acid glycoprotein, and is highly bound to erythrocytes. The distribution of tacrolimus between whole blood and plasma depends on several factors such as hematocrit, temperature of separation of plasma, drug concentration, and plasma protein concentration. In a U.S. study, the ratio of whole blood concentration to plasma concentration ranged from 12 to 67 (mean 35).[12]

Tacrolimus is extensively metabolized in the liver and small intestine microsomes utilizing the cytochrome P-450 enzymes.[13] Nine different metabolites of tacrolimus have been identified; several of the metabolites have been found and tested in whole blood.[14-18]

The use of tacrolimus is associated with serious toxic side effects, primarily nephrotoxicity.[19, 20] At the present time it is not clear whether the nephrotoxicity of tacrolimus is the result of parent drug, metabolites, or a combination of both. Other adverse side effects include neurotoxicity, hypertension, insomnia, and nausea.[21]

BIOLOGICAL PRINCIPLES OF THE PROCEDURE

The ARCHITECT Tacrolimus assay is a delayed one-step immunoassay for the quantitative determination of tacrolimus in human whole blood using CMIA technology with flexible assay protocols, referred to as Chemiflex.

Prior to the initiation of the automated ARCHITECT sequence, a manual pretreatment step is performed in which the whole blood sample is extracted with a precipitation reagent and centrifuged. The supernatant is decanted into a Transplant Pretreatment Tube, which is placed onto the ARCHITECT iSystem.

1. Sample, assay diluent, and anti-tacrolimus coated paramagnetic microparticles are combined to create a reaction mixture. The tacrolimus present in the sample binds to the anti-tacrolimus coated microparticles.
2. After a delay, tacrolimus acridinium-labeled conjugate is added to the reaction mixture. The tacrolimus on the acridinium-labeled conjugate competes for the available binding sites on the microparticles.
3. After further incubation and washing, Pre-Trigger and Trigger Solutions are added to the reaction mixture.
4. The resulting chemiluminescent reaction is measured as relative light units (RLUs). There is an indirect relationship between the amount of tacrolimus in the sample and the RLUs detected by the ARCHITECT iSystem optics.

For additional information on system and assay technology, refer to the ARCHITECT System Operations Manual, Section 3.

REAGENTS

Kit Contents

ARCHITECT Tacrolimus 1L77

REF	1L77-25
Σ	100
MICROPARTICLES	1 x 6.6 mL
CONJUGATE	1 x 7.8 mL
ASSAY DILUENT	1 x 8.9 mL

MICROPARTICLES Anti-tacrolimus (mouse, monoclonal) coated microparticles in EDTA buffer with protein (bovine) stabilizer. Minimum concentration: 0.09% solids. Preservatives: sodium azide and ProClin 950.

CONJUGATE Tacrolimus acridinium-labeled conjugate in citrate buffer with protein (bovine) stabilizer. Minimum concentration: 5.0 ng/mL. Preservative: ProClin 300.

ASSAY DILUENT Assay Diluent containing MES buffer and sodium chloride. Preservatives: ProClin 950 and ProClin 300.

Other Reagents

PRE-TRIGGER SOLUTION ARCHITECT Pre-Trigger Solution containing 1.32% (w/v) hydrogen peroxide.

TRIGGER SOLUTION ARCHITECT Trigger Solution containing 0.35 N sodium hydroxide.

WASH BUFFER ARCHITECT Wash Buffer containing phosphate buffered saline solution. Preservatives: antimicrobial agents.

Warnings and Precautions

- IVD
- For *In Vitro* Diagnostic Use

Safety Precautions

CAUTION: This product requires the handling of human specimens. It is recommended that all human-sourced materials be considered potentially infectious and handled in accordance with the OSHA Standard on Bloodborne Pathogens. Biosafety Level 2 or other appropriate biosafety practices should be used for materials that contain or are suspected of containing infectious agents.[22-25]

The following warnings and precautions apply to: MICROPARTICLES	
	
WARNING	Contains methylisothiazolones and sodium azide.
H317	May cause an allergic skin reaction.
EUH032	Contact with acids liberates very toxic gas.
Prevention	
P261	Avoid breathing mist / vapors / spray.
P272	Contaminated work clothing should not be allowed out of the workplace.
P280	Wear protective gloves / protective clothing / eye protection.
Response	
P302+P352	IF ON SKIN: Wash with plenty of water.
P333+P313	If skin irritation or rash occurs: Get medical advice / attention.
P362+P364	Take off contaminated clothing and wash it before reuse.
Disposal	
P501	Dispose of contents / container in accordance with local regulations.

The following warnings and precautions apply to: CONJUGATE and ASSAY DILUENT	
	
WARNING	Contains methylisothiazolones.
H317	May cause an allergic skin reaction.
Prevention	
P261	Avoid breathing mist / vapors / spray.
P272	Contaminated work clothing should not be allowed out of the workplace.
P280	Wear protective gloves / protective clothing / eye protection.
Response	
P302+P352	IF ON SKIN: Wash with plenty of water.
P333+P313	If skin irritation or rash occurs: Get medical advice / attention.
P362+P364	Take off contaminated clothing and wash it before reuse.
Disposal	
P501	Dispose of contents / container in accordance with local regulations.

Safety Data Sheets are available at www.abbottdiagnostics.com or contact your local representative.

For a detailed discussion of safety precautions during system operation, refer to the ARCHITECT System Operations Manual, Section 8.

Reagent Handling

- Do not use reagent kits beyond the expiration date.
- **Do not pool reagents within a kit or between kits.**
- Before loading the reagent kit on the system for the first time, the microparticle bottle requires mixing to resuspend microparticles that may have settled during shipment. For microparticle mixing instructions, refer to the **PROCEDURE, Assay Procedure** section of this package insert.
- **Septums MUST be used to prevent reagent evaporation and contamination and to ensure reagent integrity. Reliability of assay results cannot be guaranteed if septums are not used according to the instructions in this package insert.**
  - To avoid contamination, wear clean gloves when placing a septum on an uncapped reagent bottle.
  - Once a septum has been placed on an open reagent bottle, **do not invert the bottle** as this will result in reagent leakage and may compromise assay results.
  - Over time, residual liquids may dry on the septum surface. These are typically dried salts and have no effect on assay efficacy.

For a detailed discussion of handling precautions during system operation, refer to the ARCHITECT System Operations Manual, Section 7.

Reagent Storage

When stored and handled as directed, reagents are stable until the expiration date.

	Storage Temperature	Maximum Storage Time	Additional Storage Instructions
Unopened/ Opened*	2-8°C	Until expiration date	May be used immediately after removal from 2-8°C storage. Store in upright position.
On board	System temperature	30 days	Discard after 30 days. Recalibration may be required to obtain maximum onboard reagent stability. For information on tracking onboard time, refer to the ARCHITECT System Operations Manual, Section 5.

* Reagents may be stored on or off the ARCHITECT iSystem. If reagents are removed from the system, store them at 2-8°C (with septums and replacement caps) in an upright position. For reagents stored off the system, it is recommended that they be stored in their original trays and boxes to ensure they remain upright. **If the microparticle bottle does not remain upright (with a septum installed) while in refrigerated storage off the system, the reagent kit must be discarded.** For information on unloading reagents, refer to the ARCHITECT System Operations Manual, Section 5.

Indications of Reagent Deterioration

When a control value is out of the specified range, it may indicate deterioration of the reagents or errors in technique. Associated test results are invalid, and samples must be retested. Assay recalibration may be necessary. For troubleshooting information, refer to the ARCHITECT System Operations Manual, Section 10.

INSTRUMENT PROCEDURE

The ARCHITECT Tacrolimus assay file must be installed on the ARCHITECT iSystem prior to performing the assay.

For detailed information on assay file installation and viewing and editing assay parameters, refer to the ARCHITECT System Operations Manual, Section 2.

For information on printing assay parameters, refer to the ARCHITECT System Operations Manual, Section 5.

For a detailed description of system procedures, refer to the ARCHITECT System Operations Manual.

Alternate Result Units

Edit assay parameter "Result concentration units" to select an alternate unit.

Conversion formula(s):

(Concentration in Default result unit) x (Conversion factor) = (Concentration in Alternate result unit)

Default result unit	Conversion factor	Alternate result unit
ng/mL	1.2438	nmol/L
	1.0	µg/L

SPECIMEN COLLECTION AND PREPARATION FOR ANALYSIS

Specimen Types

Verified specimen types to be used with this assay:

Specimen Types	Collection Tubes
Whole blood	EDTA

- The instrument does not provide the capability to verify specimen type. It is the responsibility of the operator to verify that the correct specimen types are used in the assay.
- It is recommended that specimens be labeled with both the time of collection as well as the last drug administration.

Specimen Conditions

- Do not use specimens with the following conditions:
  - heat-inactivated
  - cadaver specimens or any other body fluids
  - obvious microbial contamination
- To prevent cross contamination, use of disposable pipettes or pipette tips is recommended.

Preparation for Analysis

- Follow the tube manufacturer's processing instructions for specimen collection tubes.
- Mix thawed specimens thoroughly by low speed vortexing or by inverting 10 times. Visually inspect the specimens. If layering or stratification is observed, continue mixing until specimens are visibly homogeneous.
- Follow the Manual Pretreatment Procedure in the **PROCEDURE** section.

Specimen Storage

Specimen Type	Storage Temperature	Maximum Storage Time
Whole blood	2-8˚C	≤ 7 days[26]
	-10˚C or colder	> 7 days

Recovery of tacrolimus in frozen whole blood specimens has been reported as > 90% at 6 months, but a loss of 46% occurs by 9 months.[1]

Specimens must be mixed thoroughly after thawing to ensure consistency of the results.

Discard any remaining pretreated samples after testing is complete. ARCHITECT Tacrolimus tests cannot be reordered. A retest requires that the Manual Pretreatment Procedure in the **PROCEDURE** section be repeated.

Specimen Shipping

- Package and label specimens in compliance with applicable state, federal, and international regulations covering the transport of clinical specimens and infectious substances.
- Do not exceed the storage limitations listed above.

PROCEDURE

Materials Provided

- 1L77 ARCHITECT Tacrolimus Reagent Kit
- 1L77-55 ARCHITECT Tacrolimus Whole Blood Precipitation Reagent
- 1P06 Transplant Pretreatment Tubes

Materials Required but not Provided

- ARCHITECT Tacrolimus Assay file obtained from the ARCHITECT iSystem e-Assay CD-ROM found on www.abbottdiagnostics.com.
- 1L77-01 ARCHITECT Tacrolimus Calibrators
- Commercial Controls
- Vortex Mixer
- Laboratory microcentrifuge
- Polypropylene Centrifuge Tubes compatible with laboratory microcentrifuge
- ARCHITECT Pre-Trigger Solution
- ARCHITECT Trigger Solution
- ARCHITECT Wash Buffer
- ARCHITECT Reaction Vessels
- ARCHITECT Septum
- ARCHITECT Replacement Caps
- Precision Micropipettes
- Pipettes or pipette tips (optional) to deliver the volumes specified on the patient or control order screen.
- Precision Dispenser, or equivalent
- 2.5 mL Combitips, or equivalent for Precision Dispenser

For information on materials required for maintenance procedures, refer to the ARCHITECT System Operations Manual, Section 9.

Manual Pretreatment Procedure

The ARCHITECT Tacrolimus assay requires a manual pretreatment step for all whole blood patient specimens, ARCHITECT Tacrolimus Calibrators and commercial controls.

Use only ARCHITECT Tacrolimus Whole Blood Precipitation Reagent (1L77-55).

Once the Manual Pretreatment Procedure has been initiated, all steps must be completed in immediate succession.

Note: If specimen requires dilution, it must be diluted prior to the manual pretreatment step. Refer to the **Specimen Dilution Procedures** section of this package insert.

Warning: Only Transplant Pretreatment Tubes (LN 1P06) are acceptable when pretreating tacrolimus samples for use on the ARCHITECT iSystem. Reliability of other ARCHITECT assay results may be affected if the Transplant Pretreatment Tubes are not used with the ARCHITECT Tacrolimus assay.

Warning: All pretreated samples (specimens, calibrators or controls) must be tested within 30 minutes of being decanted into the Transplant Pretreatment Tubes and placed on the ARCHITECT iSystem. All ARCHITECT Tacrolimus samples must be priority loaded. Priority loading of samples prevents evaporation that will impact the assay results. No more than 100 Tacrolimus samples may be loaded onto the i2000 system at the same time. No more than 24 Tacrolimus samples may be loaded onto the i1000 system at the same time. For information on priority loading of samples, refer to the ARCHITECT Systems Operation Manual, Section 5.

Note: An ARCHITECT Tacrolimus Sample Pretreatment Guide outlining the pretreatment steps is also available from the ARCHITECT Customer Support Center or your Abbott Representative.

Manual Pretreatment Procedure

Attention: To obtain optimal results for the ARCHITECT Tacrolimus assay the manual pretreatment steps listed below must be followed precisely.

1. **Mix** each sample (specimen, calibrator, or control) thoroughly by slow inversion of the container **5 - 10** times. Older whole blood specimens may take a longer mixing time. Visual inspection is recommended to assure the specimen is adequately mixed.
2. **Precision pipette 200 µL** of each sample into a microcentrifuge tube or equivalent polypropylene centrifuge tube (e.g. round bottom) immediately after mixing. Use a different tube for each sample.

Note: A new pipette tip **must** be used each time **200 µL** is aspirated. Do not wipe pipette tip. Do not over aspirate. Do not reuse pipette tips between replicates. The use of positive displacement pipettes, the practice of pre-wetting the tip, and reverse pipetting are not recommended, since they may generate error codes and add greater imprecision to the assay.

3a. **Set** a Precision Dispenser (Repeater Pipette) to dispense **200 µL**. **Fill** the dispenser with a sufficient volume of the ARCHITECT Tacrolimus Whole Blood Precipitation Reagent from the blue-labeled bottle.

Purge air bubbles from the dispenser by dispensing a small amount of the precipitation reagent into a suitable waste container.

Note: To prevent leaking, do not place a filled repeater pipette on the lab bench. The ARCHITECT Tacrolimus Whole Blood Precipitation Reagent is highly volatile. Keep it tightly closed when not in use to prevent evaporation.

3b. **Add 200 µL** of ARCHITECT Tacrolimus Whole Blood Precipitation Reagent to the contents of the first centrifuge tube with the end of the dispensing syringe tip touching the wall of the centrifuge tube.

Warning: Each individual tube **must** be capped and vortexed immediately after addition of the ARCHITECT Tacrolimus Whole Blood Precipitation Reagent, before adding the precipitation reagent to subsequent tubes.

3c. **Cap** the first tube and vortex **immediately**.

3d. **Vortex** vigorously for **5 - 10** seconds. Use the maximum vortex setting.

Warning: Failure to vortex each tube immediately after addition of the ARCHITECT Tacrolimus Whole Blood Precipitation Reagent will lead to erroneous assay results.

Note: Visual inspection is required to ensure that the mixture of the sample with the precipitation reagent is uniform, smooth and homogeneous.

No unmixed portion of the mixture should be present at the bottom of the tube. If unmixed sample remains, dislodge it by inverting the tube and tapping the bottom, then re-vortex the sample. This is an indication that the initial vortexing process was inadequate. Immediate vortexing minimizes the time available for aggregate formation. Not all vortex mixers may provide adequate mixing.

Repeat the "add, cap and vortex" process for each subsequent sample. For each tube, use a consistent vortexing time and complete the **"add, cap and vortex"** process before proceeding to the next tube. **Do not** dispense the ARCHITECT Tacrolimus Whole Blood Precipitation Reagent into all the tubes at once. Each individual tube **must** be capped and vortexed immediately after addition of the ARCHITECT Tacrolimus Whole Blood Precipitation Reagent before adding precipitation reagent to the subsequent tubes.

4. **Load** each tube into a microcentrifuge taking care to balance the rotor. A balance tube can be added if necessary. Only an even number of tubes can be centrifuged at one time.

   Centrifuge the tubes for a minimum of 4 minutes at > 9500 x g RCF, or 38,500 g-minutes.
5. **Remove** each tube from the centrifuge and **inspect** for the presence of a well-formed pellet and clear supernatant.
6. **Uncap** each tube and **decant** (pour off) the supernatant into the **Transplant Pretreatment Tube**, when the ARCHITECT iSystem is ready to accept samples.

Warning: Do not disturb the pellet. **Do not pipette the supernatant** as this will help ensure that the pellet is not disturbed.

Note: Use a different Transplant Pretreatment Tube for each sample.

Warning: Only Transplant Pretreatment Tubes (LN 1P06) are acceptable when pretreating tacrolimus samples for use on the ARCHITECT iSystem. Reliability of other ARCHITECT assay results may be affected if the Transplant Pretreatment Tubes are not used with the ARCHITECT Tacrolimus assay.

Warning: All pretreated samples (specimens, calibrators or controls) must be tested within 30 minutes of being decanted into the Transplant Pretreatment Tubes and placed on the ARCHITECT iSystem. All ARCHITECT Tacrolimus samples must be priority loaded. Priority loading of samples prevents evaporation that will impact the assay results. No more than 100 Tacrolimus samples may be loaded onto the i2000 system at the same time. No more than 24 Tacrolimus samples may be loaded onto the i1000 system at the same time. For information on priority loading of samples, refer to the ARCHITECT Systems Operation Manual, Section 5.

7. **Vortex** the Transplant Pretreatment Tube for **5 - 10** seconds.
8. **Transfer** the Transplant Pretreatment Tube to the ARCHITECT sample carrier.

Note: Place the Transplant Pretreatment Tube so it touches the bottom of the carrier.

Discard any remaining pretreated samples after testing is complete. ARCHITECT Tacrolimus tests cannot be reordered. A retest requires that the Manual Pretreatment Procedure be repeated.

Assay Procedure

- Before loading the reagent kit on the system for the first time, the microparticle bottle requires mixing to resuspend microparticles that may have settled during shipment. After the first time the microparticles have been loaded, no further mixing is required.
  - **Invert the microparticle bottle 30 times.**
  - Visually inspect the bottle to ensure microparticles are resuspended. If microparticles are still adhered to the bottle, continue to invert the bottle until the microparticles have been completely resuspended.
  - **If the microparticles do not resuspend, DO NOT USE. Contact your local Abbott representative.**
  - Once the microparticles have been resuspended, place a septum on the bottle. For instructions about placing septums on bottles, refer to the **Reagent Handling** section of this package insert.
- Load the reagent kit on the ARCHITECT iSystem.
  - Verify that all necessary reagents are present.
  - Ensure that septums are present on all reagent bottles.
- Order calibration, if necessary.
  - For information on ordering calibrations, refer to the ARCHITECT System Operations Manual, Section 6.
- Order tests.
  - For information on ordering patient specimens and controls and for general operating procedures, refer to the ARCHITECT System Operations Manual, Section 5.
- No more than 3 replicates may be sampled from the same Transplant Pretreatment Tube.

- **All pretreated samples (specimens, calibrators or controls) must be tested within 30 minutes of being decanted into the Transplant Pretreatment Tubes and placed on the ARCHITECT iSystem.**
- **All ARCHITECT Tacrolimus samples must be priority loaded. Priority loading of samples prevents evaporation that will impact the assay results. No more than 100 Tacrolimus samples may be loaded onto the i2000 system at the same time.** No more than **24** Tacrolimus samples may be loaded onto the i1000 system at the same time. For information on priority loading of samples, refer to the ARCHITECT Systems Operation Manual, Section 5.
- With the Transplant Pretreatment Tube, use the sample gauge to ensure sufficient patient specimen is present for the ARCHITECT Tacrolimus assay.

- Prepare calibrators and controls.
  - Refer to the Manual Pretreatment Procedure in the **PROCEDURE** section.
- Load pretreated samples.
  - For information on loading samples, refer to the ARCHITECT System Operations Manual, Section 5.
- Press RUN.
- For additional information on principles of operation, refer to the ARCHITECT Operations Manual, Section 3.
- For optimal performance, it is important to perform routine maintenance as described in the ARCHITECT System Operations Manual, Section 9. When a laboratory requires more frequent maintenance, follow those procedures.

Specimen Dilution Procedures

Specimens with a tacrolimus value exceeding 30.0 ng/mL are flagged with the code "> 30.0 ng/mL" and may be diluted using the Manual Dilution Procedure.

Manual Dilution Procedure

Suggested dilution: 1:2

Specimen must be diluted before pretreatment.

1. Add 150 µL of the patient specimen to 150 µL of ARCHITECT Tacrolimus Calibrator A, then proceed with the Manual Pretreatment Procedure in the **PROCEDURE** section.
2. The operator must enter the dilution factor in the Patient or Control order screen. The system will use this dilution factor to automatically calculate the concentration of the sample before dilution and report the result. The result should be > 3.0 ng/mL before the dilution factor is applied.

For detailed information on ordering dilutions, refer to the ARCHITECT System Operations Manual, Section 5.

Calibration

- Test Calibrators A-F in duplicate. The calibrators should be priority loaded.
- Only one pretreated sample of each ARCHITECT Tacrolimus Calibrator is required to perform a calibration on the ARCHITECT iSystem. This provides adequate volume to run each calibrator in duplicate.

  A single sample of each control level must be tested to evaluate the assay calibration. Ensure that assay control values are within the ranges specified in the respective control package insert.
- Calibration Range: 0.0 - 30.0 ng/mL.
- Once an ARCHITECT Tacrolimus calibration is accepted and stored, all subsequent samples may be tested without further calibration unless:
  - A reagent kit with a new lot number is used or
  - Controls are out of range.
- For detailed information on how to perform an assay calibration, refer to the ARCHITECT System Operations Manual, Section 6.

Quality Control Procedures

The recommended control requirement for the ARCHITECT Tacrolimus assay is that a single sample of each control level be tested once every 24 hours each day of use. If the quality control procedures in your laboratory require more frequent use of controls to verify test results, follow your laboratory-specific procedures.

Commercial controls are suitable for this purpose.

Additional controls may be tested in accordance with local, state, and/or federal regulations or accreditation requirements and your laboratory's quality control policy.

Each laboratory should establish control ranges to monitor the acceptable performance of the assay. If a control is out of its specified range, the associated sample results are invalid and the samples must be retested. Recalibration may be indicated.

Verification of Assay Claims

For protocols to verify package insert claims, refer to the ARCHITECT System Operations Manual, Appendix B.

The ARCHITECT Tacrolimus assay belongs to method group 6.

RESULTS

The ARCHITECT Tacrolimus assay uses a 4 Parameter Logistic Curve fit data reduction method (4PLC, Y-weighted) to generate a calibration curve.

Flags

Some results may contain information in the Flags field. For a description of the flags that may appear in this field, refer to the ARCHITECT System Operations Manual, Section 5.

Measurement Range (Reportable Range)

The measurement range for the ARCHITECT Tacrolimus assay is 2 ng/mL (minimum reportable value based on Functional Sensitivity) to 30 ng/mL.

LIMITATIONS OF THE PROCEDURE

- Results should be used in conjunction with other data; e.g., symptoms, results of other tests, and clinical impressions.
- If the tacrolimus results are inconsistent with clinical evidence, additional testing is recommended.
- The concentration of tacrolimus in a given specimen determined with assays from different manufacturers can vary due to differences in assay methods and reagent specificity.
- **Immunoassays are nonspecific and cross react with metabolites. When elimination of tacrolimus is impaired (e.g. during cholestasis), tacrolimus metabolites may accumulate. The immunoassay may overestimate the concentration of tacrolimus. In such cases, the use of a specific assay (e.g. Liquid Chromatography Mass Spectrometry/Mass Spectrometry [LC/MS/MS]) could be considered.** Refer to the **SPECIFICITY** section below for estimates of cross-reactivity of ARCHITECT Tacrolimus to some metabolites of tacrolimus. Refer to the **METHOD COMPARISON** section below for representative data comparing patient results from the ARCHITECT Tacrolimus assay to the IMx Tacrolimus II assay and an LC/MS/MS method.
- Heterophilic antibodies in human serum can react with reagent immunoglobulins, interfering with *in vitro* immunoassays. Patients routinely exposed to animals or to animal serum products can be prone to this interference, and anomalous values may be observed. Additional information may be required for diagnosis.[27]
- Specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies (HAMA).[28, 29] Specimens containing HAMA may produce anomalous values when tested with assay kits (such as ARCHITECT Tacrolimus) that employ mouse monoclonal antibodies.[28]

EXPECTED VALUES

CAUTION: No firm therapeutic range exists for tacrolimus in whole blood. The complexity of the clinical state, individual differences in sensitivity to immunosuppressive and nephrotoxic effects of tacrolimus, co-administration of other immunosuppressants, type of transplant, time post-transplant and a number of other factors contribute to different requirements for optimal blood levels of tacrolimus. Therefore, individual tacrolimus values cannot be used as the sole indicator for making changes in treatment regimen and each patient should be thoroughly evaluated clinically before changes in treatment regimens are made. Each user must establish his or her own ranges based on clinical experience.

Therapeutic ranges vary according to the commercial test used, and therefore should be established for each commercial test. Values obtained with different assay methods cannot be used interchangeably due to differences in assay methods and cross-reactivity with metabolites, nor should correction factors be applied. Therefore, consistent use of one assay for individual patients is recommended.

The Consensus Document has reported that the therapeutic range of tacrolimus is not clearly defined, but target 12-hour trough whole blood concentrations are 5-20 ng/mL early post-transplant. Higher concentrations are associated with an increase incidence of adverse effects. Twenty-four hour trough concentrations are 33-50% less than the corresponding 12-hour trough levels.[1]

SPECIFIC PERFORMANCE CHARACTERISTICS

Precision

The ARCHITECT Tacrolimus assay is designed to have precision of ≤ 10% total CV.

A study was performed with the ARCHITECT Tacrolimus assay based on guidance from the Clinical and Laboratory Standards Institute, (CLSI, formerly NCCLS) document EP5-A2.[30] Abbott Immunosuppressant-MCC (levels 1, 2 and 3) and five whole blood panels were assayed, using two lots of reagents, on two instruments, in replicates of two at two separate times per day for 20 days. Each reagent lot used a single calibration curve throughout the study. Data from this study are summarized in the following table.*

		Reagent		Mean	Within Run		Total	
Sample	Instrument	Lot	n	(ng/mL)	SD	%CV	SD	%CV
Level 1	1	1	80	3.0	0.1	3.7	0.1	4.9
Level 1	2	2	80	2.9	0.2	5.8	0.2	6.7
Level 2	1	1	80	7.8	0.2	2.4	0.3	3.6
Level 2	2	2	80	8.5	0.2	2.7	0.4	4.2
Level 3	1	1	80	14.5	0.4	2.5	0.5	3.5
Level 3	2	2	80	15.7	0.5	2.9	0.6	4.0
Panel 1	1	1	80	5.5	0.2	3.6	0.2	4.4
Panel 1	2	2	80	5.9	0.2	4.0	0.3	5.2
Panel 2	1	1	80	14.0	0.5	3.5	0.6	4.2
Panel 2	2	2	80	15.3	0.6	4.1	0.7	4.7
Panel 3	1	1	80	4.8	0.2	4.4	0.2	5.2
Panel 3	2	2	80	4.9	0.2	5.0	0.3	6.3
Panel 4	1	1	80	10.1	0.2	2.4	0.4	4.4
Panel 4	2	2	80	11.2	0.5	4.1	0.6	5.3
Panel 5	1	1	80	21.2	0.7	3.3	0.9	4.4
Panel 5	2	2	80	22.4	0.8	3.6	1.3	5.7

*Representative data; results in individual laboratories may vary from these data.

Recovery

The ARCHITECT Tacrolimus assay is designed to have a mean recovery of 100 ± 10% of the expected value.

A study was performed where known concentrations of tacrolimus were added to aliquots of whole blood specimens. The concentration of tacrolimus was determined using the ARCHITECT Tacrolimus assay and the resulting percent recovery was calculated. Data from this study are summarized in the following table.*

Specimen	Endogenous Concentration (ng/mL)	Tacrolimus Added (ng/mL)	Measured Concentration (ng/mL)	% Recovery[a]
1	0.1	6.9	6.9	99
		9.3	9.3	99
		15.2	16.4	107
		18.8	18.8	99
2	0.2	6.9	7.1	100
		9.3	9.5	100
		15.2	16.2	105
		18.8	19.1	101
3	0.1	6.9	6.9	98
		9.3	9.7	103
		15.2	16.1	105
		18.8	19.3	102
				Mean Recovery = 102%

[a] % Recovery = $\frac{\text{Measured Concentration}}{\text{Endogenous Concentration + Tacrolimus Added}} \times 100$

*Representative data; results in individual laboratories may vary from these data.

Dilution Linearity

The ARCHITECT Tacrolimus assay is designed to have a mean recovery of 100 ± 10% of the expected results for diluted samples.

A dilution linearity study was performed by diluting high concentration tacrolimus whole blood specimens with the ARCHITECT Tacrolimus Calibrator A. The concentration of tacrolimus was determined for each dilution of sample and the percent (%) recovery was calculated. Data from this study are summarized in the following table.*

Specimen	Dilution Factor	Observed Concentration (ng/mL)	Calculated Concentration[a] (ng/mL)	% Recovery[b]
1	Undiluted	29.4	---	---
	1:1.11	26.7	29.6	101
	1:1.25	23.0	28.8	98
	1:1.43	20.7	29.6	101
	1:1.67	17.3	28.9	98
	1:2.5	11.7	29.3	99
	1:5	6.0	30.0	102
	1:10	2.8	28.0	95
2	Undiluted	27.8	---	---
	1:1.11	25.6	28.4	102
	1:1.25	23.3	29.1	105
	1:1.43	20.1	28.7	103
	1:1.67	17.9	29.9	108
	1:2.5	11.9	29.8	107
	1:5	5.8	29.0	104
	1:10	2.9	29.0	104
3	Undiluted	28.1	---	---
	1:1.11	25.3	28.1	100
	1:1.25	22.8	28.5	101
	1:1.43	20.1	28.7	102
	1:1.67	17.2	28.7	102
	1:2.5	11.7	29.3	104
	1:5	5.9	29.5	105
	1:10	2.8	28.0	100
				Mean Recovery = 102%

[a] Calculated Concentration = Observed Concentration x Dilution Factor

[b] % Recovery = $\frac{\text{Calculated Concentration}}{\text{Undiluted Observed Concentration}} \times 100$

* Representative data; results in individual laboratories may vary from these data.

Sensitivity

The ARCHITECT Tacrolimus assay is designed to have a limit of detection of ≤ 1.5 ng/mL, which is below the reportable range of the ARCHITECT Tacrolimus assay. The limit of detection of the ARCHITECT Tacrolimus assay, defined as the concentration at two standard deviations above the ARCHITECT Tacrolimus Calibrator A (0 ng/mL), was calculated to be 0.3 ng/mL* at the 95% level of confidence (based upon one study with n=24 runs, 10 replicates calibrator A and 4 replicates calibrator B per run).

*Representative data; results in individual laboratories may vary from these data.

Functional Sensitivity

The ARCHITECT Tacrolimus assay is designed to have a functional sensitivity of ≤ 2 ng/mL.

A study was performed where whole blood specimens were spiked with tacrolimus to achieve approximate concentrations from 0.2 to 4.4 ng/mL. These were tested in replicates of ten, twice a day, for five days using one reagent and calibrator lot for a total of 100 replicates per panel. The total % CVs were calculated and plotted against the mean concentration. A reciprocal curve was fitted through the data and the functional sensitivity value was calculated as the concentration corresponding to the 20% CV level of the fitted curve. At the upper 95% confidence limit, the lowest ARCHITECT Tacrolimus assay value exhibiting a 20% CV was calculated to be 0.8 ng/mL, which is below the reportable range of the ARCHITECT Tacrolimus assay.*

*Representative data; results in individual laboratories may vary from these data.

Specificity

A study was performed with the ARCHITECT Tacrolimus assay based on guidance from CLSI document EP7-A2.[31] Aliquots of whole blood specimens were supplemented with tacrolimus, targeting values ranging from 5 to 22 ng/mL. These specimens were spiked with cross-reactant solutions. Data from this study are summarized in the following table.*

Tacrolimus metabolites that have been detected in human blood were tested in the ARCHITECT Tacrolimus assay. Physiological concentrations of the tacrolimus metabolites in whole blood and the clinical significance of the tacrolimus metabolites have not been defined.

Purified tacrolimus metabolites are not commercially available for cross-reactivity testing. Tacrolimus metabolites were prepared *in vitro* by incubating tacrolimus with liver microsomes prepared from phenobarbital-treated rats in the presence of NADPH generating system under aerobic condition or bioconverted by incubating tacrolimus with an actinomycete. Oxidative metabolites formed in the reaction medium were isolated and identified. Purified samples were analyzed by HPLC, mass spectrometry, and NMR spectroscopy.

Metabolite[b]	Amount Added (ng/mL)	Mean Excess Concentration Detected (ng/mL, n=5)	% Cross Reactivity[a]
M-I (13-*O*-demethyltacrolimus)	10	0.8	8
M-II (31-*O*-demethyltacrolimus)	10	9.4	94
M-III (15-*O*-demethyltacrolimus)	10	4.5	45
M-IV (12 hydroxytacrolimus)	10	0.8	9

[a] Cross-reactivities as estimated by interference with the measurement of tacrolimus in whole blood specimens.

[b] Metabolites MV through MVIII have not been assessed to determine the possible effect on assay performance.

*Representative data; results in individual laboratories may vary from these data.

Interference

The ARCHITECT Tacrolimus assay is designed to have a mean recovery of 100 ± 10% in the presence of the pharmaceutical substances, potentially interfering endogenous substances and potentially interfering clinical conditions at the levels below.

A study based on guidance from the CLSI document EP7-A2[31] was performed for the ARCHITECT Tacrolimus assay.

Potentially Interfering Pharmaceutical Substances

Whole blood specimens with tacrolimus concentrations between 4.9 and 19.8 ng/mL were supplemented with the following potentially interfering pharmaceutical substances. The average recovery observed during the study ranged from 95% to 104%.*

Test Compound	Test Concentration	Test Compound	Test Concentration
Acetaminophen	20 mg/dL	Kanamycin B Sulfate	6 mg/dL
Acyclovir	3.2 µg/mL	Ketoconazole	50 µg/mL
Allopurinol	5 mg/dL	Labetalol	17.1 µg/mL
Amikacin*$2H_2O$	15 mg/dL	Lidocaine	6 mg/dL
Amphotericin B	5.8 µg/mL	Lovastatin	20 µg/mL
Apresoline	100 µg/mL	Minoxidil	60 µg/mL
Azathioprine	1 mg/dL	Mycophenolic Acid	500 µg/mL
Bromocriptine	8 µg/mL	Mycophenolic Acid Glucuronide	1800 µg/mL
Carbamazepine	12 mg/dL	N-Acetyl-Procainamide	12 mg/dL
Cephalosporine	100 µg/mL	Nadolol	1.2 µg/mL
Chloramphenicol	25 mg/dL	Nicardipine	0.5 µg/mL
Chloroquine	1.5 µg/mL	Penicillin G Na^+	100 µg/mL
Cimetidine	10 mg/dL	Phenobarbital	15 mg/dL
Ciprofloxacin	7.4 µg/mL	Phenytoin	10 mg/dL
Clonidine	0.01 µg/mL	Prazosin	25 µg/mL
Colchicine	0.09 µg/mL	Prednisolone	100 µg/mL
Cortisone	1.2 µg/mL	Prednisone	100 µg/mL
Cyclosporine	3200 ng/mL	Primidone	10 mg/dL
Digitoxin	80 ng/mL	Probucol	600 µg/mL
Digoxin	4.8 ng/mL	Procainamide	10 mg/dL
Diltiazem	60 µg/mL	Propranolol	0.5 mg/dL
Disopyramide	3 mg/dL	Quinidine	5 mg/dL
Erythromycin	20 mg/dL	Ranitidine	20 mg/dL
Fluconazole	30 µg/mL	Rifampin	5 mg/dL
Flucytosine	40 µg/mL	Sirolimus	60 ng/mL
Furosemide	2 mg/dL	Spectinomycin	100 µg/mL
Ganciclovir	1000 µg/mL	Ticlopidine	150 µg/mL
Gemfibrozil	100 µg/mL	Tobramycin	2 mg/dL
Gentamicin	12 mg/dL	Trimethoprim	40 µg/mL
Hydrocortisone	1.2 µg/mL	Valproic Acid	50 mg/dL
Itraconazole	50 µg/mL	Vancomycin	6 mg/dL
Kanamycin A Sulfate	6 mg/dL	Verapamil	10 µg/mL

Potentially Interfering Endogenous Substances

Whole blood specimens with tacrolimus concentrations between 5.5 and 18.0 ng/mL were supplemented with the following potentially interfering endogenous substances. The average recovery observed during the study ranged from 96% to 105%.*

Potentially Interfering Substance	Concentration
Triglycerides	800 mg/dL
Hematocrit	≤ 25%, ≥ 55%
Bilirubin	40 mg/dL
Total Protein	3 g/dL
Total Protein	12 g/dL
Cholesterol	500 mg/dL
Uric Acid	20 mg/dL

*Representative data; results in individual laboratories may vary from these data.

Potentially Interfering Clinical Conditions

The ARCHITECT Tacrolimus assay was evaluated using specimens with HAMA and RF to further assess the clinical specificity. Five specimens positive for HAMA and five specimens positive for RF were evaluated for % recovery with tacrolimus spiked at two concentrations into each specimen between 7.1 and 20.0 ng/mL. Mean percent recovery results are summarized in the following table.*

Clinical Condition	Number of Specimens	Mean % Recovery
HAMA	10	97
RF	10	99

*Representative data; results in individual laboratories may vary from these data.

Method Comparison

The ARCHITECT Tacrolimus assay is designed to have a correlation coefficient of ≥ 0.90 for specimens between 2 – 30 ng/mL when compared to the IMx Tacrolimus II assay.

A study was performed to compare the ARCHITECT Tacrolimus assay to the IMx Tacrolimus II assay using human whole blood EDTA specimens from liver and kidney transplant patients receiving tacrolimus therapy. Regression analysis was performed using the Passing-Bablok[32] method. Data from this study are summarized in the following table.*

ARCHITECT Tacrolimus vs IMx Tacrolimus II			
Number of Observations	Intercept (95% CI[a])	Slope (95% CI)	Correlation Coefficient
124	0.37 (0.00 to 0.68)	0.81 (0.75 to 0.88)	0.90

[a] Confidence Interval (CI)

Specimen Range (ARCHITECT): 2.2 ng/mL to 14.8 ng/mL

Specimen Range (IMx): 2.1 ng/mL to 15.9 ng/mL

*Representative data; variables such as differences in sampling size and sample population may impact the correlation of the assay, therefore, results in individual laboratories may vary from these data. The ARCHITECT Tacrolimus assay is designed to have a correlation coefficient of ≥ 0.90 for specimens between 2 – 30 ng/mL when compared to LC/MS/MS.

Additional testing of the above samples was completed with LC/MS/MS where regression analysis was performed using the Passing-Bablok[32] method. Data from this study are summarized in the following table.*

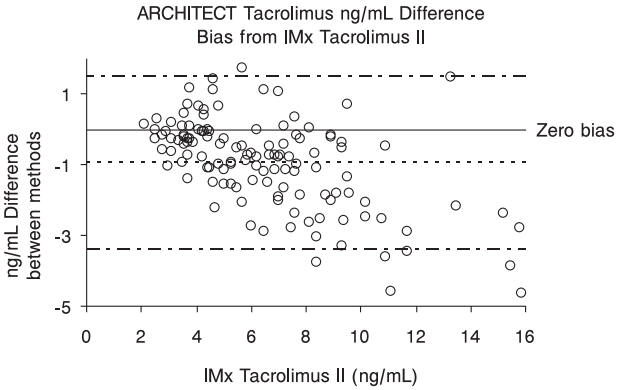
ARCHITECT Tacrolimus vs LC/MS/MS			
Number of Observations	Intercept (95% CI)	Slope (95% CI)	Correlation Coefficient
125	0.22 (0.02 to 0.48)	1.07 (1.01 to 1.12)	0.92

Specimen Range (ARCHITECT): 2.1 ng/mL to 14.8 ng/mL

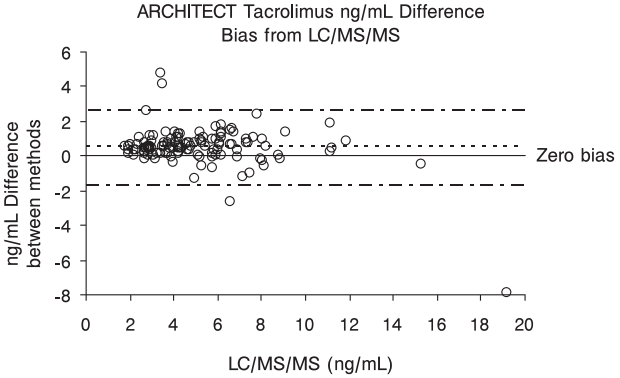
Specimen Range (LC/MS/MS): 1.78 ng/mL to 19.20 ng/mL

*Representative data; variables such as differences in sampling size and sample population may impact the correlation of the assay, therefore, results in individual laboratories may vary from these data.

A bias analysis of the ARCHITECT Tacrolimus vs. IMx Tacrolimus II assay was performed on the same 124 human whole blood EDTA samples in the range of 2 to 30 ng/mL. The following representative data are provided to aid in understanding the differences between these two assays. The average ng/mL difference bias exhibited by ARCHITECT Tacrolimus vs. IMx Tacrolimus II assay in this study was -0.94 ng/mL. The 95% confidence interval of the ng/mL difference bias is -1.16 ng/mL to -0.71 ng/mL. Results of the study are summarized below.



A bias analysis of the ARCHITECT Tacrolimus vs. LC/MS/MS was performed on the same 125 human whole blood EDTA samples in the range of 2 to 30 ng/mL. The following representative data are provided to aid in understanding the differences between these two assays. The average ng/mL difference bias exhibited by ARCHITECT Tacrolimus vs. LC/MS/MS in this study was 0.51 ng/mL. The 95% confidence interval of the ng/mL difference bias is 0.31 ng/mL to 0.71 ng/mL. Results of the study are summarized below.



*Representative data; results in individual laboratories may vary from these data.

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Key to Symbols

	Consult instructions for use
	Manufacturer
	Sufficient for
	Temperature limitation
	Use by/Expiration date
ASSAY DILUENT	Assay Diluent
CONJUGATE	Conjugate
CONTAINS: AZIDE	Contains Sodium Azide. Contact with acids liberates very toxic gas.
CONTROL NO.	Control Number
EC REP	Authorized Representative in the European Community
INFORMATION FOR USA ONLY	Information needed for United States of America only
IVD	*In Vitro* Diagnostic Medical Device
LOT	Lot Number
MICROPARTICLES	Microparticles
PRECISION DISPENSER	Precision Dispenser
PRE-TRIGGER SOLUTION	Pre-Trigger Solution
PRODUCED FOR ABBOTT BY	Produced for Abbott by
PRODUCT OF USA	Product of USA
REACTION VESSELS	Reaction Vessels
REAGENT LOT	Reagent Lot
REF	List Number
REPLACEMENT CAPS	Replacement Caps
SEPTUM	Septum
SN	Serial number
STERILE R	Sterilized using irradiation
TRIGGER SOLUTION	Trigger Solution
WASH BUFFER	Wash Buffer
WARNING: SENSITIZER	Warning: May cause an allergic reaction.


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