Imperial College London

Imperial College Healthcare NHS Trust

Exploring Immunosuppressant Medication Adherence in Kidney Transplant Recipients

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Protocol authorised by:

Name & Role	Date	Signature
Prof David Taube, Study Supervisor Imperial College Healthcare NHS Trust Transplant Research Group		

Study Management Group

Chief Investigator:
Dawn Goodall

Co-investigators:
Prof David Taube
Dr Michelle Willicombe
Dr Adam Mclean

Statistician:
N/A

Study Management:
Imperial College Healthcare NHS Trust Transplant Research and Operations Group

Study Coordination Centre

For general queries, supply of study documentation, and collection of data, please contact:

Study Coordinator: Dawn Goodall
Address: Renal and Transplant clinic
Hammersmith Hospital, W12 0HS
Tel: 0203 313 4247
Mobile: 07962258199
E-mail: dawn.goodall@imperial.nhs.uk

Clinical Queries

Clinical queries should be directed to Dawn Goodall who will direct the query to the appropriate person

Sponsor

Imperial College London and Imperial College Healthcare NHS Trust are the main research sponsors for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Joint Research Compliance Office
Imperial College London & Imperial College Healthcare NHS Trust
2nd Floor Medical School Building
St Mary's Hospital
Praed Street
London
W2 1NY
Tel: 020759 41862

Funder

NIHR Imperial Biomedical Research Centre

This protocol describes the Exploring Immunosuppressant Medication Adherence in Kidney Transplant Recipients study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS

AMR	Antibody mediated rejection
DSAb	Donor specific antibody
ICRTC	Imperial College Renal and Transplant Centre
SOT	Solid organ transplant

KEYWORDS

Adherence, Medication, Immunosuppressant, Kidney transplant

STUDY SUMMARY

TITLE Exploring Immunosuppressant Medication Adherence in Kidney Transplant Recipients

DESIGN Qualitative - Focus groups

AIMS To describe the beliefs, understanding and experience of immunosuppressant medication adherence in our current transplant patient population

OUTCOME MEASURES

What our transplant patients' understanding is of the terms immunosuppressant medication adherence and immunosuppressant medication nonadherence.

How our transplant patients define immunosuppressant medication nonadherence

What importance our transplant patients attach to medication adherence?

Whether patients understand that medication nonadherence may affect the outcome of their kidney transplant

The common practical and perceptual barriers to medication adherence identified by our transplant patients

Interventions our transplant patients have used to try and improve their medication adherence

Interventions our transplant patients have found effective to improve their medication adherence

Interventions our transplant patients have not found to be effective to improve their medication adherence

The support transplant patients have had with medication adherence since their transplant

The support transplant patients feel could have helped them to better adhere to their medicines up to now

The support our transplant patients feel would help them to adhere better to their medicines in the future

POPULATION Kidney Transplant Recipients

ELIGIBILITY Kidney Transplant Recipients transplanted and under active follow up at ICRTC

DURATION 7.5 months

1. INTRODUCTION

1.1 BACKGROUND

Organs for transplantation remain a scarce and precious resource with over 5000 patients currently on the kidney transplant waiting list. A kidney transplant costs approximately £17,000 in the first year and £5,000 per subsequent year. If the transplant fails, the patient must return to dialysis at an estimated cost of £30,800 per year. While short term outcomes have improved steadily over the last 15-20 years, longer term outcomes haven't and after 10 years approximately 30% of kidney transplants have failed.

Nonadherence to immunosuppressive medication is increasingly being associated with these poor long term outcomes (1-7) as it has been shown to be a potent risk factor for the development of de novo donor specific antibody (DSAb) and antibody mediated rejection (AMR) with AMR being a leading cause of kidney transplant failure(8-11). In a prospective study undertaken by Sellares et al(8) investigating the causes of kidney transplant failure in a series of patients who underwent an indicative biopsy it was shown that 64% of the transplants that failed were due to rejection, every rejection loss had evidence of AMR by the time of failure and among the rejection losses, 47% were independently identified by their clinician as being nonadherent.

Studies have estimated that 30-50% of transplant patients are nonadherent to their immunosuppressive medication(1, 3, 5, 12) and that graft loss is seven times more likely in a nonadherent compared to an adherent patient(13). Nonadherence to immunosuppression can start at any time after the transplant; sometimes within weeks but also after months or years(3, 14). A prospective cohort study undertaken by Massey(14, 15). and colleagues identified that self-reported nonadherence to immunosuppression medication increased significantly between 6 weeks and 6 months post-transplant from 17% to 27% and that by 18 months, the rate of nonadherence had reached 31% They assessed patient's perceptions of the importance of medication adherence over time and while it was initially high, it decreased significantly over time.

In a meta-analysis of adherence rates among solid organ transplant (SOT) recipients, nonadherence to immunosuppression medication was shown to be the highest in the kidney transplant recipients at 35.6 cases per 100 persons per year (PPY) compared to 14.5 cases per 100 PPY for heart recipients and 6.7 cases per 100PPY for liver recipients(16). This higher rate of nonadherence in the kidney transplant recipients is possibly because the consequences of nonadherence are higher in other SOTs. Adherence with therapy is one of the criteria when listing a patient for transplant and it is possible that recipients of SOTs other than the kidney may be subject to more stringent psychosocial selection criteria.

There are many reasons why patients do not adhere to their medication and their barriers to adherence can change over time. Adherence is difficult to measure accurately and currently, there is no universally agreed standard by which to measure nonadherence post-transplant; neither is there a panacea for 'treating' medication nonadherence. Many interventions and tools can be utilised with patients to improve adherence such as provision of information regarding the requirements for treatment, possible adverse effects and likely duration of therapy, reducing the complexity of medication regimes, diary cards, alarms and compliance aids. To achieve the best outcome, interventions should be tailored to the individual patient but in practice, this can be difficult to achieve. Patients who are nonadherent to immunosuppressant medication will often be nonadherent to other medicines prescribed for them, clinic attendance, diet, exercise, alcohol, smoking and illicit drug use. All of these factors will contribute to the overall morbidity and mortality of the patient.

1.2 RATIONALE FOR CURRENT STUDY

To describe the beliefs, understanding and experience of immunosuppressant medication adherence in our current kidney transplant patient population

2. STUDY OBJECTIVES

- To describe our transplant patients' understanding of the terms immunosuppressant medication adherence and immunosuppressant medication nonadherence.
- To describe how our transplant patients define immunosuppressant medication nonadherence
- To establish what importance our transplant patients attach to medication adherence
- To determine whether our transplant patients understand that medication nonadherence may affect the outcome of their kidney transplant
- To establish the common practical and perceptual barriers to medication adherence identified by our transplant patients
- To identify the types of interventions that our transplant patients have used to try and improve their medication adherence
- To identify the types of intervention that our transplant patients have found effective to improve their medication adherence
- To identify the types of intervention that our transplant patients have not found to be effective to improve their medication adherence
- To determine the support our transplant patients have had with medication adherence since their transplant
- To determine what support our transplant patients feel could have helped them to better adhere to their medicines up to now
- To determine what support our transplant patients feel would help them to adhere better to their medicines in the future

3. STUDY DESIGN

This study will collect qualitative data from a series of focus groups with kidney transplant recipients to explore their beliefs, understanding and experience of immunosuppressant medication adherence. The focus groups will also explore with the participants the support that they have received to facilitate their immunosuppressant medication adherence and what support they feel should be available to them and to others to optimise immunosuppressant medication adherence in all our transplant patients. The outcomes of the focus groups will be used to inform clinical practice in addition to a prospective trial aimed at improving immunosuppressant medication adherence though regular, intensive, pharmacist led, tailored medication adherence support.

Five focus groups will be undertaken. Each focus group will include six patients and will last for approximately one to one and a half hours. All the patients will be kidney transplant patients who were transplanted and are followed up at Imperial College Renal and Transplant Centre (ICRTC).

Patients will be recruited for the study through adverts placed in the transplant out-patient clinic at Imperial College Healthcare NHS Trust and in the Kidney Patient's Association newsletter. Any patients who express an interest in the study having seen the recruitment adverts will be directed to Dawn Goodall, The Chief Investigator. Dawn Goodall or another member of the research team, all of whom are members of the direct transplant clinical healthcare team will approach patients while in clinic to discuss participation in the study with them. The chief investigator, who is a member of the transplant clinical care team, will also

identify potential participants from the Imperial College Renal and Transplant Centre registry of current maintenance transplant patients and will telephone patients to invite them to participate. The participants will be selected to ensure a mix of patients by clinical and demographic criteria.

The focus groups will take place on the Hammersmith Hospital site. Each focus group will be audio and video recorded. Field notes will be taken during the focus groups to record key data or events identified by the lead researcher.

Each focus group will be transcribed and the content coded. A preliminary analysis will be made after each focus group to inform, adapt and develop the questions for the following focus group. Codes from each focus group will be categorised and themes identified. Analysis will be in content and narrative format.

An informed consent will be obtained from every participant prior to inclusion in the study. No investigations, treatment or assessments of patients will be undertaken as part of this study.

3.1 STUDY OUTCOME MEASURES

- What our transplant patients' understanding is of the terms immunosuppressant medication adherence and immunosuppressant medication nonadherence.
- How our transplant patients define immunosuppressant medication nonadherence
- What importance our transplant patients attach to medication adherence?
- Whether patients understand that medication nonadherence may affect the outcome of their kidney transplant
- The common practical and perceptual barriers to medication adherence identified by our transplant patients
- Interventions our transplant patients have used to try and improve their medication adherence
- Interventions our transplant patients have found effective to improve their medication adherence
- Interventions our transplant patients have not found to be effective to improve their medication adherence
- The support transplant patients have had with medication adherence since their transplant
- The support transplant patients feel could have helped them to better adhere to their medicines up to now
- The support our transplant patients feel would help them to adhere better to their medicines in the future

4. PARTICIPANT ENTRY

4.1 PRE-REGISTRATION EVALUATIONS

Kidney Transplant Recipients transplanted and under active follow up at ICRTC.

4.2 INCLUSION CRITERIA

Kidney transplant recipients transplanted and under the active follow up of ICRTC.
Speak and understand English
18 years and above

4.3 EXCLUSION CRITERIA

Unable to speak and understand English
Below 18 years

4.4 WITHDRAWAL CRITERIA

Patient unwilling to continue participation in the focus groups

5. ADVERSE EVENTS

5.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*

- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.3 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.3.1 Non serious AEs

All such events, whether expected or not, should be recorded.

5.3.2 Serious AEs

An SAE form should be completed and faxed to the Chief Investigator within 24 hours. However, relapse and death due to kidney transplantation, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the West Midlands – Edgbaston REC where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs
Fax 0208 383 8543, attention Dawn Goodall
Please send SAE forms to: Dawn Goodall
Tel: 0208 383 4247 (Mon to Fri 09.00 – 17.00)

6. ASSESSMENT AND FOLLOW-UP

If, as a result of the discussion, any patient realises that they are not taking their medicines as well as they thought, support will be available for them in the transplant outpatient's clinic. The pharmacist who is running the focus groups will help the patient to organise this.

7. STATISTICS AND DATA ANALYSIS

Each focus group will be transcribed by the Chief Investigator and the content coded. A preliminary analysis will be made after each focus group to inform, adapt and develop the questions for the following focus group. Following completion of all the focus groups, the Chief Investigator will undertake a full analysis of all the focus groups. Codes from each focus group will be categorised and themes identified. All analysis will take place at Imperial College Healthcare NHS Trust.

Data and all appropriate documentation will be stored for a minimum of 5 years after the completion of the study, including the follow-up period.

8. REGULATORY ISSUES

8.1 ETHICS APPROVAL

The Chief Investigator has obtained approval from the West Midlands - Edgbaston Research Ethics Committee and the HRA. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2 CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment. If a patient gives consent and participates in a focus group but then loses capacity, the contents of the focus group and their contribution to it will still be used in full.

8.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act. The chief investigator and other members of the research team are members of the healthcare team caring for the participants therefore have access to their personal information. Confidential patient information will be stored only on the hospital computer systems. Non-anonymised data will be available to study clinicians only. All electronic data will be pseudonymised (ie each patient = unique number). The unique number will be allocated to the patient at the time of recruitment. The identifier will be stored securely on the hospital computer system. Written consent forms will be stored in the study file which will be stored securely on the hospital premises. A copy will be scanned and recorded on their electronic patient record. The focus groups will be audio and video recorded and transcribed by Dawn Goodall, the Chief Investigator. The transcription will take place as soon as possible after the focus group has taken place and the aim will be to complete the transcription within 2 weeks. The recordings will be destroyed following transcription and checking. Participants will not be identified by name in the transcriptions. Quotes will be included in the writing up of the study to illustrate themes that emerge from the qualitative analysis however they will be anonymised and participants will not be identified.

8.4 INDEMNITY

Imperial College Healthcare NHS Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England, which apply to this study

8.5 SPONSOR

Imperial College London and Imperial College Healthcare NHS Trust will act as the main sponsors for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6 FUNDING

NIHR Imperial Biomedical Research Centre are funding this study. Each participant will be given a £25 incentive to attend the focus groups in addition to their travel expenses. Refreshments will be provided at each focus group.

8.7 AUDITS

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through Imperial College NHS Healthcare Trust Transplant Research and Operations Group.

10. PUBLICATION POLICY

The aim is to publish the outcome of the study in a high impact, peer reviewed journal.

11. REFERENCES

1. Kidney Disease: Improving Global Outcomes Transplant Work G. KDIGO clinical practice guideline for the care of kidney transplant recipients. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2009;9 Suppl 3:S1-155.
2. De Bleser L, Matteson M, Dobbels F, Russell C, De Geest S. Interventions to improve medication-adherence after transplantation: a systematic review. Transplant international : official journal of the European Society for Organ Transplantation. 2009;22(8):780-97.
3. Fine RN, Becker Y, De Geest S, Eisen H, Ettenger R, Evans R, et al. Nonadherence consensus conference summary report. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2009;9(1):35-41.
4. Denhaerynck K, Steiger J, Bock A, Schafer-Keller P, Kofer S, Thannberger N, et al. Prevalence and risk factors of non-adherence with immunosuppressive medication in kidney transplant patients. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2007;7(1):108-16.
5. Morrissey PE, Flynn ML, Lin S. Medication noncompliance and its implications in transplant recipients. Drugs. 2007;67(10):1463-81.
6. Prendergast MB, Gaston RS. Optimizing medication adherence: an ongoing opportunity to improve outcomes after kidney transplantation. Clinical journal of the American Society of Nephrology : CJASN. 2010;5(7):1305-11.
7. Schafer-Keller P, Steiger J, Bock A, Denhaerynck K, De Geest S. Diagnostic accuracy of measurement methods to assess non-adherence to immunosuppressive drugs in kidney transplant recipients. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2008;8(3):616-26.
8. Sellares J, de Freitas DG, Mengel M, Reeve J, Einecke G, Sis B, et al. Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and nonadherence. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2012;12(2):388-99.
9. Roberts DM, Jiang SH, Chadban SJ. The treatment of acute antibody-mediated rejection in kidney transplant recipients-a systematic review. Transplantation. 2012;94(8):775-83.
10. Wiebe C, Gibson IW, Blydt-Hansen TD, Karpinski M, Ho J, Storsley LJ, et al. Evolution and clinical pathologic correlations of de novo donor-specific HLA antibody post kidney transplant. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2012;12(5):1157-67.
11. Hughes s, De Freitas, D, Worthington, J., Strickland-Hodge, B. Preventing donor-specific antibodies after transplant. Clinical Pharmacist. 2014(Jan / Feb 2014).
12. Organisation WH. ADHERENCE TO LONG-TERM THERAPIES Evidence for action. World Health Organisation; 2003. Report No.: WHO/MNC/03.01.
13. Butler JA, Roderick P, Mullee M, Mason JC, Peveler RC. Frequency and impact of nonadherence to immunosuppressants after renal transplantation: a systematic review. Transplantation. 2004;77(5):769-76.

14. Massey EK, Tielen M, Laging M, Timman R, Beck DK, Khemai R, et al. Discrepancies between beliefs and behavior: a prospective study into immunosuppressive medication adherence after kidney transplantation. Transplantation. 2015;99(2):375-80.
15. Massey EK, Tielen M, Laging M, Beck DK, Khemai R, van Gelder T, et al. The role of goal cognitions, illness perceptions and treatment beliefs in self-reported adherence after kidney transplantation: a cohort study. Journal of psychosomatic research. 2013;75(3):229-34.
16. Dew MA, DiMartini AF, De Vito Dabbs A, Myaskovsky L, Steel J, Unruh M, et al. Rates and risk factors for nonadherence to the medical regimen after adult solid organ transplantation. Transplantation. 2007;83(7):858-73.

11. APPENDICES

Participant Information Sheet
Consent form
Recruitment poster