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Summary

Almost 9% of deceased donors in the United States are classified by the CDC as "high risk for transmission of HIV" based on a set of behavioral criteria introduced in 1985 and formalized in 1994. When these criteria were originally developed, they were based on estimates of prevalent HIV disease, and the CDC recommended that organs not be used from Infectious Risk Donors (IRDs) except in extenuating circumstances. However, with significant advances in viral testing, the risks are much lower, the diseases of concern have changed, and the original behavioral criteria are less relevant to the predictions required for clinical decision-making than they were in 1985 and 1994. As a result, discard rates for IRD kidneys are significantly higher than their non-IRD counterparts despite good outcomes in those who do receive them.

The central problem is that selecting a recipient that will benefit from an IRD kidney is difficult. First, no systematic estimates of the risk of undetected HIV or hepatitis C (HCV) with various IRD behaviors exist, so clinical decision-making is based more on intuition and anecdote than on evidence. Second, no studies exist that compare, in a given patient, the risk of death while waiting for a better kidney offer with the risk of undetected viral infection from IRDs. We hypothesize that subgroups of patients exist for whom the risks of dialysis while waiting for a better kidney offer far exceed the risks of HIV or HCV transmission from IRDs, and that defining this subgroup will increase comfort with and utilization of IRDs. This seems to be a concept intuitive to transplant surgeons, as identification of a target recipient profile was associated with significantly higher likelihood of using kidneys from IRDs in a national survey.

In an effort to inform and improve utilization of IRD kidneys, we propose to systematically review the literature on incidence of HIV and HCV seroconversion in various behavioral risk groups, estimate the predicted probabilities of HIV and HCV transmission in IRDs, and design a Markov decision process model for identifying the recipients who are likely to benefit significantly from IRD kidneys compared with waiting on dialysis.

The research described in this proposal will directly address, through a novel mathematical approach, a critical clinical need. A successful Markov decision process model will be immediately useable clinically throughout the country, and will with high likelihood increase provider comfort with kidneys from a currently underutilized subgroup of deceased donors.

Public Health Relevance

Although kidney transplantation offers potentially significant benefit to the tens of thousands of patients on the waiting list, there is reluctance to use kidneys from almost 10% of donors who, based on studies of behavioral risk from over 20 years ago, are flagged as having increased (although still very low) risk of carrying HIV. Because the risk of death on the waiting list is now so high, we suspect that, for some patients, the risk of transmitting an undetected infection from these donors is much lower than the risk of dying while waiting for a better kidney. The goal of this project is to update the antiquated behavioral risk flags, quantify the true risk associated with these donors, and use novel mathematical methods to identify patients who will benefit from kidney transplants from this underutilized supply of donors.

Resources and Environment

Clinical Resources:
Department of Surgery: The [redacted] is one of the highest-volume surgical centers in the country. Under the direction of Dr. [redacted] there are 55 full-time faculty surgeons and a large educational program including 43 categorical surgical residents and several subspecialty fellows. There are ample resources available for the successful completion of this project. These include state of the art library and computer facilities, abundant conferences and grand rounds on clinical research topics including research methods, clinical conferences, and the ethical conduct of research. Dr[redacted] is the Director of Information Technology for the Department of Surgery.

Comprehensive Transplant Center and Division of Transplant Surgery: This is a high-volume, internationally respected combined medical and surgical clinical and research center where Dr. [redacted] holds his clinical appointment and where the study subjects for much of his research are drawn. There are 20 faculty members, 35 clinical nurses and nurse practitioners, and over 40 research assistants who are involved in the clinical care of transplant patients as well as translational and clinical research related to transplantation. Dr. [redacted] is also the Director of Clinical Research for the Division of Transplant Surgery.

Computing Resources:
Dr. [redacted] research group owns and maintains a Linux high performance computing cluster which has been custom designed for data collection, data management, and statistical analysis (see Equipment section). Dr. [redacted] research group also owns 10 dual-core personal computers equipped with database, graphics, word processing, statistical, and bibliographic software.

Office Resources:
Dr[redacted] esources include a 500 square foot clinical office and a separate 1200 square foot research office at the [redacted]

Library Resources:
The [redacted] University maintains several libraries with book collections numbering over 2.5million volumes. Professional research librarians staff all facilities. The [redacted] Medical Library, located on the J[redacted] Medical Institution's [redacted] campus provides a variety of resources that support the teaching, research, and patient care goals of the Institutions. Faculty, staff, and students can search a range of databases and take advantage of the library's information services and classes. The [redacted] provides access to remote and local online databases, including the [redacted] Online Catalog that lists books, journal titles, software, and audiovisual programs at seven [redacted] braries; Med 2000+ database of MEDLINE, AIDLIN, Health Administration and Planning, BioethicLine, CancerLit, and PsycInfo; Current Contents/Science Editions; and WelchWeb (a hypertext source for Welch and Internet resources).

Equipment

Dr. [redacted] research group owns and maintains a Linux high performance computing cluster which has been custom designed for data collection, data management, and statistical analysis. This computing environment consists of one dual-Pentium Xeon processor Master Host Node (running GNU Linux 2.6, Linux Networx cluster integration software, and Clusterworx 3.2 cluster management software), one dual-Pentium Xeon processor Large Memory Node (with 16 GB of RAM), 16 Pentium Xeon processors with standard memory (2 GB of RAM), 1Gbit inter-node connectivity, and 1 TB of distributed redundant storage. All hardware is housed in the basement of the 1830 building at the [redacted] Medical Campus, in a locked rack enclosure within a locked server room where all of the [redacted] patient-oriented computing servers are located. The server is accessed via SFTP and SSH-2 secure remote connections, with password-protected individual user accounts. Statistical computing resources include multi-user licenses for multi-processor STATA, SAS, distributed C++, LEDA applied mathematical tools, and CPLEX optimization tools.

INTRODUCTION / SUMMARY OF CHANGES

This is a resubmission of an R21 which received a score of 27 on first submission. Underlined text indicates a direct quote from the summary statement. Noted as strengths of the application were that it addresses a significant clinical problem, that it is likely to have a positive impact on decision-making and clinical outcomes for many patients, that it involves an extremely well-qualified investigative team with expertise in renal transplant, clinical investigations, biostatistics, medical decision making, and informatics, and that it will be conducted in an outstanding research environment. Additional strengths noted were the investigative team's relevant preliminary work, the use of a sound approach, and the potential to move the field forward.

We greatly appreciate the insightful comments and concerns of the Study Section, and feel that the proposal is significantly stronger as a result. Given that the original submission used the 15-page format, much of the original text has been condensed, and these changes are not marked. **Throughout the body of the grant, additions that address the concerns summarized below are indicated in bold**.

It is not clear how large the potential pool of likely suitable articles is to draw estimates of key parameters for the meta-analysis.. it would be nice to know that at least some of those have useable information, rather than just meeting search criteria. We have started to review these articles and, fortunately, indeed do find useable information. We have added to the proposal some details on the nature of the eligible articles and the number we from which expect to have usable information based on our preliminary work.

The literature search for the meta-analysis does not include reviewing the gray literature or talking to experts in the field to find additional relevant material. We have added details and preliminary data regarding various hand-search approaches that will supplement the automated library searches.

What will the investigators do to develop pooled estimates if heterogeneity exists? Heterogeneity is quite likely, and we have added details (in brief, because of page restrictions) of how we plan to estimate the distribution (including variance) of risk and incorporate this into sensitivity analyses of the model.

The model seems to omit rejection and return to the waiting state. To keep things simple, we had illustrated the IRD transplant and all potential outcomes except death as the "S" states. We apologize for the confusion that this caused, and we have now added states for allograft failure and waiting with HCV/HIV.

The proposed survival models may be too restrictive for broader age range. We agree that appropriate model fit will be critical. We have significantly expanded the description of our survival modeling plan, including a broader class of distributions and various other approaches for improving fit. We show some preliminary modeling as evidence of the feasibility of these distributions to capture these events accurately.

Only HIV patients with well controlled disease are considered candidates for kidney transplantation. Can outcomes of such patients automatically be translated to individuals who contract HIV as a result of transplantation? We agree and have provided several alternative approaches and sensitivity analyses to confirm that clinical recommendations resulting from the model are not sensitive to this assumption.

The utilities proposed in 5.3.2 are problematic. The 0.8 for waiting on dialysis needs better grounding and definitely needs to be time varying as the patients age or their condition deteriorates. We agree that in a standard CEA, we would need to determine utilities that could be compared across the entire spectrum of health. We have clarified that our goal is not to study cost-effectiveness, but rather to study comparative outcomes. As such, we have used relative utilities. We have expanded our proposal to include as much justification as possible for the relative utility of 0.8 on dialysis versus 1.0 with a functioning kidney which is considered the "best-available standard" in our field. We have also expanded our methods to account for and examine the effects of various models of declining utility (modeling dialysis separately from transplantation).

Even if a small number of recipients contract HIV from infectious-risk kidneys, this would have a negative impact on future decisions by clinicians and potential recipients... The investigators do not discuss this. We have conducted a study that showed that provider reluctance to use IRD kidneys indeed occurred after a broadly publicized HIV transmission. However, this study also showed that *appropriate recipient profiles* improve comfort with these kidneys. As with many other types of risky kidneys, evidence-based literature provides justification to centers for using them; we feel that IRD kidneys will be no exception. We also address the potential negative patient response to transmission in the state utility sensitivity analysis.

Sensitivity of the results to discounting? This is a great point that we inadvertently omitted. We have added several analyses to test the sensitivity of our interferences to various discounting rates.

The application must provide a justification for the exemption with sufficient information about the involvement of the human subjects to allow a determination by peer reviewers and NIH staff that the claimed exemption(s) is/are appropriate. We have added justification for our claimed exemption, including an exemption determination from our IRB as well as details about the de-identified nature of the data.

SPECIFIC AIMS

Almost 9% of deceased donors in the United States are classified by the Centers for Disease Control and Prevention (CDC) as "high risk for transmission of HIV" based on a set of behavioral criteria introduced in 1985 [7-8] and formalized in 1994 [9-10]. When these criteria were developed, they were based on seropositivity estimates of prevalent HIV disease, and the CDC recommended that organs not be transplanted from Infectious Risk Donors (IRDs) with these behaviors "unless the risk to the recipient of not performing the transplant is deemed to be greater than the risk of HIV transmission." IRD criteria range from hemophilia to incarceration to injection drug use, and likely represent a wider range of infectious risk than was observed 15-25 years ago. Furthermore, with significant advances in serologic testing, the relevant clinical concern is now that of an undetected "window period" infection (one that occurs in the period between exposure and serologic detectability) and, by default, these CDC criteria are currently being applied in practice to predict this incidence rather than their originally intended purpose of predicting prevalence. Finally, the risk of transmitting hepatitis C virus (HCV) through solid organ transplantation is currently higher than that of transmitting HIV, and these criteria have been adopted as by-default predictors of this risk as well.

Aside from the increased risk of transmitting these viral diseases, 88% of IRDs qualify as ideal donors in terms of predicted function following kidney transplantation (KT) [11]. However, equipoise exists regarding the use of IRDs, and discard rates for IRD kidneys are significantly higher than their non-IRD counterparts despite good outcomes in those who do receive them [12]. Additionally, use of kidneys from IRDs is further declining in light of negative provider response to a recent high-profile transmission of HIV and HCV through solid organ transplantation [13-15].

We hypothesize that subgroups of patients exist for whom the risk of death on dialysis while waiting for a better kidney offer far exceeds the risk of death resulting from viral transmission from IRDs, and that defining these subgroups will increase comfort with and utilization of IRDs. This seems to be a concept intuitive to transplant surgeons, as identification of a target recipient profile was associated with significantly higher likelihood of using kidneys from IRDs in a national survey [15-16]. However, no studies exist to guide in the selection of an appropriate target IRD recipient profile. Furthermore, no systematic studies exist that estimate of risk associated with various IRD behaviors. We thus propose:

1. To estimate HIV and HCV incidence and prevalence in adults meeting current CDC criteria for IRDs.

   Brief Methodology: We will perform a systematic review of HIV and HCV incidence rates reported in adults meeting any of the seven IRD behavioral risk categories identified by the CDC. From these studies, we will estimate the predicted probability distributions of HIV and HCV window period infections in IRDs.

2. To explore risk profiles of other potential IRD subgroups not currently flagged by CDC criteria.

   Brief Methodology: We will review articles identified in Aim 1, as well as other studies of HIV and HCV incidence, for other potential subgroups with measurable incidence of HIV and HCV seroconversion. Once these subgroups are identified, we will conduct a systematic review of HIV and HCV incidence rates similar to that conducted in Aim 1, this time focused on these novel non-CDC-flagged potential IRD subgroups.

3. To design a Markov decision process model for identifying the recipients who are likely to benefit significantly from IRD kidneys compared with waiting on dialysis.

   Brief Methodology: Using predicted probability distributions determined in Aims 1 and 2, as well as parametric models of survival and transplant rates based on United States Renal Data Systems (USRDS) and United Network for Organ Sharing (UNOS) data, we will build a Markov decision process model to compare predicted survival between kidney transplantation with a currently available IRD versus waiting for the next appropriate non-IRD kidney.

This research will ensure that clinical decision-making regarding the use of IRDs is evidence-based and in the best interest of patients. A successful Markov decision process model will be immediately useable clinically throughout the country, and will with high likelihood increase provider and patient comfort with, and hence utilization of, kidneys from a subgroup that comprises approximately 9% of deceased donors in the United States.

A. SIGNIFICANCE

A.1. Infectious Risk Donors (IRDs). The CDC issued two sets of guidelines for minimizing the transmission of HIV through solid organ transplantation, first in 1985 [8] and then in 1994 [9]. The primary component of these guidelines was a list of behavior exclusionary criteria, from which "persons who meet any of the criteria" were recommended to "be excluded from donation of organs or tissues unless the risk to the recipient of not performing the transplant is deemed to be greater than the risk of HIV transmission." When these criteria were developed, they were based on seropositivity estimates of prevalent HIV disease [17-24]. However, with significant advances in serologic testing changing the relevant clinical question from one of prevalence to one of incidence, these criteria are currently applied, by default, to predict the incidence of a "window period" infection (one that occurs in the period between exposure and serologic detectability) [10]. In addition, these criteria have also been adopted to predict this risk of HCV transmission. Currently, the CDC defines an IRD as someone falling into one of seven behavioral categories (Appendix 1). Both applications of these criteria (predicting HCV and HIV window period infections) are markedly different from their originally intended purpose, and a 2009 national consensus committee determined that the CDC recommendations need to be revised [6]. This multidisciplinary group concluded that the current (1994) CDC "guidelines have not been updated to reflect current understanding of infection transmission and may not be accurate for risk factor assessment or appropriate for exclusion of donors." Furthermore, the committee recommended that "donor behavioral risks associated with a higher risk of HIV infection should be updated to emphasize risk factors for newly acquired (incident) infection. Definitions should be expanded beyond HIV to include HCV as well as consideration of behaviors (e.g., drug snorting) which are not currently part of the CDC definitions."

A.2. Donor Testing for HIV/HCV and Window Period Infections. In solid organ transplantation, evidence suggests that HIV or HCV infection in the donor is assuredly transmitted to the recipient [10, 25]. Because of this, all potential donors are tested by ELISA for the presence of these diseases as required by UNOS [26]. However, ELISA testing for HIV or HCV requires the development of antibodies and, as such, fails to detect recent infections during a lengthy window period, the time between infection and serologic detectability [27-32]. It is this risk of recent, undetected infection in the donor that has never been quantified and, as such, remains a disincentive. Nucleic Acid Testing (NAT) is a newer testing method that significantly shortens the window period from approximately 22 days to 9 days for HIV and from 66 days to 7 days for HCV. NAT is not currently required by UNOS, and use of NAT varies widely [11]. While NAT attenuates the infectious risk, it is expensive and time consuming, potentially increasing ischemic time (with resulting decreased graft survival). Perhaps the biggest disadvantage of NAT is its higher rate of false positives that could lead to discard of viable organs [10, 33]. As such the power of NAT relies on the pre-test probability, and NAT is best limited to populations at highest risk of incident infection; identifying these populations is critical to appropriate use of NAT. Even with NAT, the risks of undetected window period infection still exist, and it remains critical for clinical decision-making to understand these risks in various deceased donor subgroups.

A.3. End Stage Renal Disease (ESRD). The burden of ESRD in the United States is significant, with over one half-million prevalent cases reported in 2008 [34]. Furthermore, the incidence of ESRD has been increasing steadily, from 76.3 per million in 1980, to 199.3 per million in 1990, to 326.0 per million in 2000 to 350.7 per million in 2005. For many ESRD patients, kidney transplantation (KT) improves both survival and quality of life [35-36]. However, the organ supply is limited, with a waiting time of 3-10 years depending on blood type and geographic location. Death rates on the waiting list exceed 50% in some subgroups. It is thus imperative that the transplant community maximize utilization of available organs, including IRDs.

A.4. Transplantation using IRD Kidneys. The biggest disincentive to using organs from IRDs is the potential to transmit certain infectious diseases, most commonly HIV and HCV. However, this risk has never been quantified. A recent high-profile case highlights this disincentive, as four recipients contracted HIV and HCV from an IRD donor who tested negative for both diseases by ELISA [14]. **Provider emotional responses to this transmission were extreme, and likely out of proportion to true risk: in a national study, we showed that over 30% of transplant surgeons changed their practice based on this isolated event, the majority of whom decreased use of IRD kidneys (manuscript in press, Appendix 2).**

A.5. Preliminary Data Supporting Significance. In a study of 2,574 IRDs, **we showed that IRDs comprise 8.6% of available kidneys, and are in general from younger, non-hypertensive donors with better predicted allograft function equivalent to that of ideal Standard Criteria Donors (SCDs)** [11]. We found that use of IRDs for kidney transplantation varies by transplant center around the country [11, 15-16]. Despite the high quality of kidney function among IRDs, we found that **IRD kidneys are much more likely to be**

discarded than their non-IRD counterparts, with almost 2,000 IRD kidneys discarded between 2004-2009. The adjusted odds of discarding an IRD kidney were 48% higher than those of a non-IRD kidney, and 67% higher among donors under 50. To understand IRD utilization, we surveyed 422 transplant surgeons representing 89% of total transplant volume in the United States [16]. We found that utilization varied significantly by IRD behavior, raising question to the current use of a single "IRD" designation, and supporting the conclusions made by the recent national consensus conference (A.1) that the current CDC "guidelines have not been updated to reflect current understanding of infection transmission" [6]. **Although having a defined recipient profile was associated with >2-fold higher willingness to use IRD kidneys [16], provider survey responses and national practice patterns of IRD kidney use were not consistent with a practice of targeting appropriate recipients.** This likely results from the lack of studies quantifying the risks and benefits of IRD kidney transplantation among various subgroups of potential recipients.

A.6. Limitations of the Literature. A recent study suggests that outcomes following transplantation of IRD kidneys are similar to those following transplantation of kidneys from ideal donors [12], although this study is limited by short follow-up and confounding by indication (the latent factors affecting recipient selection). Evidence suggests that using IRD kidneys in general would be more beneficial to the transplant community than not using them [37], although the inferences of this study are limited to those of a "greater good" rather than those for a particular patient. No studies to date have succeeded in providing clinicians the critical recommendations that are needed when considering IRD kidney transplantation: which patients would benefit from the IRD kidney and which patients would be better off waiting for the next available organ?

A.7. Significance. Provider comfort with kidneys from IRDs is declining as a result of a recent high-profile HIV and HCV transmission, fear of lawsuits, and fear of regulatory repercussions. A predefined profile for an acceptable target recipient is associated with much higher likelihood of using these kidneys. The research described in this proposal will directly address, through a novel mathematical approach, the clinical need to identify an acceptable target recipient profile for IRD kidneys. Estimates of HIV and HCV incidence in various subgroups (including those flagged by, as well as those currently not flagged by, the CDC) will assist in clinical decision-making regarding IRDs. More importantly, these estimates will inform a Markov decision process model to assist in quantifying risk/benefit associated with these kidneys. A successful Markov model will be immediately useable clinically throughout the country, and will likely increase provider comfort with and utilization of kidneys from a subgroup that comprises about 9% of deceased donors in the United States.

B. INNOVATION

B.1. Target Recipient Profile Development for Non-Ideal Kidneys. The concept of identifying appropriate recipients for various types of non-ideal organs is not new to the transplant community. The clinical question at hand, when an organ offer is made, is always the following: is the patient to whom the organ was offered better off waiting for the next available organ or receiving the organ being offered? These questions have typically been answered using survival benefit models [38-43]. In general, these models compare one cohort that received a treatment at some point during the study with another cohort that was never treated, grouping them into time-dependent risk sets and comparing them with non-proportional Cox regression models [39, 44]. This approach was successfully used to generate an algorithm to guide providers in selecting appropriate recipients of ECD kidneys. **We wish to answer a similar question, but similar methods cannot be used, because both the population of interest and the counterfactual population are not observable**.

B.2. Markov Decision Process Models. In situations where both populations are not observable in the state required to answer the study question, discrete event models are needed to combine that which has been observed in the population of interest (captured as raw survival data) and that which has not been observed in the population of interest but can be deduced from other populations (captured as predicted probability distributions). For example, to study the long-term effect of IRD transplants, given the very low rate of infectious transmission, long-term national data for tens of thousands of recipients of IRD kidneys would be needed. Unfortunately, the CDC IRD flag has only been captured in the national UNOS registry since July 2004, and too few actual recipients have been followed to truly understand outcomes. However, many other studies in the literature have studied the incidence of HIV and HCV seroconversion in the behavioral categories flagged by the CDC, and combining these rates with known window period durations and known outcomes stratified by recipient HIV and HCV status can help estimate the long-term outcomes of this particular non-observable transplant recipient population. These outcomes can then be compared to a counterfactual population which is indeed observable, using a Markov decision process model.

C. APPROACH

C.1. Aim 1: To estimate HIV and HCV incidence and prevalence in adults meeting current CDC criteria.

Overview. We will conduct a systematic review of HIV and HCV incidence and prevalence rates in the CDC-defined IRD risk categories. These estimates remain un-quantified and will be an important contribution to the literature *per se*. Additionally, we will calculate the distribution of predicted probabilities of window period seroconversion for use in our Markov decision process model (C.3).

Search Strategy. A systematic review will be conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria [45], using an expansion of our pilot-tested search strategy (C.1P). **Our preliminary search will be expanded by including the following:** (1) articles since November 2008; (2) EMBASE and Cochrane searches; (3) specific searches of keywords from the seven CDC IRD behavioral criteria, in combination with *HIV* or *hepatitis C*; (4) bibliographies of eligible articles; **(5) gray literature (proceedings, theses, clinical trials registries); and (6) conversations with experts in the field, such as members of the national IRD consensus committee in which the P.I. participated (A.1)**.

Inclusion Criteria. All sources providing original estimates of HIV prevalence or incidence, HCV prevalence or incidence in CDC-defined risk populations in the United States and Canada will be eligible for inclusion in our study. To reflect current understanding of infectious transmission and risk (as recommended by the national consensus conference), all estimates must be calculated using data collected on or after January 1, 1995.

Abstract Identification and Review. All identified abstracts will be screened by two independent reviewers and marked as eligible or ineligible for the full-text review based on the above inclusion criteria. A third reviewer and the P.I. will adjudicate all disagreements, with consensus reached through joint reassessment when necessary. Those without sufficient information for definitive exclusion will be included in the full-text review.

Data Abstraction. A data abstraction form has been designed and pilot tested (Appendix 3). Two independent reviewers will abstract data from each of the articles identified as eligible based on the abstract screen. A third reviewer and the P.I. will compare the abstractions of the two original reviewers and adjudicate disagreements. For those found to be ineligible, the reason for ineligibility will be captured.

Statistical Analysis. Heterogeneity will be formally assessed using the Cochran Q statistic, the I^2 statistic, and χ^2 tests [46-47]. Meta-regression techniques will be used to explore potential sources of heterogeneity, if applicable [48-49], as has been previously done by the P.I. [50]. Pooled estimates of prevalence/incidence will be obtained by a modified Mantel-Haenszel method [46]; since standard methods of calculating confidence intervals risk artificially narrow intervals in the setting of heterogeneity, confidence intervals will be calculated to allow for extra-binomial variation [51]. **Reported estimates will be explored using histograms, distribution plots with medians and quantiles, and standard meta-analytical estimates. These will determine state transition probabilities, as well as distributions (particularly in the case of significant heterogeneity) from which to draw in discrete-event simulation sensitivity analyses for the Markov model.**

C.1P. Preliminary Systematic Search to Assess Feasibility of Aim 1.

Search Strategy. On November 27, 2008 we performed a search of PubMed/Medline to identify any abstracts indexed between January 1, 1995 and our search date that included MeSH terms (1) *HIV* and *prevalence*, (2) *HIV* and *seroprevalence*, (3) *HIV* and *incidence*, (4) *HIV* and *seroepidemiologic studies*, (5) *hepatitis c* and *prevalence*, (6) *hepatitis c* and *incidence*, and (7) *hepatitis c* and *seroepidemiologic studies*. To identify abstracts published in 2008 that might not have yet be indexed, we performed an additional search for any of the above combinations in the *title* and *abstract* of articles published between January 1, 2008 and our search date. Additional inclusion criteria were English language and human studies. We excluded articles with MeSH terms indicating they were performed in geographic regions outside the United States or Canada.

Abstract Identification and Review. We identified 3,298 abstracts, which were screened by 2 reviewers and marked for full-text review based on the inclusion criteria above. A third reviewer, and the P.I., adjudicated all disagreements. A total of 278 abstracts were identified as eligible for full-text review. **Hand search of bibliographies of eligible articles identified an additional 91 abstracts, for a total of 369 articles for full-text review.** A data abstraction form was designed and pilot tested using a 10% sample of these articles (Appendix 3). **A sample of 40% of these articles was used to study feasibility for meta-analysis, in other words how useable the articles were in identifying HIV or HCV prevalence and incidence among various risk groups. In this sample, 58% demonstrated useful data. Extrapolating these findings, we would expect 214 *useful* articles *before* inclusion of 2008-2010, gray literature, and experts in the field.**

C.2. Aim 2: To explore risk profiles of other potential IRDs not currently flagged by CDC criteria.

Overview. We will review articles of HIV and HCV incidence, as identified in Aim 1, and search for other potential IRD subgroups (that were not identified by the CDC in their most recent 1994 recommendations) with measurable incidence of HIV and HCV seroconversion. Once these subgroups are identified, we will conduct a systematic review of HIV and HCV incidence rates similar to that conducted in Aim 1, this time focused on these novel non-CDC-flagged potential IRD subgroups.

Search Strategy. First we will review all articles identified in Aim 1 for potential subgroups not flagged by the CDC but which seem to have measurable HIV or HCV incidence or prevalence beyond that of the general population. Examples of potential subgroups were identified in our preliminary study (below). Once these are identified, we will use the same strategy as in Aim 1, except instead of specifically searching for the CDC IRD behavioral criteria, we will specifically search for the novel non-CDC-flagged potential IRD subgroups.

Inclusion Criteria. All peer-reviewed manuscripts providing original estimates of HIV prevalence, HIV incidence, HCV prevalence, or HCV incidence in the novel subgroups and drawn from populations in the United States and Canada on or after January 1, 1995 will be eligible for inclusion in our study.

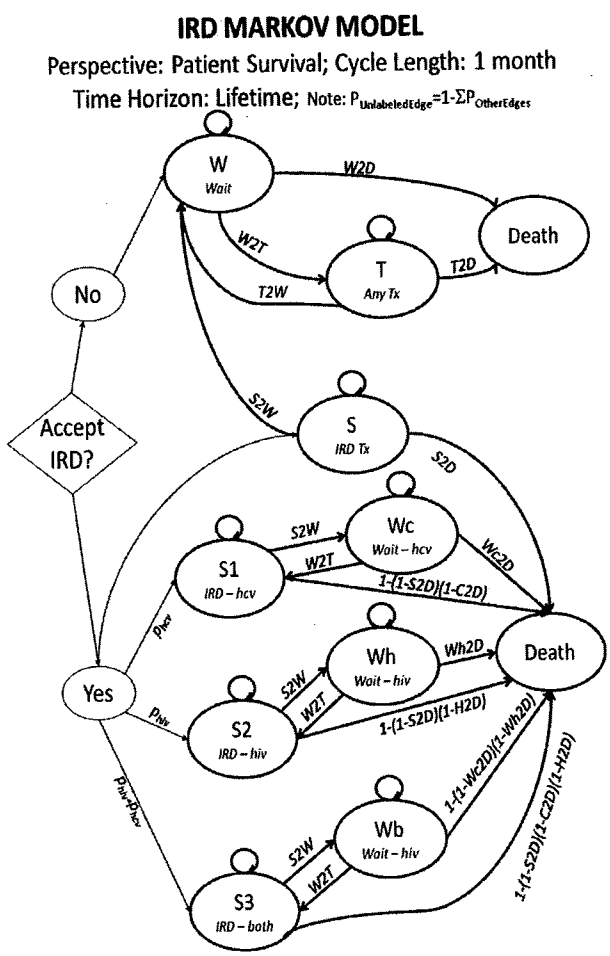
The remaining systematic review and pooled estimates will be conducted as described in Aim 1.

C.2P. Preliminary Feasibility Assessment for Potential IRD subgroups Not Flagged by CDC. We reviewed articles from our preliminary search (C.1P) for potential subgroups that were not identified by the current (1994) CDC criteria but seemed to be at increased risk of window period HIV/HCV infections. Some of these potential subgroups, with example references, are listed in the table to the right.

STDs; Anal or Genital sores [1]
Tattoo by non-professional, accidental needle stick, or other blood borne exposure in past 6 months [2]
Homeless [3]
Physical evidence of recent injection [4]
Unprotected sex with high risk individual [5]
Intranasal drug use [6]

C.3. Aim 3: To design a Markov decision process model for identifying the recipients who are likely to benefit significantly from IRD kidneys compared with waiting on dialysis.

Overview. We will design a Markov decision process model that answers the clinically relevant question: *should a given patient (a) accept the current IRD kidney offer or (b) wait for the next available non-IRD kidney*. State transition probabilities will be derived from observed transplant populations as well as populations with the behavioral characteristics of IRDs. The result will be a clinically applicable tool that providers can use for patient selection, allocation decisions, and risk/benefit counseling (to right, and Appendix 4). **The goal of this model is not cost-effectiveness evaluation, but rather to compare relative outcomes between these two choices.**



Elements of Markov Decision Process Model. Patients awaiting renal transplantation will be entered into the Markov model. Alternatives considered will be IRD therapy (accept an IRD kidney) and standard therapy (await the next available non-IRD kidney). Outcomes will be survival with a one-month long cycle length, a individual patient perspective, and a lifetime horizon. Quality-adjusted survival will be studied with a **relative utility of 1.0 for transplantation, 0.8 for waiting on dialysis [52-55], 3% annual discounting, and sensitivity analyses with varying discounting and utilities (both time-varying and static)**. Data sources are delineated below, and **uncertainty will be modeled based on the distribution of the estimates as well as sensitivity analysis**. States will include waiting (W), non-IRD kidney (average quality) (T), IRD kidney (SCD-quality) without viral infection (S), IRD with an undetected viral infection (S1, S2, S3), **waiting after viral transmission and allograft loss (Wc, Wh, Wb),** and death.

Data Sources: p_{hcv} and p_{hiv}. A number of estimates of HIV and HCV seroconversion probabilities will result from Aims 1/2. Since currently organs are dichotomized as IRD/non-IRD, the current clinical question is based on whether or not to accept "an IRD kidney" rather than "a kidney from a donor with a risk factor." As such, we will need to estimate the "average" seroconversion probabilities for the "average" IRD, exploring several different averaging schemes, including weighted averages based on reports of the distributions of IRDs. We will also allow for stratified estimates based on behavior, for situations where these characteristics are known.

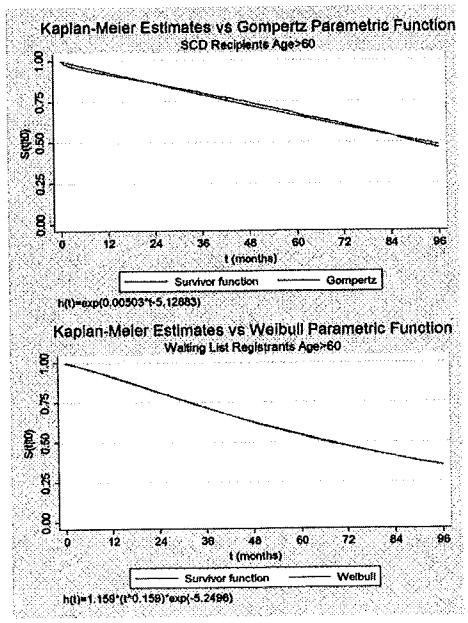
Data Sources: **C2D, H2D, Wc2D, Wh2D**. **Three approaches will be taken for these outcomes which are currently unobservable in national registry data *per se*.** First, we will analyze outcomes of HCV(+) and HIV(+) patients who have been waitlisted or transplanted, per UNOS/USRDS. **Second, since those with stable HCV or HIV may not represent those infected at the time of transplant (immunosuppression), we will adjust observed estimates based on reports of infection at the time of transplant (see preliminary data below). Finally, we will model death to occur at 1-year following HCV or HIV infection, to see if patient subgroups benefit from IRD transplantation even under the most pessimistic assumptions.**

Data Sources: **T2W, T2D, S2W, S2D**. The probabilities of allograft loss or death following kidney transplant of an "average" kidney (T) and one with the characteristics of an IRD kidney (but without infectious transmission, which will be modeled separately) (S), are observable in the national registry (A.4). Both death-censored allograft loss and death functions following kidney transplantation will be estimated from 86,283 deceased donor kidney transplants between January 1, 2000 and February 20, 2009, as reported to UNOS.

Data Sources: **W2T, W2D**. The probabilities of transplantation or death (mutually censored) while on the kidney waiting list is observable among 288,403 registrants for the UNOS deceased donor waiting list during our study period. We will censor any live donor recipients at the time of live donor transplantation, since they do not draw from the deceased donor pool following a successful live donor transplant.

Parametric Survival Models. For all probability estimates where observed transplant patient data exist, parametric survival (or time-to-event) models will be constructed. **Several classes of distributions will be explored, including but not limited to exponential, Weibull, Gompertz, and generalized gamma functions. Parametric estimates will be carefully compared with observed data in terms of applicability to various patient subgroups (stratified by important covariates). Standard censoring models will be compared with competing risk (subhazard/subdistribution-based) models [56-59] to account for potential informative censoring.** Those functions that best fit the observed data will be converted to state transition probabilities $p(t)$, where t is the cycle number, using the property $p(t) = 1 - S(t+1)/S(t)$.

Statistical Analysis. Parametric survival functions and competing risk models will be estimated using Stata 11.0 and/or R on our Linux 10-node cluster computer. Markov decision process models will be implemented in TreeAge Pro (TreeAge Software, Williamstown, MA) using the Monte Carlo micro-simulation and discrete event simulation options to allow for per-trial sampling distributions. These will be compared to a simpler Markov cohort expected value model to test robustness to modeling assumptions. Probabilistic sensitivity analysis will also be performed using the same software [60-61].



C.3P. Preliminary Feasibility Assessment for Parametric Modeling of Waiting List and Post-Transplant Outcomes.

Parametric Survival Modeling using USRDS/UNOS Data. One critical component will be the ability to parametrically model event probabilities in various states. Two national registries collect relevant longitudinal data. USRDS tracks patients from the time they start dialysis, collecting detailed comorbidity information and capturing (a) if and when they join the deceased donor kidney waiting list, (b) if and when they receive a kidney transplant, and (c) if and when they die. UNOS captures less detail regarding comorbidities but more detail regarding waiting list and transplant events. The two registries are linked so that analyses can benefit from their combined strengths. For preliminary exploration, we selected two state transitions for a sub-population of adults over 60: post-transplant death following standard criteria donor (SCD) transplantation, and waiting list death. A variety of parametric survival models were explored, and excellent correlation between observed outcomes and the parametric estimates were confirmed.

Outcomes and HIV/HCV infection. These estimates are informed by several transplant recipient subgroups: (a) HCV positive transplant recipients; (b) HIV positive transplant recipients, (c) HCV negative recipients of HCV positive kidneys; (d) HIV negative recipients of HIV positive kidneys.

Outcomes after KT in the Setting of HCV. Many centers transplant HCV positive patients with kidney failure [62]. Also, a number of centers transplant HCV positive kidneys into HCV negative recipients, under the assumption that most transplant recipients will not live long enough to manifest the sequelae of HCV, which usually progress over decades [63]. These experiences can be directly studied using the USRDS/UNOS registries, and can as such be used to estimate outcomes of IRD recipients who become infected with HCV.

Outcomes after KT in the Setting of HIV. Since the widespread adoption of highly active antiretroviral therapy (HAART) in 1994, dialysis patients with well controlled HIV have been considered candidates for kidney transplantation [64]. **We have studied outcomes of HIV positive recipients using national data [65] [10]. In addition, some reports exist of inadvertent HIV transmission to HIV negative recipients [14].**

C.4. Timeline

Task	Year 1: Month						Year 2: Month					
	2	4	6	8	10	12	2	4	6	8	10	12
Finalize selection of articles for Aim 1												
Review and analyze HIV/HCV incidence												
Identify new potential IRD subgroups												
Design Markov model												
Test & revise Markov model with clinicians												
Prepare publications												

C.5. Some Potential Limitations and Proposed Solutions

Aim 1, Inadequate Studies for Some IRD Categories. In the case that estimates are not available, we will interpolate estimates based on other risk categories, choosing confidence intervals to reflect a greater degree of uncertainty. Since these distributions are then used in the discrete event simulations of the Markov decision process models (Aim 3), results will appropriately reflect this uncertainty. In addition, we will perform sensitivity analyses to confirm that inferences are not sensitive to this modeling assumption.

Aims 1 and 2, Inadequate Studies of Incidence. We will estimate incidence from prevalence studies using two techniques: (1) those described by Zou and the Tissue Safety Study Group in their 2004 NEJM article [66], and (2) those used by the World Health Organization and the ALPHA Network (Analyzing Longitudinal Population-Based HIV data on Africa) [67]. These incidence estimates derived from prevalence studies will be compared to those obtained directly, and heterogeneity testing will be used to determine if these can be combined.

Aims 1 and 2, Standard Errors Not Reported. In studies where exact data on the recruitment pool are available, we will calculate SEs using exact methods. Otherwise, pooled estimates will have to be based on the subset of studies where SEs are reported, which may introduce a systematic bias [68]. We will perform sensitivity analyses (drawing SEs from a prior distribution) to study the potential effects of these biases.

Aims 1 and 2, Large Study Bias. Combining frequency estimates drawn from sites with drastically different background population sizes is potentially problematic, as studies are weighted by inverse squared SE, and studies drawn from much larger populations will have much smaller SE's and thus exert too much influence on the pooled estimate [69-70]. We will examine the population sizes of the studies to be pooled and, when applicable, explore various methods for accounting for this bias, including sample size "capping" [71-73].

Aim 3, Inability to Properly Fit Parametric Survival Models. Several approaches will be considered. First, **alternate parameterizations are available and will be explored (log-normal, log-logistic, generalized gamma, etc).** Second, stratification on the most important covariates will be explored; with stratification, model assumptions and fit are relaxed such that they need only apply within each stratum. The P.I. has been successful at meeting model assumptions using stratification in other survival models [74-75].

Aim 3, Declining Utility, Discounting, and Modeling Negative Response to Isolated Transmission. The base case will use 3% annual discounting, which be varied in sensitivity analyses. However, utility after transplantation and utility on dialysis may decline at different rates; these differential rates will also be tested in sensitivity analyses. Finally, the negative emotional response and stigma associated with HIV or HCV disease may be significant; this will be evaluated in sensitivity analyses as a significant drop in utility (to 0.1) or as the equivalent of death one year following disease transmission.

Human Subjects Research

(new text appears here to address study section concerns regarding the human subjects nature of this research)

In consultation with Dr. [redacted], we have determined that secondary data analysis of the United States Renal Data System (USRDS) dataset and United Network for Organ Sharing (UNOS) data is not considered human subjects research.

In the datasets that we use from USRDS and UNOS, there is no identifying information (such as name, social security number, or address). All center-level information is completely de-identified and encrypted so there is no way for us to determine at which transplant or dialysis center a patient received treatment.

The [redacted] has determined that analyses of the data we receive from USRDS and UNOS qualify for an exemption under 45 CFR 46.101(b):

(4) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that participants cannot be identified, directly or through identifiers linked to the participants.

Given that this is not considered human subjects research, it does not require descriptions for Protection of Human Subjects, Inclusion of Women and Minorities, Targeted/Planned Enrollment, or Inclusion of Children.