INPLASY

Kidney transplantation from hepatitis C-positive donors in the direct-acting antiviral era: acute rejection, graft and patient outcomes, and antiviral safety in hepatitis C-positive and hepatitis C-negative recipients: protocol for a systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

Support - No support.

Review Stage at time of this submission - Data extraction.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2026100039

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 9 October 2026 and was last updated on 17 November 2026.

INTRODUCTION

Review question / Objective Primary question: in adults with hepatitis C virus (HCV) infection who receive a deceased-donor kidney-alone transplant in the direct-acting antiviral (DAA) era (transplants on or after January 1, 2014), is transplantation of a kidney from an HCV-positive donor (D+/R+) associated with different patient survival, graft survival, and delayed graft function (DGF) compared with (a) transplantation of a kidney from an HCV-negative donor (D-/R+) or (b) remaining on the waitlist, or being treated before transplantation while awaiting an HCV-negative kidney?

PICOS. Population: adult HCV-positive (antibody or nucleic acid test [NAT] positive) kidney transplant recipients or candidates. Exposure: a kidney from an HCV-positive donor (antibody, NAT, or both). Comparators: D-/R+ recipients and HCV-positive waitlisted candidates. Outcomes: patient survival, all-cause and death-censored graft survival, and DGF. Study designs: randomized trials, cohort and registry studies, and decision-analytic models.

Secondary question (prespecified, analyzed separately and never pooled with the primary comparison): outcomes of HCV-negative recipients of HCV-positive kidneys (D+/R-) compared with D-/R- recipients or HCV-negative waitlisted candidates.

Rationale Kidney transplantation confers a survival advantage on dialysis patients with HCV infection. Before DAAs, HCV-positive candidates who accepted HCV-positive kidneys reached transplantation sooner, but in a propensity-matched registry analysis of transplants performed from 2001 to 2015 they had higher risks of death and allograft loss than recipients of HCV-negative kidneys. DAAs changed both sides of this trade-off: trials of D+/R- transplantation reported near-universal cure with early DAA therapy, allocation of HCV-viremic kidneys shifted toward HCV-negative recipients, and donor HCV status was removed from the Kidney Donor Profile Index calculation.

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Whether the historical penalty of D+/R+ transplantation persists in the DAA era determines how transplant programs counsel HCV-positive candidates: accept an HCV-positive kidney and treat after transplantation, or treat on dialysis and wait for an HCV-negative kidney. Existing meta-analyses pool studies across eras and recipient serostatus and cannot answer this question. Because U.S. national registry analyses (OPTN, UNOS, SRTR) draw on overlapping data, the synthesis must also avoid counting the same recipients more than once.

Condition being studied Chronic hepatitis C virus infection in adults with kidney failure who are candidates for, or recipients of, a deceased-donor kidney transplant, and the use of kidneys from HCV-positive deceased donors (antibody positive and/or NAT positive, that is, viremic) in the era of interferon-free direct-acting antiviral therapy.

METHODS

Search strategy All databases were searched on October 8, 2026. Strategies combine three concept blocks: (1) hepatitis C; (2) kidney transplantation; (3) donor, viremia, NAT, or DAA terms, with controlled vocabulary where available. Limits: 2014-2026, English, and exclusion of editorials, letters, notes, comments, case reports, and errata where the interface permits. CENTRAL and ClinicalTrials.gov were searched without date limits; records dated before 2014 were removed before screening.

MEDLINE (PubMed): (("Hepacivirus"[Mesh] OR "Hepatitis C"[Mesh] OR "hepatitis C"[tiab] OR HCV[tiab] OR hepacivirus[tiab]) AND ("Kidney Transplantation"[Mesh] OR "kidney transplant*"[tiab] OR "renal transplant*"[tiab] OR "kidney allograft*"[tiab] OR "renal allograft*"[tiab]) AND ("Tissue Donors"[Mesh] OR donor*[tiab] OR viremic[tiab] OR viraemic[tiab] OR "NAT positive"[tiab] OR "nucleic acid test*"[tiab] OR "HCV-positive"[tiab] OR "HCV-infected"[tiab] OR "Antiviral Agents"[Mesh] OR "direct-acting antiviral*"[tiab] OR DAA[tiab] OR glecaprevir[tiab] OR pibrentasvir[tiab] OR sofosbuvir[tiab] OR velpatasvir[tiab] OR elbasvir[tiab] OR grazoprevir[tiab] OR ledipasvir[tiab])) AND ("2014/01/01"[dp] : "2026/10/08"[dp]) AND english[la] NOT ("Case Reports"[pt] OR "Editorial"[pt] OR "Comment"[pt])

Embase (embase.com): ('hepatitis c'/exp OR 'hepatitis c virus'/exp OR 'hepatitis c':ti,ab OR hcv:ti,ab OR hepacivirus:ti,ab) AND ('kidney transplantation'/exp OR 'kidney graft'/exp OR 'kidney transplant*':ti,ab OR 'renal transplant*':ti,ab OR 'kidney allograft*':ti,ab OR 'renal allograft*':ti,ab) AND ('donor'/exp OR 'antivirus agent'/exp OR donor*:ti,ab OR viremic:ti,ab OR viraemic:ti,ab OR 'nat positive':ti,ab OR 'nucleic acid test*':ti,ab OR 'hcv positive':ti,ab OR 'hcv infected':ti,ab OR 'direct acting antiviral*':ti,ab OR daa:ti,ab OR glecaprevir:ti,ab OR pibrentasvir:ti,ab OR sofosbuvir:ti,ab OR velpatasvir:ti,ab OR elbasvir:ti,ab OR grazoprevir:ti,ab OR ledipasvir:ti,ab) AND [english]/lim AND [2014-2026]/py NOT ('case report'/de OR [editorial]/lim OR [letter]/lim OR [note]/lim)

Scopus: TITLE-ABS-KEY("hepatitis C" OR hcv OR hepacivirus) AND TITLE-ABS-KEY("kidney transplant*" OR "renal transplant*" OR "kidney allograft*" OR "renal allograft*") AND TITLE-ABS-KEY(donor* OR viremic OR viraemic OR "NAT positive" OR "nucleic acid test*" OR "HCV-positive" OR "HCV-infected" OR "direct-acting antiviral*" OR daa OR glecaprevir OR pibrentasvir OR sofosbuvir OR velpatasvir OR elbasvir OR grazoprevir OR ledipasvir OR antiviral*) AND PUBYEAR > 2013 AND PUBYEAR < 2027 AND LANGUAGE(english) AND NOT DOCTYPE(ed OR le OR no OR er)

Web of Science Core Collection: TS=("hepatitis C" OR HCV OR hepacivirus) AND TS=("kidney transplant*" OR "renal transplant*" OR "kidney allograft*" OR "renal allograft*") AND TS=(donor* OR viremic OR viraemic OR "NAT positive" OR "nucleic acid test*" OR "HCV-positive" OR "HCV-infected" OR "direct-acting antiviral*" OR DAA OR glecaprevir OR pibrentasvir OR sofosbuvir OR velpatasvir OR elbasvir OR grazoprevir OR ledipasvir OR antiviral*) AND PY=(2014-2026) AND LA=(English) NOT DT=(Editorial Material OR Letter OR Correction)

Cochrane CENTRAL (Title Abstract Keyword): ("hepatitis C" OR HCV OR hepacivirus) AND ((kidney NEXT transplant*) OR (renal NEXT transplant*) OR (kidney NEXT allograft*) OR (renal NEXT allograft*)) AND (donor* OR viremic OR viraemic OR (nucleic NEXT acid NEXT test*) OR antiviral* OR DAA OR glecaprevir OR pibrentasvir OR sofosbuvir OR velpatasvir OR elbasvir OR grazoprevir OR ledipasvir)

Europe PMC: the same three concept blocks, 2014-2026.

ClinicalTrials.gov: condition "hepatitis C" AND other terms "kidney transplant".

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Participant or population Kidney transplant recipients of HCV-positive donor kidneys, in two strata analysed separately and never pooled: HCV-positive recipients (D+/R+; primary) and HCV-negative recipients of HCV nucleic acid test-positive donor kidneys (D+/R-; secondary).

Intervention Transplantation of a kidney from an HCV-positive deceased donor, defined by antibody, NAT, or both (D+/R+), with any DAA strategy (treatment before transplantation, early after transplantation, or deferred).

Comparator (1) HCV-positive recipients of kidneys from HCV-negative donors (D-/R+); (2) HCV-positive candidates who remained on the waitlist or on dialysis, or who were treated with DAAs before transplantation while awaiting an HCV-negative kidney, including decision-analytic models parameterized for DAA-era practice. Secondary comparison: D+/R- versus D-/R- recipients or HCV-negative waitlisted candidates.

Study designs to be included Randomized trials; prospective and retrospective cohort studies, including national registry analyses; decision-analytic and cost-effectiveness models; for the secondary comparison, prospective trials enrolling at least 10 D+/R- recipients. Conference abstracts with extractable data are eligible. Case reports, series without a comparator, and reviews are excluded.

Eligibility criteria Transplants performed on or after January 1, 2014. Mixed-era studies are eligible only when DAA-era estimates are reported separately; an era-pooled estimate accompanied by a formal test of era interaction is retained as flagged supporting evidence. Center-level cohorts whose accrual began before 2014 are retained as flagged supporting evidence only if HCV-positive recipients were transplanted under a planned post-transplant DAA strategy (rule clarified during full-text assessment). Adult deceased-donor kidney-alone transplants only. No restriction by country. English-language reports.

Information sources MEDLINE (PubMed), Embase (embase.com), Scopus, Web of Science Core Collection, Europe PMC, and Cochrane CENTRAL, searched on October 8, 2026 through the University of Miami Louis Calder Memorial Library; ClinicalTrials.gov, searched the same day. Meeting abstracts indexed in Embase and Web of Science are included. The reference list of the most recent meta-analysis on donor HCV status was hand-searched, citations of included studies were checked, and trial registrations were linked to their publications.

Main outcome(s) Acute rejection (biopsy-proven, or clinically diagnosed and treated) within the first post-transplant year; patient survival, graft survival and delayed graft function.

Additional outcome(s) T-cell-mediated and antibody-mediated rejection; de novo donor-specific antibodies; eGFR; SVR12 and virologic failure; serious DAA-related adverse events and discontinuations; fibrosing cholestatic hepatitis; HCV-associated glomerulonephritis; CMV and BK polyomavirus infection.

Data management Records from all sources are exported and deduplicated by PubMed identifier, normalized title, and DOI; DOI matches are accepted only when titles also agree, because meeting-abstract supplements can share one DOI. Screening decisions and reasons for exclusion are kept in a structured screening log. Data are extracted on a piloted form: design, data source, study period, sample size, donor HCV definition, DAA strategy and timing, follow-up, and every eligible outcome as reported, with its source location. Back-calculated counts and reviewer-derived estimates are flagged. The screening log, extraction data, and analysis code will be provided as supplementary material.

Quality assessment / Risk of bias analysis Comparative non-randomized studies are assessed with ROBINS-I (confounding, selection of participants, classification of exposure, deviations from intended interventions, missing data, measurement of outcomes, selection of the reported result). Single-arm trials are described without a comparative risk-of-bias rating, and decision-analytic models are appraised for structure, perspective, time horizon, and sources of inputs. Certainty of evidence for each outcome is rated with GRADE. All authors take part in screening, extraction, and appraisal; disagreements are resolved by consensus.

Strategy of data synthesis U.S. registry analyses (OPTN, UNOS, SRTR) with overlapping calendar windows are treated as one population. For each comparison, one index dataset is chosen by a prespecified hierarchy: adjusted or propensity-matched estimates over unadjusted ones, then a design restricted to the DAA era, then the largest sample; the remaining registry analyses are summarized narratively. Registry and center-level evidence are synthesized separately, and center-level cohorts are pooled only when they come from distinct centers, with companion reports

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contributing once per outcome. Meta-analysis is performed when at least two non-overlapping studies report compatible effect measures: random-effects model with restricted maximum likelihood (REML) estimation of between-study variance and Hartung-Knapp-Sidik-Jonkman confidence intervals, modified so that they are never narrower than the conventional random-effects interval; 95% prediction intervals when three or more studies contribute; heterogeneity summarized with tau-squared, I-squared, and Cochran's Q. Odds ratios use a 0.5 continuity correction for studies with a single zero cell; studies with no events in either arm are excluded from ratio estimates. Where pooling is not possible, results are synthesized by comparison and outcome following SWiM guidance, without vote counting. Primary (D+/R+) and secondary (D+/R-) estimates are never combined. Analyses use Python 3 (NumPy, SciPy).

Subgroup analysis Results are presented separately by donor HCV definition (antibody-positive versus NAT-positive, viremic donors) and by data source (national registry versus center-level cohorts). Formal subgroup analysis and meta-regression are not performed when fewer than 10 studies contribute to a synthesis.

Sensitivity analysis (1) Exclusion of back-calculated event counts; (2) addition of cohorts with internally inconsistent reporting or external registry comparators; (3) Mantel-Haenszel fixed-effect odds ratios without continuity correction for sparse outcomes; (4) for registry evidence, comparison of the index DAA-era estimate with overlapping or era-pooled analyses, presented as supporting evidence.

Language restriction English-language reports only.

Country(ies) involved United States.

Other relevant information Amended 16 November 2026. The original record covered outcomes in D+/R+ recipients. This version adds acute rejection as a main outcome, the D+/R- stratum, DAA safety outcomes and a separate narrative synthesis of registry analyses; these were specified in protocol version 1.0 (25 October 2026) before screening. Findings are reported in two manuscripts.

Keywords hepatitis C; kidney transplantation; direct-acting antivirals; HCV-positive donors; organ allocation; delayed graft function; graft survival; meta-analysis.

Dissemination plans Publication in a peer-reviewed transplantation journal, with the search strategies, screening log, extraction data, and analysis code provided as supplementary material.

Contributions of each author

Author 1 - Marco Ladino - Conceived and designed the review, screened records, extracted and verified data, assessed risk of bias, interpreted the findings, drafted and critically revised the protocol and manuscript, and approved the final version.
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