Point: Steady Progress and Current Challenges in Clinical Islet Transplantation

The field of β-cell replacement therapies has evolved substantially over the last decades. The lesson learned from recent islet transplantation trials in patients with unstable type 1 diabetes is that primary goals are the achievement of stable, normalized glycemic control in the absence of severe hypoglycemic episodes with improvement of quality of life and the prevention of progressive, chronic diabetes complications. Insulin independence, although desirable, should not be considered the main objective, particularly in light of the sustained positive effects achieved even with a "marginal" functional islet mass via restoration of C-peptide secretion and reduction of insulin requirements. As present limitations of islet transplantation are progressively overcome, the clinical application will greatly expand from the currently limited indication in controlled clinical research trials to more widely available cellular therapies and regenerative medicine solutions that will eventually be offered as standard treatment to the majority of patients with insulin-requiring diabetes.

Vantyghem et al. (1) in the article in this issue of *Diabetes Care* evaluated the predictive value of primary graft function on long-term clinical outcomes of islet transplantation alone (ITA). Surrogate measures have been proposed to monitor or predict β-cell function, but they are not yet fully validated (2–4). In this report, the use of the β-score in the early post-transplant period allowed to quantify primary graft function that, when "optimal," was associated with prolonged graft survival and better metabolic control following islet transplantation (1). In agreement with previous reports using the "Edmonton Protocol" (5–10), this trial resulted in a significant improvement of metabolic control and long-term graft function (~70% having measurable C-peptide at 5 years). Importantly, the investigators also showed prolonged insulin independence in 57% of the patients at 5 years, with the subjects with optimal primary graft function exhibiting the highest success rates (~70% insulin free and 100% of functioning grafts >4 years) (1). Similar long-term insulin independence rates have been reported using novel protocols based on lymphodepleting agents in combination with maintenance immunosuppressive regimens minimizing β-cell toxicity that have shown sustained insulin independence for >3 years (~60%) (9) and even at 5 years (~50%) (11). Collectively, these encouraging results indicate that ITA may lead to long-term insulin independence rates that are comparable to those of pancreas transplant alone (~60% at 5 years) (12) and justify the need for reassessment of islet transplantation as clinical option for β-cell replacement.

The treatment of choice for patients with type 1 diabetes consists of exogenous insulin therapy with tailored diet and physical exercise (13). The importance of achieving tight glycemic control has been well established (13,14). Intensive insulin therapy can delay the onset and reduce the progression of chronic diabetes complications (14), but unfortunately, it is associated with a significantly increased number and severity of hypoglycemic episodes (15), particularly in patients with long-standing diabetes with autonomic neuropathy and hypoglycemia unawareness. Indeed, the risk of experiencing severe hypoglycemia is significantly higher under intensive insulin compared with conventional regimen (relative risk to experience ≥1 episode = 3.28) with the same individual being at higher risk for multiple episodes (22% of subjects with ≥5 episodes vs. 4%, respectively) (15).

Tight glycemic control throughout the day still remains difficult to attain using conventional insulin therapy, and the risk for long-term diabetes complications has not completely been eliminated. The use of novel insulin formulations, infusion pumps, and glucose monitoring systems has substantially improved diabetes care in recent years, contributing to a significant amelioration of quality of life and to the reduction of chronic complications and of side effects associated with conventional insulin therapy in patients with type 1 diabetes. Patients with erratic daily glycemic excursions, progressive complications, and hypoglycemia unawareness are highly susceptible to multiple severe hypoglycemic events, at times life threatening. Attaining stable metabolic control in this brittle patient population is of utmost importance also in view of the significant mortality rate in such subjects, with apparently normal renal function, while waiting for a pancreas transplant (~8% at 4 years for pancreas transplant alone) (16). Thus, medical therapy cannot attain the desirable therapeutic efficacy in such a selected population of subjects with type 1 diabetes.

Restoration of β-cell function is a highly desirable goal for patients with unstable type 1 diabetes. β-Cells are highly specialized glucose sensors able to secrete insulin in "real time" to finely regulate glucose homeostasis. Indeed, physiological metabolic control is attained after transplantation of pancreatic islets either as isolated cell clusters or as vascularized pancreas organ. Pancreas transplantation, despite improving glucose control, chronic complications, and quality of life and having long graft function and survival, still has a relatively high perioperative mortality and morbidity and specific limitations (12,16). Alternatively, allogeneic pancreatic islet transplantation can be an attractive, minimally invasive, and safer option for this group of patients with unstable type 1 diabetes, by inducing restoration of physiological glucose sensing and insulin delivery. Islet transplantation occurs by gravity infusion of the heparinized islet product from a closed-bag system via microembolization into the hepatic portal venous system, with the islets entrapping in its peripheral branches, at presinusoid level because of the size restriction followed by their engraftment and neovascularization from the hepatic vasculature, with instant function and survival. This interventional radiology procedure is performed by percutaneous transhepatic catheterization of the main portal vein branches under fluoroscopic and ultrasound guidance with local anesthesia and conscious sedation and with close monitoring of portal pressure; it

lasts ~1 h, and allows patient discharge from hospital within 48 h, once clinically stable and without complications (6,17).

Clinical trials in the 1980s and 1990s were performed in islet-after-kidney (IAK) and simultaneous islet-kidney (SIK) transplantation recipients using corticosteroids and high-dose calcineurin inhibitors (CNI) or purine antagonists (8,17). Such protocols were mainly focused on preserving the kidney graft function and were associated with diabetogenic effects. Clinical outcomes were overall poor, with many cases of primary graft nonfunction, low rates of insulin independence at 12 months (~10%), and limited graft survival. Steady progress in islet cell processing, novel immunosuppressive strategies, and improved patient management have led to increasing success rates of islet transplantation in the last 30 years (17). In the late 1990s, the introduction of a steroid-sparing immunosuppressive protocol (the Edmonton Protocol), consisting of an induction with anti-CD25 antibody and maintenance with low-dose CNI and high-dose mammalian target of rapamycin (mTOR) inhibitors, resulted in sustained (>12 months) insulin independence in recipients of sequential ITA (18). This approach has proven reproducible (even with some modifications) and also applicable for SIK and IAK transplants (1,6–10,19–21). Collectively, ~650 islet transplants in 325 recipients have been reported since 1999 by the Collaborative Islet Transplant Registry (CITR) (22). Common achievements of these studies are the improved glucose control and the reduction of insulin requirements with normalization of A1C as well as absence of severe hypoglycemia, even in patients with partial graft function requiring exogenous insulin. Islet transplantation is also associated with a significant improvement of quality of life that parallels the positive metabolic effects together with prevention of severe hypoglycemia and restoration of hypoglycemia awareness (8,23). Insulin independence is usually obtained when adequate islet numbers, generally from two or more donor pancreata, are transplanted (i.e., ~10,000–14,000 islet equivalents per kilogram of recipient's body weight). The rate of insulin independence at 1 year is ~70% (and even higher in the most experienced centers), with virtually all patients maintaining a functioning graft (positive C-peptide), while under adequate immunosuppression levels (1,6–10,19–21). Similar results have been replicated in a small series of single-donor ITA receiving lower (marginal) islet masses (<10,000 islet equivalents/kg body wt) while using specific lymphodepleting and anti-inflammatory treatments at induction and conversion to CNI-free maintenance therapy, which included the purine synthesis inhibitor mycophenolate acid (19,20). As a result of fewer systemic and β-cell negative side effects, current islet transplantation studies increasingly include this drug in their maintenance regimen.

Following islet transplantation, physiological β-cell response to secretagogues is restored to a certain extent, including improved first-phase insulin secretion upon intravenous stimulation and increased overall C-peptide levels following oral challenge (3). As mentioned, the neurohormonal and symptomatic responses to hypoglycemia (e.g., glucagon and epinephrine) are altered in patients with type 1 diabetes. Although an initial report suggested that intrahepatic islet transplantation did not restore hypoglycemia hormonal counterregulation and symptom recognition (24), more recent studies have shown normalization of the glycemic thresholds for activation of counterregulatory hormone and symptom responses to hypoglycemia, though the magnitude of such responses remained impaired (25,26). Glucagon secretion was also normally suppressed by hyperinsulinemia in these patients (25). It is conceivable that all the above-mentioned phenomena contribute to the observed posttransplant improvement of metabolic control and to the restoration of hypoglycemia awareness after islet transplantation (27).

Overall, sustained graft survival is achieved in the majority of islet transplant recipients, with >70% of them retaining C-peptide levels, normalized A1C, nearly-absent severe hypoglycemia, and significantly reduced insulin requirements (~50% from pretransplant dose) at 5 years under the Edmonton Protocol (1,5). Notably, both the improvement in quality of life and the restoration of hypoglycemia awareness persist long term (23,27). However, the rate of insulin independence may progressively decline after transplantation, reaching ~10% at 5 years despite maintaining islet graft function (5).

Recent trials have generally relied on the use of multiple donor islets to attain insulin independence. The number and quality of islets obtained from a donor pancreas remain quite variable, and <50% of glands processed with the intent to transplant yield adequate islet numbers (28). The success rate of clinical islet isolations improves (≥60%) when organ recovery is performed by a local team involved with the transplant program (28). In an attempt to minimize competition with vascularized pancreas transplantation, islet transplant programs are generally offered pancreata that have previously been offered and turned down for whole organ transplant as well as glands obtained from older and obese donors that are considered less than optimal for surgical implant (29,30). Notably, this pancreas allocation scheme does not account for potential limitations in islet potency and longevity of such organs that could negatively affect long-term outcomes of islet transplantation (30). Notwithstanding the steady increase in organ donation, pancreas recovery rates remain unsatisfactory and much lower than those for other solid organs; e.g., >8,000 multiorgan donors were available through the United Network for Organ Sharing (UNOS) in 2006 (of these, ~2,000 pancreata were recovered and only ~1,440 used for transplant [http://optn.transplant.hrsa.gov/data/annualReport.asp]). In the period 2000–2004, the poor utilization of potential islet donor pancreata was recorded in the U.S. (30). In particular, from the overall pool of pancreata available, 22.3% ("optimal" glands) were used for whole organ transplant; from the remaining pool, 48.5% were considered "suitable islet donors" (11% "optimal" and 89% "standard"), but only 2.1% of them were actually used for islet transplantation (30). Therefore, a wide margin for improvements in organ allocation and utilization exists that include the use of "optimal" donors and a fair allocation between islets and whole pancreas transplant programs. In addition, changes in the current cost structure of pancreas procurement, which differentiate the payment based on the transplant suitability of the islet tissue products (determined after completion of the manufacturing process) rather than based on the acceptance of whole organ transplantation, will help reduce the overall economic burden of islet transplantation (31). In light of the promising results obtained with single-donor marginal islet mass infusions, when adequate donor-organ selection and targeted recipient immune interventions are implemented (20), the number of islet transplants could be substantially improved with the cur-

rently available donor pool and potentially satisfy the demand for the relatively contained targeted population that would greatly benefit from islet transplantation.

Type 1 diabetes–related micro- and macrovasculopathy are the main causes of chronic end-stage renal disease (ESRD) requiring dialysis, blindness, and limb amputations and deformities, with associated disabilities, comorbidities, and death (32). Their impact is ~10% of the total health care expense in western countries, with >100 billions USD spent every year in the U.S. alone and >200 billions USD worldwide (32). Stabilization or reduction of the progression of retinopathy and neuropathy has been reported after islet transplantation (33). In IAK recipients, improvement of cardiovascular and endothelial function, amelioration of the atherothrombotic profile, and reduction of cardiovascular events with better patient survival rates have been reported when compared with those of recipients of renal transplant alone (90% at 7 years vs. 50%, respectively) (34,35). In addition, the longevity of the concomitant renal allograft appears to be significantly prolonged following the achievement of a better metabolic control associated with islet transplantation (36), although additional factors (i.e., better organ quality of the kidney grafts transplanted in recent years) also significantly contribute to such improvements (37).

The restoration of C-peptide production following islet transplantation may also contribute to some of the improvement of diabetes complications observed posttransplant. Indeed, putative mechanisms accounting for the possible beneficial effects of C-peptide include reduction of nerve dysfunction and increase in myocardial and renal blood flow as well as in peripheral vascular districts and tissues (i.e., skeletal muscle), as suggested from studies in subjects with long-standing type 1 diabetes receiving C-peptide infusion. These events, in turn, may contribute to improve cardiovascular and renal function, thus possibly reducing the progression of diabetic angiopathy and related complications (38).

A current hurdle to more widespread use of islet transplantation includes the need for chronic immunosuppression and its associated untoward side effects. The rate and type of immunosuppression-related complications observed in islet transplant recipients under the Edmonton Protocol are not different from those reported in solid organ transplants (mainly opportunistic infections and drug-related toxicity) and were expected based on the pharmacological profile of the current immunosuppressive agents (39). From data of more than 300 islet recipients during ~10 years of monitoring, procedure- and infusion-related serious adverse events (e.g., abdominal bleeding) were extremely rare (<6% in the 1st year), with only 2 of 111 cases that were not fully resolved. Novel radiological techniques, intracatheter tract coagulants, and recipient peritransplant antithrombotic prophylaxis have significantly reduced their occurrence (22). Regarding immunosuppression therapies, despite common infections (e.g., skin and urinary tract) and direct drug effect (e.g., myelodepression and gastrointestinal disturbs), only 96 serious adverse events possibly or definitely related to immunosuppression have been reported, with 82 resolved with no sequelae, 17 with sequelae, 6 with persistent condition, and only one death (viral meningitis). Six other deaths were reported not directly related to the islet transplant or its medications. Neoplasms occurred in 14 islet recipients, but just 4 were possibly related to immunosuppression (squamous and basal cell skin cancers, papillary thyroid carcinoma, and ovarian cysts) (22).

The negative effects of CNI and mTOR inhibitors on renal function have been widely recognized. The potential negative impact of these drugs on the progression of diabetic nephropathy in nonuremic subjects needs to be fully evaluated. In the context of islet transplantation, decline of renal function has been reported in some studies (7,40,41), whereas more recent reports have shown stable renal function and lack of worsening of diabetic nephropathy in long-term follow-up (8,42,43) or an initial decline of renal function that stabilizes without further worsening in the long term (9). Notably, strict selection of islet transplant candidates without previous renal dysfunction (i.e., microalbuminuria and low estimated glomerular filtration rates) and timely implementation of nephroprotective and antihypertensive therapies (i.e., inhibitors and/or angiotensin receptor blockers) may have accounted for the different clinical outcomes (43). Immunosuppressive protocols void of nephrotoxicity are highly desirable; indeed, ongoing clinical trials are showing promising results in patients undergoing conversion of either CNI or mTOR inhibitors to mycophenolate acid maintenance, with preservation of both renal and islet function (8,9,42,43).

Several factors may contribute to the progressive islet graft dysfunction and failure observed over time under the Edmonton Protocol in addition to the recipient immune response. After an initial islet mass loss following the intraportal infusion, as a result of an instant blood-mediated inflammatory reaction and the deleterious graft hypoxia until engraftment and neovascularization, the intrahepatic islets are chronically exposed and damaged by the high levels of lipids, glucose, and immunosuppressive drugs and by the local inflammatory milieu (44). Direct β-cell toxicity and functional impairment consequent to exposure to CNI have been widely recognized. Experimental evidence supports the antiproliferative effects of mTOR inhibitors and CNI that may result in impaired islet engraftment (i.e., altered neovascularization and tissue remodeling) and reduced β-cell self-renewal (45). Additionally, increased lipid levels are commonly associated with immunosuppression (mainly mTOR inhibitors) and may result in β-cell lipotoxicity contributing to loss of functional islet mass over time (39).

Reproducible, single-donor islet transplantation is indeed a highly desirable goal (20). This is particularly important considering the risk of recipient sensitization to donor alloantigens that is an expected finding following solid organ transplantation (46–48). Islets from HLA-mismatched, ABO compatible donors are used (with the exception of SIK recipients) in an attempt to minimize the risk of recurrent autoimmunity. Adequate immunosuppression in islet transplant recipients appears to prevent the development of alloantibodies and to neutralize their potentially negative impact on graft survival, even in the presence of low degree of panel-reactive alloantibodies pretransplant (47,48). Nevertheless, posttransplant development of donor-specific and non–donor-specific alloantibodies may be detected after drug dose reduction (i.e., for medical reasons), while it invariably occurs when immunosuppression is withdrawn (i.e., at islet graft failure) (47,48). Although the significance of this phenomenon and its potential impact on long-term islet graft function or subsequent allografts have not been established, there is a concern for potentially limiting future therapeutic options (i.e., subsequent islet, pancreas, or renal transplantation for ESRD) (47). Se-

lection of subjects with slow progression of diabetic nephropathy who will unlikely develop ESRD as well as attempting more stringent donor-recipient HLA matching may contribute to reduce the risk of allosensitization in islet transplant recipients (43). It is conceivable that development of tailored immunosuppression weaning protocols after islet graft loss may be of assistance in reducing the risk of allosensitization.

Persistence or recurrence of autoimmunity has been described in islet transplant recipients and has been associated with lower rates of insulin independence and shorter graft survival (49). Selective destruction of β-cells within islet allografts by histopathology analysis, measurable changes of autoantibody levels (i.e., anti-GAD65 and anti-insulinoma–associated protein 2), and/or detection of autoreactive cytotoxic and memory T-cells to β-cell–specific epitopes have been described (50). A close monitoring of immune activation and β-cell function markers during the follow-up may be of assistance in detecting early islet graft distress and possibly guide timely therapeutic interventions (i.e., metabolic support or immunotherapy) to preserve islet mass long term (10). This has been shown, for instance, with the use of exenatide to preserve islet function after detection of graft dysfunction (51).

Overcoming the current challenges of islet transplantation requires a sequential, integrated approach aimed at enhancing the yield and quality of islet cells from a single-donor pancreas, as well as improving the survival and function of the transplanted islets using safer and more effective cytoprotective and immunomodulatory approaches (17,44). Increased islet yields have been obtained using more efficient pancreas recovery and preservation as well as islet isolation and purification strategies (17,44). Peritransplant interventions aimed at reducing inflammation and conferring cytoprotection to islet cells (i.e., reducing β-cell death) have shown promise in enhancing engraftment and improving long-term outcomes. In the clinical setting, tumor necrosis factor-α blockade enhances islet engraftment and survival (6,20,22). Similarly, glucagon-like peptide synthetic analogs (i.e., exenatide) have been introduced to enhance β-cell function and possibly survival after transplantation, with encouraging results in patients with suboptimal islet masses both at the time of the islet transplant and after development of graft dysfunction (51,52). Translational experimental models have provided evidence that cytoprotective agents (e.g., lisofylline, caspase and Jun NH_2-terminal kinase inhibitors) not only reduce islet cell loss but also may favor the efficacy of tolerogenic protocols by modulating local inflammation and immune responses (44,53,54). Although current immunosuppressive agents prevent rejection via nonspecific antiproliferative effects, this has a costly trade-off in terms of untoward side effects, including organ and β-cell toxicity. Compared with standard protocols, powerful lymphodepleting induction agents (i.e., thymoglobulin, anti-CD52, anti-CD3, and anti-CD20 antibodies) are showing promising results in terms of safety profile and improvement in islet graft function (19,20,55,56). Immunomodulatory agents, selectively targeting costimulatory signals of T-cell activation and/or adhesion molecules, are becoming available for clinical applications and may have relatively lower side effects and islet or organ toxicity (i.e., lack of diabetogenicity and nephrotoxicity) as well as possibly promote immune tolerance in specifically designed protocols (57). Many of the above-mentioned agents are currently under evaluation in the National Institutes of Heath (NIH)–sponsored Clinical Islet Transplantation (CIT) Consortium (www.citisletstudy.org) carrying on phase II-III randomized ITA and IAK trials both in North America and Europe. Primary objectives of the CIT trials are the confirmation and improvement of the success rate of islet transplantation and the standardization of the isolation and transplant procedures, toward approval of islet transplantation as standard of care, reimbursable by health insurance.

Attempting to induce immune tolerance to the transplanted tissues is an appealing perspective for islet transplantation (57). There is an increasing body of experimental data supporting the value of adjuvant cellular transplants (i.e., bone marrow–derived cells, mesenchymal cells, regulatory T-cells, and tolerogenic dendritic cells) in order to modulate recipient immune response and to increase the acceptance and long-term survival of islet allografts (58). Notably, recent clinical trials have shown achievement of stable mixed hematopoietic chimerism and/or operational tolerance in kidney allograft recipients using nonmyeloablative conditioning and donor hematopoietic stem cell infusion (59).

Emerging multidisciplinary approaches are showing great promise for β-cell replacement therapies in the years to come. The rapidly evolving fields of biomedical engineering and regenerative medicine will be of assistance in developing efficient ways to enhance islet engraftment and survival. Biocompatible devices and three-dimensional, functionalized polymers, in alternative implantation sites, may also provide an optimal microenvironment for cell implants and local delivery of immunomodulatory agents (60). Cotransplantation of islets with adjuvant cells (i.e., mesenchimal and endothelial cells) may contribute to local tissue remodeling, with revascularization and immune protection. Efficient encapsulation techniques that confer immune isolation while providing adequate exchange of nutrients to islet cells may allow long-term survival after transplantation using short-term or lower levels of immunosuppression (systemically or locally) (61). Availability of an unlimited source of transplantable insulin-producing cells is highly desirable to overcome the current inadequate supply of human pancreatic islet cells for transplantation. Experimental data support the great potential of adult and embryonic stem cells to generate islet cells in vitro, and current efforts are focused toward improving efficiency, potency, and safety of these cells (62). Similarly, under appropriate conditions, expansion and/or differentiation of putative pancreatic islet cell precursors (ex vivo or in vivo) as well as the use of cells that share common embryonic origin (liver cells) to β-cells show great applicative potential. Xenogeneic islets (i.e., porcine) remain a viable therapeutic option for the near future, particularly if combined with immune isolation strategies and safe immunotherapy (17).

The lesson learned from recent clinical islet transplantation trials in patients with unstable type 1 diabetes is that primary goals are as follows: *1*) the achievement of stable, normalized glycemic control, in *2*) the absence of severe hypoglycemic episodes with improvement of quality of life, and *3*) the prevention of progressive, chronic diabetes complications. Insulin independence, although desirable, at present should not be considered the main objective of islet transplantation, particularly in light of the sustained positive effects achieved with a "marginal" functional islet mass via the restoration of C-peptide secretion and

the significant reduction of insulin requirements.

The safety of the patient always remains the priority, and any attempt to improve metabolic control via islet transplantation should be indeed achieved using strategies that minimize any potential complications. In particular, overall risks and benefits should be carefully addressed for each islet transplant candidate. Strict inclusion criteria, close clinical monitoring, and prompt management of emerging complications can maximize the benefits of the transplants while minimizing side effects. Additionally, recent data have shown the relevance of the center's experience in islet cell processing (7) as well as the feasibility and containing the cost of islet transplantation consortia, with centralized cell processing facilities that supply remote transplant centers (44).

The field of β-cell replacement therapies has evolved substantially over the last decades, and notwithstanding the limited patient population size of most studies in islet transplantation, the steady progress in this field (regarding metabolic control, diabetes complications, and quality of life) justifies the renewed optimism for the potential of cellular therapies in diabetes (17). As the current limitations of islet transplantation are progressively overcome, the indication for clinical applicability of these strategies will greatly expand from the current very limited eligibility criteria in controlled clinical research trials to more widely available cellular therapies and regenerative medicine solutions that will eventually be offered as treatment to the majority of patients with insulin-requiring diabetes.

DAVIDE MINEO, MD, PHD[1,2]
ANTONELLO PILEGGI, MD, PHD[1,3]
RODOLFO ALEJANDRO, MD[1,4]
CAMILLO RICORDI, MD[1,3,4,5,6,7]

From the [1]Diabetes Research Institute, University of Miami Miller School of Medicine, Miami, Florida; the [2]Department of Internal Medicine and University Policlinic, Tor Vergata University, Rome, Italy; the [3]DeWitt-Daughtry Family Department of Surgery, University of Miami Miller School of Medicine, Miami, Florida; the [4]Department of Medicine, Division of Endocrinology, University of Miami Miller School of Medicine, Miami, Florida; the [5]Department of Biomedical Engineering, University of Miami Miller School of Medicine, Miami, Florida; the [6]Wake Forest Institute for Regenerative Medicine, Winston-Salem, North Carolina; and [7]Karolinska Institutet, Stockholm, Sweden.

Corresponding author: Camillo Ricordi, ricordi@miami.edu.

D.M. and A.P. equally contributed to this work.
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APPENDIX — For further information including transplant data and annual reports, please refer to the U.S. Department of Health and Human Services (www.hhs.gov), Organ Procurement and Transplantation Network (www.optn.org), Scientific Registry of Transplant Recipients (www.ustransplant.org), Health Resources and Services Administration (www.hrsa.gov), CITR (www.citregistry.org), and CIT Consortium (www. citisletstudy.org).

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