Proposal for new Banff Working Group: Transplantation HIV+ to HIV+

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Disclosures

Current: Shire ViroPharma, Inc.- Local pathologist in multicenter study

Previous: Alexion – Local pathologist in multicenter study

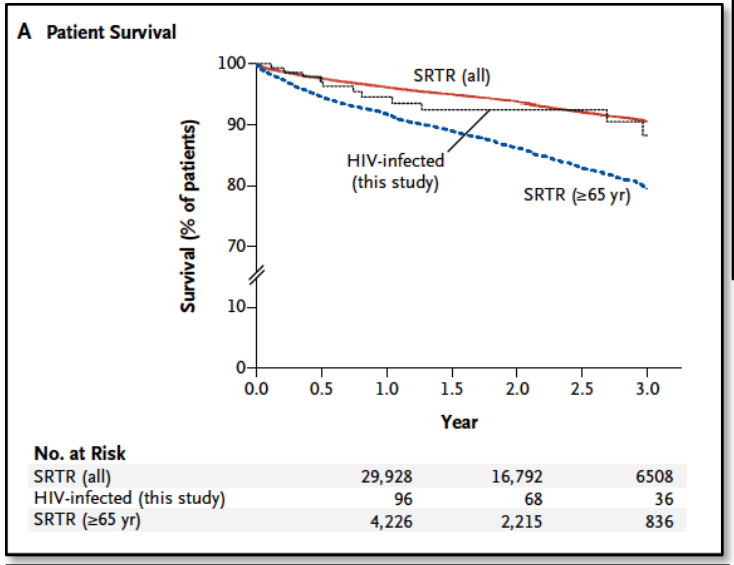
No relevance to this presentation

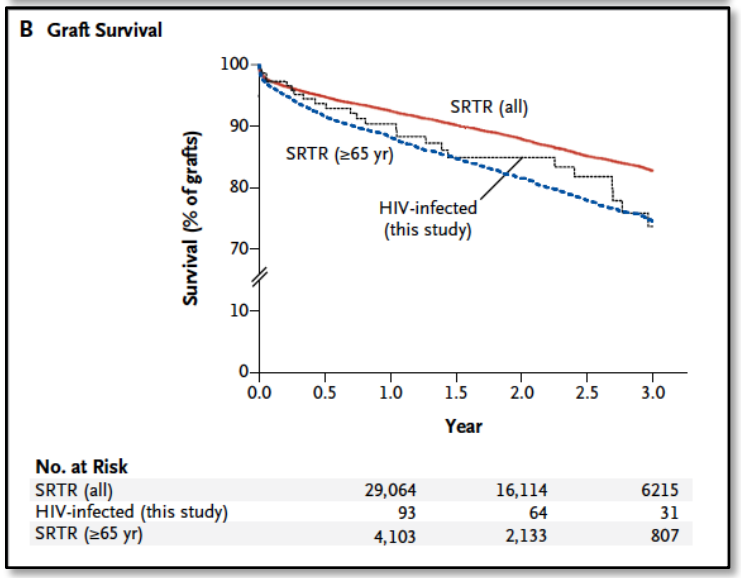
CKD/ESRD in HIV

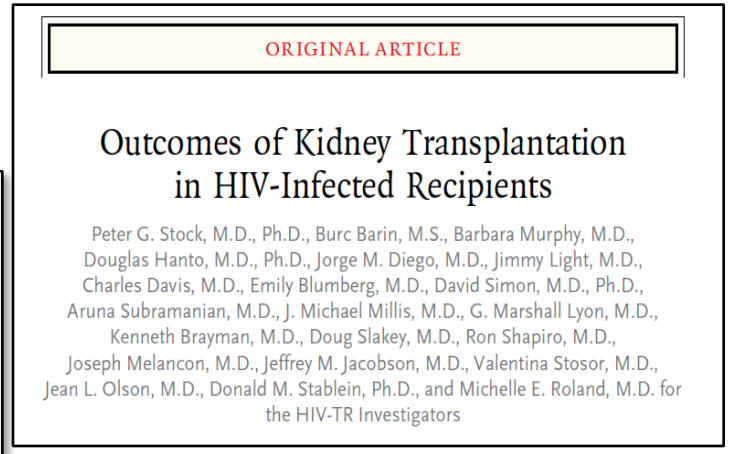
- 10-30% prevalence of chronic kidney disease
  - HIV-associated nephropathy, IC GN
  - Antiretroviral toxicity
  - Hypertension, diabetes, cardiovascular
- More than 10,000 HIV+ individuals on dialysis
- 14 fold increase in prevalent cases between 1999-2010
- Shorter survival of HIV+ individuals with ESRD than HIV- subjects
- **Transplantation has become available for HIV+ subjects in US and in other countries, with good outcomes**

Lucas G/Kalayjian R. CID 2014; SRTR data
Ahuja et al. JASN 2002
Bickel et al. HIV Med 2013

Transplantation
HIV- to HIV+







ORIGINAL ARTICLE

Outcomes of Kidney Transplantation in HIV-Infected Recipients

Peter G. Stock, M.D., Ph.D., Burc Barin, M.S., Barbara Murphy, M.D., Douglas Hanto, M.D., Ph.D., Jorge M. Diego, M.D., Jimmy Light, M.D., Charles Davis, M.D., Emily Blumberg, M.D., David Simon, M.D., Ph.D., Aruna Subramanian, M.D., J. Michael Millis, M.D., G. Marshall Lyon, M.D., Kenneth Brayman, M.D., Doug Slakey, M.D., Ron Shapiro, M.D., Joseph Melancon, M.D., Jeffrey M. Jacobson, M.D., Valentina Stosor, M.D., Jean L. Olson, M.D., Donald M. Stablein, Ph.D., and Michelle E. Roland, M.D. for the HIV-TR Investigators

Stock PG et al
NEJM 2010;363:2004-2014.

N = 150

Patient survival
1 yr: 95%; 3 yr: 91%

Graft survival
1 yr: 90%; 3 yr: 77%

Kumar MS[1], et al: **Safety and success of kidney transplantation and concomitant immunosuppression in HIV-positive patients (n=40, US).**
Kidney Int. 2005 Apr;67(4):1622-9
Patient: 1yr: 85%; 2yr: 82%
Graft: 1yr: 75%; 2yr: 71%

Qiu J[1], et al: **HIV-positive renal recipients can achieve survival rates similar to those of HIV-negative patients (n=38, US)**
Transplantation. 2006 Jun 27;81(12):1658-61.
Patient: 5yr: 91%
Graft: 5yr: 76%

Touzot M[1], et al: **Renal transplantation in HIV-infected patients: the Paris experience (n= 27).**
Am J Transplant. 2010 Oct;10(10):2263-9.
Patient: 1yr: 100%; 2yr: 98%
Graft: 1yr: 98%; 2yr: 96%

Gathogo EN[1], et al: **Kidney transplantation in HIV-positive adults: the UK experience (n=35).**
Int J STD AIDS. 2014 Jan;25(1):57-66.
Patient: 1yr: 91%; 3yr: 91%
Graft: 1yr: 91%; 3yr: 84%

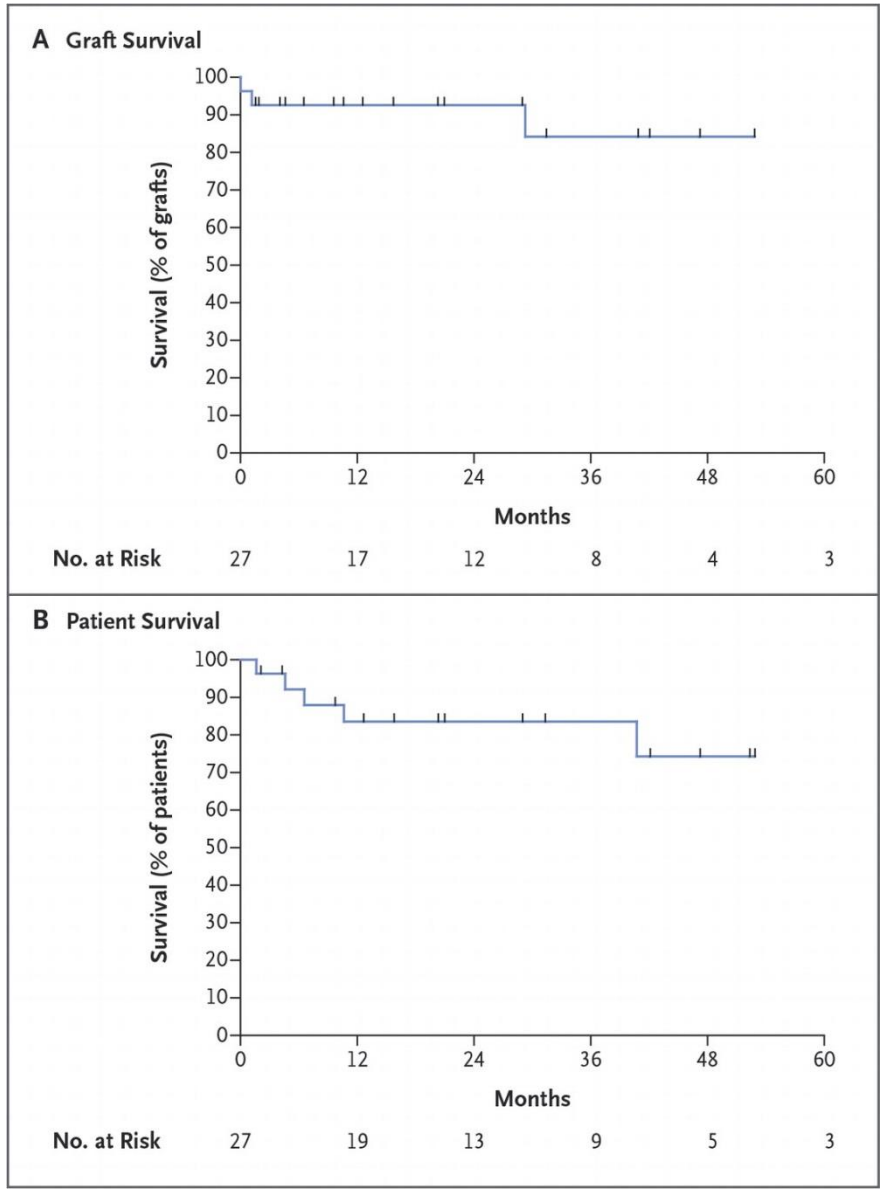
South Africa Experience

The NEW ENGLAND JOURNAL of MEDICINE

Muller et al, NEJM 2015: 372:613-620
HIV+ to HIV+ kidney transplantation: Results at 3 and 5 years

Graft and patient survival among 27 HIV+ patients who received Kidney transplant from HIV+ donor

Graft survival:
1 year 93%
3 years 84%
5 years 84%



National Organ Transplant Act, 1984/88 42 CFR 121.6 Sect 372(b):

"requires the* Organ Procurement and Transplant Network (*OPTN) to adopt and use standards for preventing the acquisition of organs from individuals known to be infected with HIV."

HOPE (HIV Organ Policy Equity HOPE ACT)

Passed by US Congress in November 2013, DHHS revoked ban on HIV+ donors in June 2015

Legalized transplant from HIV+ donor to HIV+ recipients

Only in the setting of an approved research protocol

- **Directs the Secretary to revise current regulations (specifically, 42 CFR 121.6)**
- **Directs Secretary to publish research criteria relating to HIV+ to HIV+ transplant**
- **Requires the OPTN to revise standards for the acquisition and transportation of donated HIV+ organs**

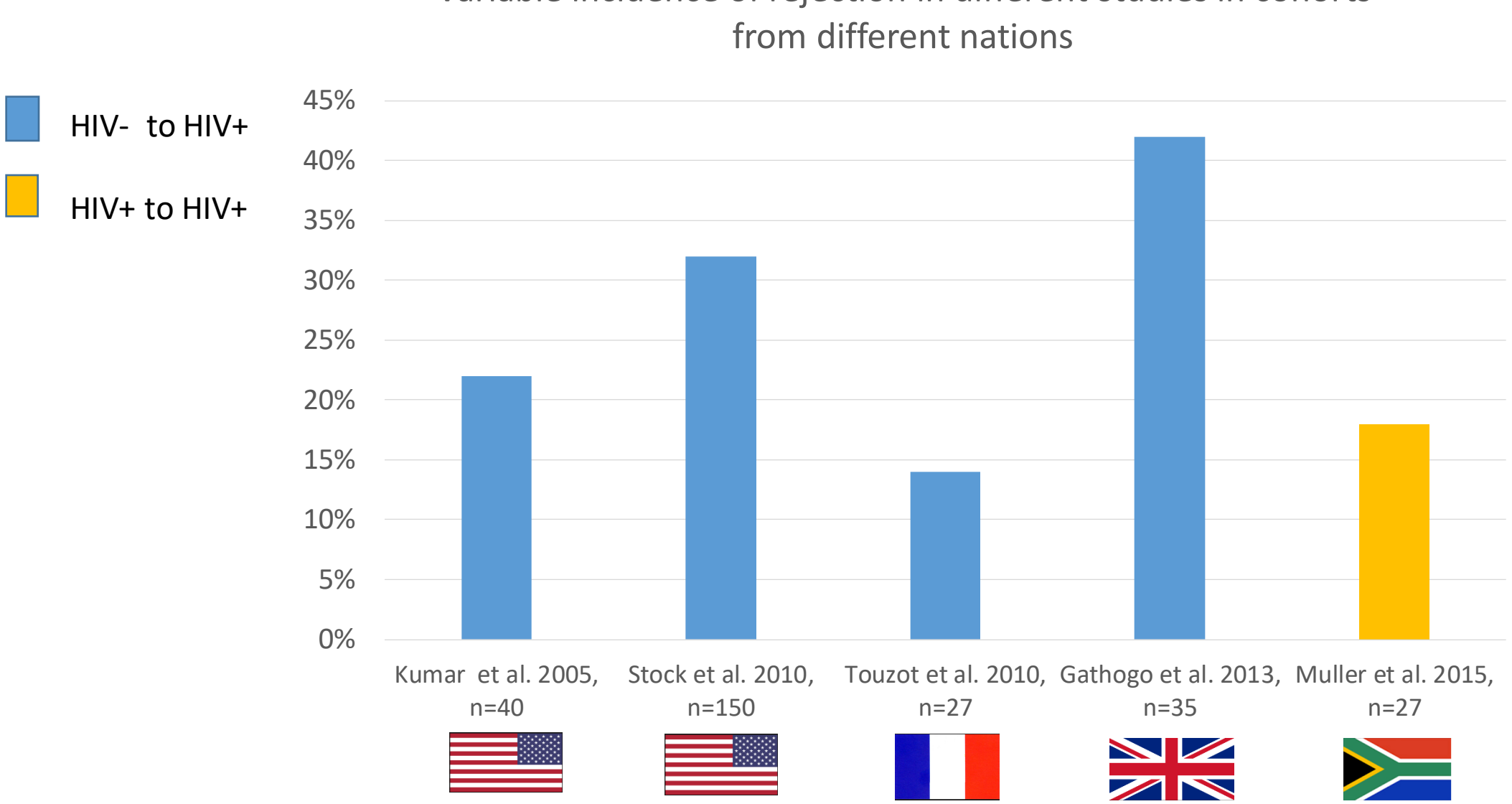
- **The HOPE Act states that "not later than 4 years after the date of enactment and annually thereafter, the Secretary shall review the results of scientific research in conjunction with the OPTN to determine whether the results warrant revision of the standards of quality."**

Estimating the Potential Pool of HIV-Infected Deceased Organ Donors in The United States

- **500-600 donors per year**

B.J. Boyarsky et al *American Journal of Transplantation 2011, 11: 1209-1217*

Increased incidence of rejection in HIV+ recipients



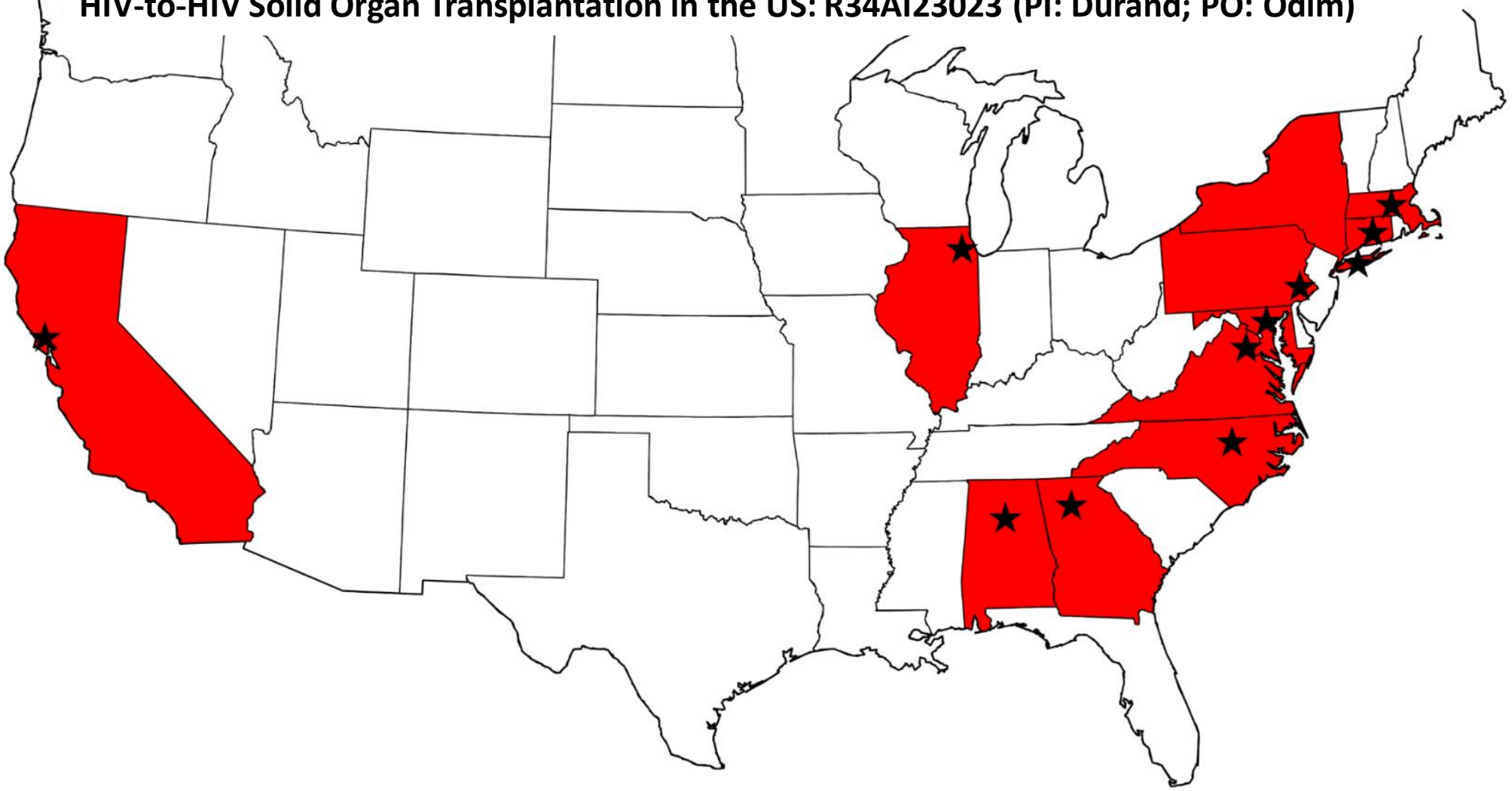
Key differences: US and S Africa

	South Africa	US
Population	53 million	316 million
Persons living with HIV	5.6 million	1.1 million
HIV+ prevalence	17.8%	0.6%
Predominant subtype	C	B
Annual HIV+ deaths	310,000	17,000
Transmitted drug resistance	< 5%	10-18%
Transplant wait list	4300	123,992
Transplant per year	229	16,896

Durand/Segev, AJT 2015; 15:2023-30

Considering these key differences the only way to learn if the use of HIVDD is feasible, safe, and effective in the US is with a carefully designed clinical trial. Planning grant:

HIV-to-HIV Solid Organ Transplantation in the US: R34AI23023 (PI: Durand; PO: Odim)



Columbia/New York-Presbyterian
Duke University Hospital
Emory University Hospital
Georgetown University Medical Center

Hahnemann University Hospital
Hospital of the University of Pennsylvania
The Johns Hopkins Hospital
Massachusetts General Hospital

Mount Sinai Medical Center
Northwestern Memorial Hospital
Rush University Medical Center
University of Alabama at Birmingham

University of California, San Francisco
University of Maryland Medical System
Weill Cornell Medical Center
Yale New Haven Hospital

Non inferiority of kidney transplants from HIV+ deceased donors compared to kidney transplants from an HIV-negative donors

Primary Endpoints

Composite event HIV related complications

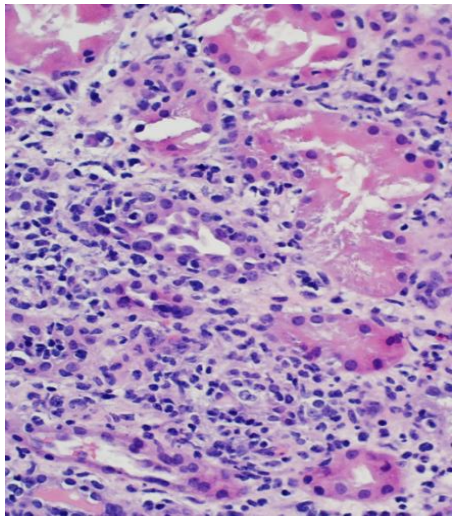
- HIV breakthrough or virologic failure
- AIDS defining illness
- Allograft rejection

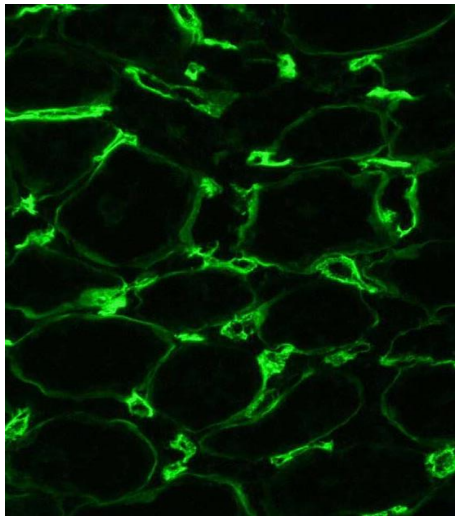
Secondary outcomes

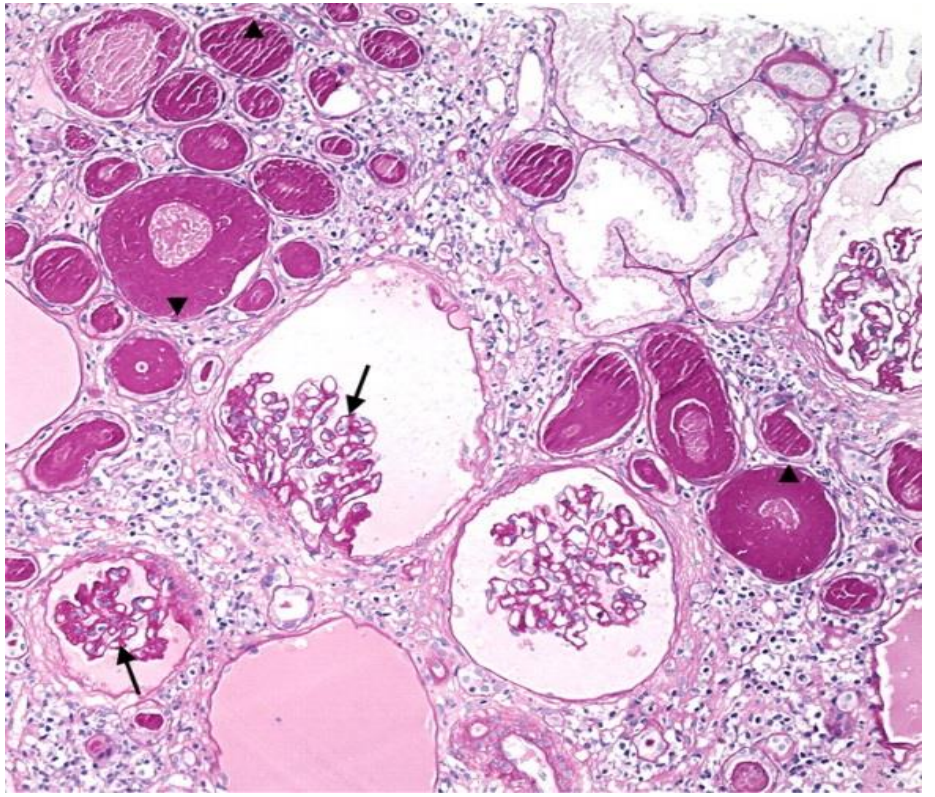
- Patient survival
- Graft survival
- Graft function
- Donor specific antibodies at 1 year
- HIV viral load
- CD4 count
- ART resistance
- X4 virus
- Non AIDS infections
- Surgical complications
- HIV-associated renal disease
- Viral malignancies

Pathology

- Allograft rejection
- Drug toxicity and interstitial nephritis (anti-retroviral, anti rejection, others)
- HIV associated Nephropathy (HIVAN)
- Immune Complex mediated glomerulopathies
- FSGS without HIVAN features
- Superinfection
- Infection involving the graft
- Diabetes
- Thrombotic microangiopathy
- Paraprotein-related disease
- ……







Pathologic Features

Banff score summary
Banff scores (0,1,2,3)
g
i
t
v
ah
cg
ci (% cortex)
ct (% cortex)
cv
mm
cv
ti
ptc (0,1,2,3), focal/diffuse
C4d (0,1,2,3)

LIGHT MICROSCOPY (not Banff)
Glomeruli total N
Glom Global sclerosis N
Glom Segm sclerosis N
Glom Ischemic changes
Glom fibrin thrombi
Glom fragmented RBC
Glom hypercellularity
Glom necrotizing lesion
Glom crescents
Glom collapsing changes
Glom mesangiolysis
Tubules
Tubular injury
Isometric vacuolization
Microcystic changes
Viral Cytopatic changes
BK, CMV, Adeno (specify)

Interstitium
Edema
Inflammation cell type
Lymphocytes
Plasmacells
Neutrophils
Eosinophils (> 5/20X HPF)
Histiocytes

IF
IgG (0,1+,2+,3+,4+)
IgA
IgM
C3
C1q
Kappa
Lambda
Albumin
Fibrinogen
PLA2R
IgG 1
IgG 2
IgG 3
IgG 4
C4d
C3d

IMMUNOSTAINS
SV40
EB in situ (EBER)
CMV
Adenovirus
Herpes V
Kappa V
Lambda
IgG4
C4d
(CD3, CD20, CD68, CD34……)

ELECTRON MICROSCOPY
Glomeruli (n examined)
GBM folded/wrinkled
GBM thickness: normal, increased, lo (nm)
GBM widened subendothelial space
GBM cytoplasmic interposition / double contours
Endothelial cells enlarged
Endothelial loss of fenestration
Intracapillary inflammatory cells
Podocyte enlargement
Podocyte microvillous transformation
Podocyte foot process effacement present : %
Mesangial expansion
Deposits (present/absent)
Deposits Localization: subepithelial
intramembranou
subendothelial
mesangial
Deposit substructure
Tubuloreticular inclusions in endothel cells
Peritubular capillaries basal lamina N layers
Deposits in tubular basement membrane
Tubular cell crystalline inclusions
Tubular mitochondrial abnormalities

FINAL DIAGNOSIS:
Adequacy (Y/N)
No rejection/Unremarkable
Borderline for rejection
Rejection
Cell mediated IA
Cell mediated IB
Cell mediated IIA
Cell mediated IIB
Antibody mediated active
Antibody mediated chronic
Concerning for AMR check DSA
Mixed rejection
Isolated V lesion
Thrombotic microangiopathy
Tubular injury
BK nephropathy
Pyelonephritis/Infection
HIVAN
FSGS
HIVICK
Glomerulopathies (other)
……

Pathologic Features

Banff score summary
Banff scores (0,1,2,3)
g
i
t
v
ah
cg
ci (% cortex)
ct (% cortex)
cv
mm
cv
ti
ptc (0,1,2,3), focal/diffuse
C4d (0,1,2,3)

LIGHT MICROSCOPY (not Banff)
Glomeruli total N
Glom Global sclerosis N
Glom Segm sclerosis N
Glom Ischemic changes
Glom fibrin thrombi
Glom fragmented RBC
Glom hypercellularity
Interstitium
Edema
Inflammation cell type
Lymphocytes
Plasmacells
Neutrophils
Eosinophils (> 5/20X HPF)
Histiocytes

IF
IgG 2
IgG 3
IgG 4
C4d
C3d

IMMUNOSTAINS

ELECTRON MICROSCOPY
Glomeruli (n examined)
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Mesangial
Deposit substructure
Tubuloreticular inclusions in endothel cells
Peritubular capillaries basal lamina N layers
Deposits in tubular basement membrane
Tubular cell crystalline inclusions
Tubular mitochondrial abnormalities

FINAL DIAGNOSIS:
Adequacy (Y/N)
No rejection/Unremarkable
Borderline for rejection
Rejection
Cell mediated IA
mediated IB
mediated IIA
mediated IIB
ody mediated active
ody mediated chronic
erning for AMR check DSA
d rejection
ted V lesion
mbotic microangiopathy
lar injury
ephropathy
onephritis/Infection
HIVAN
FSGS
HIVICK
Glomerulopathies (other)
……

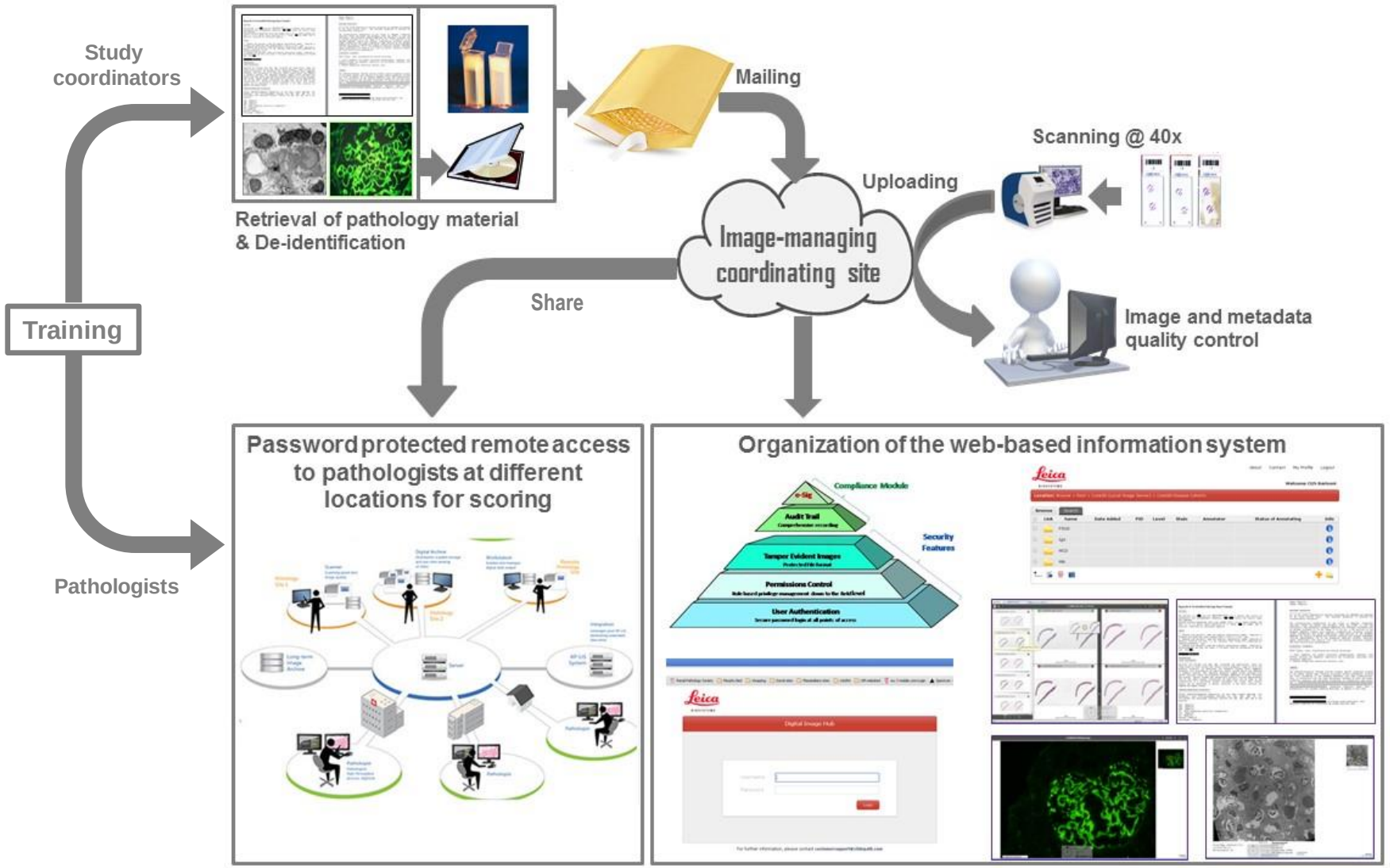
- **Uniform and detailed histological analysis of biopsy tissue**
- **Correlation of morphological tissue interrogation with clinical, molecular and experimental data collected on transplant donors and recipients.**

Digital Pathology

- Remote access by multiple users
- Ideal for multicenter studies

- Application of multiple scoring systems to same material in different studies

- Permanent library of data/images
- Platform for digital repositories



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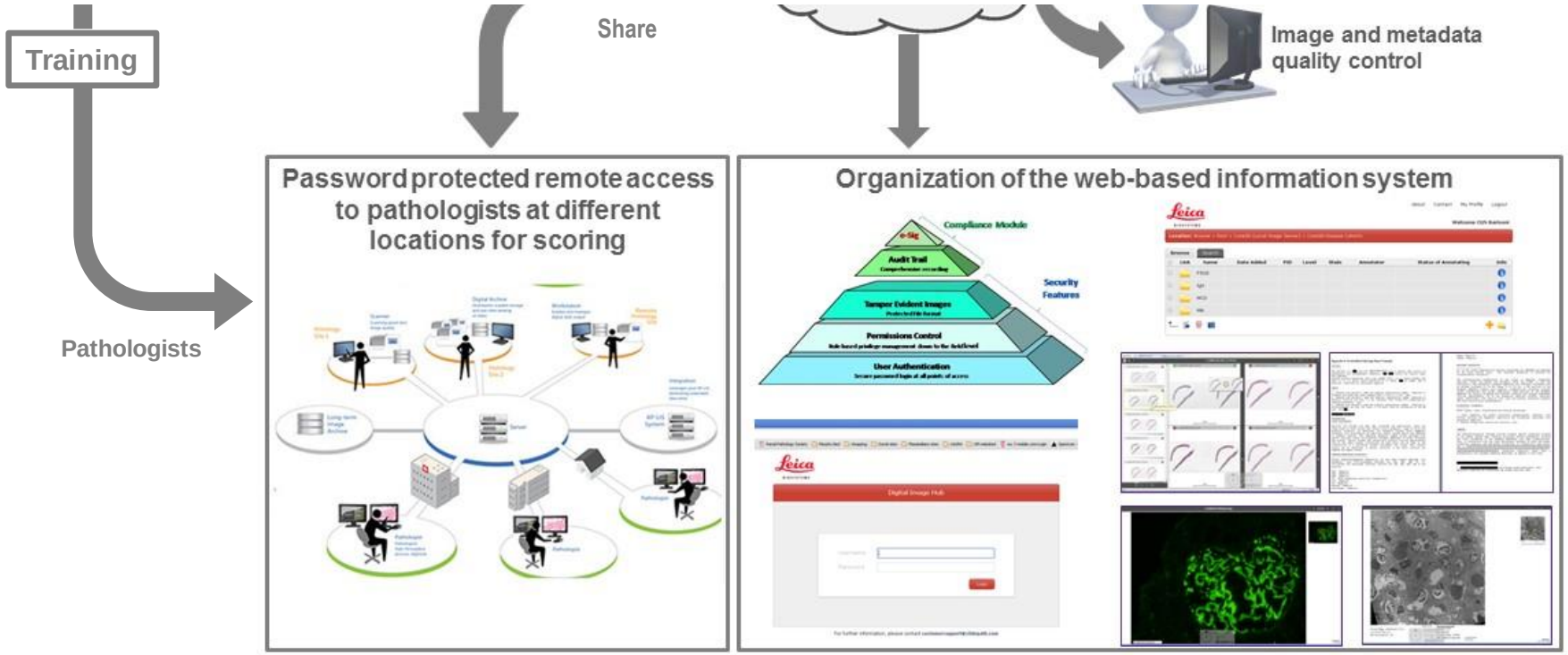
First: are we all on the same page?



Digital Pathology

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- **Test concordance on features and diagnoses on allograft biopsies:**
  - **-Whole slide imaging (WSI) of slides, digital images IF and EM accessible through a website**
  - **-Scoring sheet for LM, IF and EM features and diagnoses of each case**
  - **-Webinars**

- **Test reproducibility: Apply agreed scoring method to a sufficiently large number of available WSI of HIV allograft biopsies to examine the reproducibility of scoring among participating pathologists**

- **Examine relation / predictive value of specific features and diagnoses to rates of deterioration of graft function, selected outcomes, selected clinical/research parameters.**

- **Facilitate comparisons of results from different clinical trial**

SUMMARY

- HIV+ to HIV+ transplantation offers additional options for HIV+ patients with ESRD and liver failure. A number of national and international centers are embarking in HIV+ to HIV+ transplantation.

- HIV+ transplant recipients pose specific challenges

- Consensus on standardized histology diagnostic criteria for graft rejection as well as uniform criteria for evaluation of HIV-related allograft lesions is needed. Adherence to uniform histologic criteria are important in multicenter clinical trials.

- The main goal of this new Banff working group is to gather US and international pathologists and specialists from different medical fields to share their experience, and to develop consensus and evidence-based guidelines for these types of transplants.

THANK YOU