Research Priorities and Current Studies

End Organ Disease and Inflammation
Transformative Science Group

Turner Overton, MD, ITSG Chair
Netanya Utay, MD, ITSG Vice Chair
End-organ Disease and Inflammation TSG
Scientific Research Objectives

1. To identify strategies to reduce HIV-associated immune activation and inflammation.

2. To elucidate the specific drivers of HIV pathogenesis that can be targeted to prevent specific comorbidities common among treated HIV-infected persons.

3. To assess the impact of treatment strategies on surrogate markers of immune dysfunction and end-organ disease.

4. To test whether promising treatment strategies emerging from pilot studies decrease morbidity in treated HIV infection in larger clinical endpoint trials.
Many Challenges in Treating HIV Patients

- Comorbidities
  - Cardiovascular and Cerebrovascular disease
  - Insulin resistance/Diabetes
  - Hypertension
  - CKD
  - NAFLD/NASH
  - Malignancies

- Neuropsychiatric Complications
  - Cognitive Impairment
  - Depression/Anxiety

- Polypharmacy due to Multimorbidity
  - Drug-Drug Interactions (DDIs)

- Frailty and Functional Impairment
- Social Isolation
- Substance use and abuse
NW329: Activation, Inflammation and Non-HIV Related Events in Antiretroviral Treated and Suppressed HIV

- Case control study of 458 participants from ALLRT (longitudinal cohort study)
- Aim: to define the association of non-AIDS events with inflammation and immune activation in the setting of controlled HIV.

Areas of Focus for ITSG
(Targets for Intervention)

Leaves
End-organ diseases

Branches
Systemic inflammation
(IL-1β, IL-6, TNF)
Hypercoagulability (D-dimer)
Lymphoid Tissue Fibrosis

Roots
HIV reservoirs
CMV and other co-infections
Gut mucosal dysregulation
Unhealthy fat accumulation
Mitochondrial dysfunction
Aging

Courtesy of Peter Hunt
Where Have We Been? Cardiovascular Disease

• **ART decreases vascular inflammation**
  – **A5224s** (ATV/r or EFV + ABC/3TC or FTC/TDF)
    • ART reduces proteinuria and albuminuria
    • ART reduces inflammation and endothelial activation markers
  – **A5248** (RAL + FTC/TDF)
    • Raltegravir based therapy markedly decreases inflammatory biomarkers
      – LPS, IL-6, D-dimer, TNFR1, sCD14
      – **Still higher than negative controls**
  – **A5260s** (DRV/r vs. ATV/r vs. RAL + FTC/TDF)
    • Inflammatory biomarkers associated with oxidized lipoproteins
    • Incomplete reversal: inflammatory biomarkers declined with ART (differences based on 3rd agent): hsCRP, IL-6, D-dimer, sCD163, T cell activation

• **ART improves endothelial function**
  – **A5152s** (3 class sparing regimens: NNRTI/PI, NNRTI/NRTIs, PI/NRTIs)
    • ART improves flow-mediated dilation (FMD)

Where Have We Been?
Cardiovascular Disease/Lipids

• ART has complicated effects on lipids
  – **A5260s** (DRV/r vs. ATV/r vs. RAL + FTC/TDF)
    • oxLDL increases with ART; oxHDL decreased with ART
      – Potentially due to excess oxidative stress?
    • changes in lipids do not correlate with CIMT changes
  – **A5248** (RAL + FTC/TDF)
    • RAL increases LDL-c, oxLDL, and TG levels
    • RAL improved HDL composition and function
      – HDL cholesterol efflux function improvement
        » Correlated with 10% reduction in future CVD events
Where Have We Been?
Recent Cardiovascular Disease Focused Studies

- **A5275**: Atorvastatin on Lipids, Immune Activation, and Inflammatory Biomarkers
  - 98 ppts on ART, Median CD4 ct 552 c/mm3, LDL < 130mg/dL
  - Results:
    - Robust reduction of LDL-C (↓ 38%), oxLDL (↓ 33%)
    - No effect on biomarkers of interest
      - IL-6, sCD14, sCD163, MCP-1, IP-10, hsCRP, CD40L
      - T cell and monocyte activation
    - **Long viral suppression at entry with very low inflammatory biomarkers at entry**

- **A5331**: Aspirin on Flow-Mediated Dilation and Immune Activation
  - 121 ppts on ART, Median Age 49 yrs, Median CD4 ct 599 c/mm3
  - Results:
    - Significant reduction of serum thromboxane levels
    - No effect on FMD
    - No effect on biomarkers of interest
      - IL-6, sCD14, sCD163, D-dimer
      - T cell and monocyte activation
    - **Very low inflammatory biomarkers at entry**

Where Have We Been? Bone Disease

• **BMD declines 2-6% with ART initiation**
  – **A5224s** (ATV/r or EFV + ABC/3TC or FTC/TDF)
    • Greater BMD loss with TDF
  – **A5260s** (DRV/r vs. ATV/r vs. RAL + FTC/TDF)
    • Higher baseline inflammation biomarkers and markers of cellular activation and senescence predicted BMD loss
  – **A5303** (DRV/r +FTC + MVC vs. TDF)
    • Greater BMD loss with TDF (↓2.4%) vs. MVC (↓1.5%) at hip

• **Bisphosphonates improve BMD in treated HIV**
  – Weekly alendronate improved BMD (**A5163**)

• **VitD/calcium mitigate BMD loss with ART initiation**
  – **A5280** (EFV/FTC/TDF + VitD/Ca)

Where Have We Been?
Bone Disease

• Persistent BMD loss despite suppressive ART vs. HIV neg
  – A5224s/A5318

• Fracture incidence higher in first 96 weeks after ART initiation
  – ALLRT (A5001) Longitudinal cohort

• HCV treatment and BMD
  – A5178 (pIFN/RBV treatment of HCV/HIV coinfection)
    • IFN-based therapy reduces BMD
    • Bone turnover markers decline after HCV cure

Where Have We Been?
Neuropsychiatric Disease

- **A5271**: International Neurocognitive (NC) Normative Study
  - NC Performance Even in Treated HIV Patients Worldwide is Often Not Normal

- **ALLRT (A5001)** Aging and Neurocog Function
  - 3313 pts; median age 38 yrs; 12% >50 yrs
    - NC performance improved with ART duration
    - Despite ART, age remains a risk factor for NCI
    - Potential explanations
      - Greater comorbidities:
        - HTN, DM, Lipid disorder
      - Greater ART toxicities

Where Have We Been?
Gut Mucosal Health

**A5286: Rifaximin to Reduce Immune Activation**
- Hypothesis: Bind bacteria in gut/Prevent translocation
- Enrolled 65 ppts (43 Rifaximin; 22 controls)
- Median age: 50 yrs; Median CD4 236 c/mm3 on suppressive ART
- Results
  - Marginal Change in HLA-DR+/CD38+ CD8 cells, sCD14, LPS
  - No effect on other inflammatory biomarkers
    - D-dimer, IL-6, hsCRP

**A5296: Sevelamer to Reduce Microbial Translocation**
- Hypothesis: Bind LPS and decrease systemic inflammation
- Enrolled 40 ppts to sevelamer; no control arm
- Median age: 50 yrs; Median CD4 236 c/mm3 not on ART
- Results
  - No effect on markers of microbial translocation: LPS, sCD14
  - Modest effect on lipids
    - Decreased T chol, LDL, oxLDL
    - No effect on HDL, TG, and fasting glucose

Where Are We Now/Where Are We Going: End-organ Disease and Inflammation TSG Scientific Research Objectives

1. To identify strategies to reduce HIV-associated immune activation and inflammation.

2. To elucidate the specific drivers of HIV pathogenesis that can be targeted to prevent specific comorbidities common among treated HIV-infected persons.

3. To assess the impact of treatment strategies on surrogate markers of immune dysfunction and end-organ disease.

4. To test whether promising treatment strategies emerging from pilot studies decrease morbidity in treated HIV infection in larger clinical endpoint trials.
A5314: Effect of Reducing Inflammation with Low Dose Methotrexate on Inflammatory Markers and Endothelial Function in Treated and Suppressed HIV Infection

Protocol Co-Chairs: Priscilla Hsue and Judith Currier

Enrollment:
200 HIV participants on ART, CD4 >400 c/mm³, documented CVD or CVD risk

176 participants enrolled; study completed; analysis ongoing

Rationale
– LDMTX decreases vascular events in observational studies of HIV-uninfected persons

Key Study Objectives
– To evaluate safety of low dose methotrexate (LDMTX) therapy (Primary)
– To demonstrate LDMTX improves endothelial function (brachial artery FMD) (Secondary)
A5314: Methotrexate Results

Safety:
• 12.8% of individuals in LDMTX met primary safety endpoint vs. 5.6% in the placebo group (P=0.037)
  – The difference was lower than anticipated.

FMD:
• No change in endothelial function as assessed by FMD (%)
**Protocol Co-Chairs:** Jordan Lake and Netanya Utay  

**Enrollment:**  
54 HIV participants on ART for at least 48 weeks, HIV-1 RNA <200 copies/ml for at least 24 weeks and < 50 copies/ml at screening

---

**Rationale**  
- Telmisartan is an angiotensin receptor blocker and partial PPAR gamma agonist with putative anti-fibrotic and anti-inflammatory properties

**Key Study Objectives**  
- To evaluate whether adding telmisartan for 48 weeks to a suppressive ART regimen decreases lymphoid and/or adipose tissue fibrosis

---

44 participants randomized; study completed; analysis ongoing
• Median CD4 ct 588 c/mm³
• 35 participants in the per protocol analysis
  • 22 telmisartan
  • 13 control

Telmisartan did not decrease LN or adipose tissue fibrosis more than ART alone
A5325/30s: A Prospective Randomized Controlled Study to Evaluate the Effect of Isotretinoin on Immune Activation Among HIV-1 Infected Subjects with Incomplete CD4+ T Cell Recovery on Suppressive ART

Protocol Co-Chairs: Nina Lin and Douglas Kwon

Enrollment:
81 HIV participants on suppressive ART for at least 12 months, CD4+ count < 350 c/mm³

• Rationale:
  – Profound gut CD4+ T cell depletion occurs early in infection
  – Retinoic acid plays a prominent role in regulation of immunologic pathways, and contributes to gut mucosal integrity

• Objectives
  – Evaluate changes in CD8+ T cell activation with isotretinoin in suppressed HIV
  – Evaluate CD4+ T cell reconstitution in the gut mucosa (A5330s substudy)

76 participants enrolled in A5325; 24 in A5330s; study completed; analysis ongoing
A5325/30s: Isotretinoin Results

• Median CD4 ct 552 c/mm³
  – 34% <350 c/mm³

• Study completion
  – 40 in isotretinoin completed therapy
  – 26 in control arm

• Primary results:

<table>
<thead>
<tr>
<th></th>
<th>%DR+/CD38+</th>
<th>Isotretinoin (n=39)</th>
<th>No treatment (n=26)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Median [95% CI]</td>
<td>Median [95% CI]</td>
<td></td>
</tr>
<tr>
<td>BL - wk 16</td>
<td>CD8+ T-cells</td>
<td>+3.24 [1.44, 6.29]</td>
<td>+0.52 [-0.36, 2.41 ]</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>CD4+ T-cells</td>
<td>+1.01 [0.37, 2.26]</td>
<td>+0.17 [-0.79, 0.91]</td>
<td>0.05</td>
</tr>
</tbody>
</table>

• Conclusions
  – Isotretinoin increases circulating activated CD8+ and CD4+ T cells during treatment
    • Not durable increases
  – Similarly, several inflammatory markers increased but effect not sustained.
    • IL-6, hsCRP, sCD163, sCD14
The trial will randomize 90 HIV-infected adults 18 years of age and older - On ART, with CD4 count >200 c/mm³, and HIV VL < 50cp/mL

Rationale

- Potential to increase Th17 T cell population in gut
- Potential to shift monocyte population to less pro-inflammatory phenotype and potentially less likely to induce cardiovascular events
- Mediated through improved gut permeability

Primary Study Objective

- Assess changes in inflammatory biomarkers (main study)
- Assess changes in CD4+ cells in gut mucosa (substudy)

Followed for an additional 12 weeks off study therapy after completion of probiotic/placebo

93 participants enrolled in A5350; 42 in A5352s; study completed; analysis ongoing
A5336: Effect of Ruxolitinib on Inflammation and Immune Activation
Protocol Co-Chairs: Vincent Marconi and Jeffrey Lennox

The trial will randomize 60 HIV-infected adults 18 years of age and older - On ART, with CD4 count >350 c/mm³, and HIV VL < 50cp/mL

- Followed for an additional 7 weeks off study therapy after completion of ruxolitinib

40 ppts on ART + Ruxolitinib X 5 wks

20 ppts on ART + no drug X 12 wks

Rationale
- Janus Kinase 1&2 inhibitors decrease inflammatory cytokines in myelofibrosis, RA, psoriasis
- Potential to reduce inflammation in HIV-infected adults
- Mediated through improved gut permeability

Primary Study Objectives
- Evaluate Safety and Tolerability of Ruxolitinib
- Assess changes in inflammatory biomarkers

48/60 participants enrolled; study ongoing
A5351s: CMV Reactivation with Immunomodulatory Therapies

Prospective, observational study of participants on suppressive ART and enrolled in the ruxolitinib or sirolimus (Cure TSG) study or future studies of immunomodulatory agents as they are approved for development

Genital secretions, oral swabs, stored urine will be collected longitudinally

A5336: Ruxolitinib
A5337: Sirolimus

Rationale

– Persistent sub-clinical CMV replication in genital and oral secretions and urine is frequently found in HIV-infected individuals and is associated with increased systemic immune activation, T cell proliferation and exhaustion, and larger HIV DNA reservoir

– Therefore, it is important to capture the extent of sub-clinical CMV replication in clinical trials evaluating inflammation-related outcomes.

Primary Study Objectives

– To determine the effect of immune-modulatory interventions on seminal CMV shedding during suppressive ART

– CMV shedding in female genital tract, oral mucosa, and urine will also be evaluated

39 participants enrolled; study ongoing
A5324: Integrase & Maraviroc Intensification in Neurocognitive Dysfunction (InMIND)  
Protocol Co-Chairs: Kevin Robertson and Serena Spudich

The trial will randomize 186 HIV-infected adults 18 years of age and older  
- On ART, with HIV VL < 50cp/mL and NCI

62 ppts on ART + MVC + DOL X 96 wks

62 ppts on ART + MVC placebo + DOL X 96 wks

62 ppts on Background ART (no intensification) X 96 wks

Rationale

- NCI remains prevalent despite ART; CNS is a protected compartment
- Novel mechanisms may reduce CNS virus activity
  - R5 inhibition & integrase inhibition
- Mediated through improved gut permeability

Primary Study Objectives

- Assess changes in neurocognitive function with ART intensification

119/186 participants enrolled; study ongoing
Randomized Trial to Prevent Vascular Events in HIV

REPRIEVE (A5332/33s)

Asymptomatic HIV+ patients with no history of CVD

Placebo

Pitavastatin 4mg/day

Coronary plaque, vascular inflammation, immune activation

CV Death MI Unstable Angina Stroke Arterial Revasc

Individual components of primary endpoint

All cause death

Incidence/Progression of noncalcified plaque; High-risk plaque

Inflammatory, immunological, metabolic biomarkers

Predictors of statin effects

Statin safety and non AIDS comorbidities: DM, Infections, Cancer

Secondary Endpoints

Mechanistic Study

Primary Endpoint

Coronary plaque, vascular inflammation, immune activation

Clinical Primary Endpoint

Mechanistic

Randomization

(n=6500)

(n=800)

Screening And Consent

6 year F/u

4636/6500 enrolled

Funded by NHLBI and NIAID. Supported by KOWA Pharmaceuticals.
REPRIEVE Substudies

• A5333s: Mechanistic Substudy: CCTA at 0 and 24 months (PI: Hoffman/Ribaudo; funded by NHLBI)
  – 704/800 enrolled
  – Assess effects of pitavastatin on critical plaque and inflammatory biomarkers

• Kidney substudy (PI: Overton; funded by NIDDK)
  – 2558 enrolled
  – Assess changes in kidney function
    • Serum and urine markers

• Sex Differences substudy (PI: Zanni/Looby; funded by NIAID)
  – 4636 enrolled
  – Assess sex-based differences in Immune activation and statin-induced immunomodulation
  – Characterize the role of menopause status and ovarian reserve

• A5361s: Physical Function and Frailty (PI: Erlandson; funded by NIA)
  – 436/600 enrolled
  – Assess statin effects on physical function and muscle quality
A5322 (HAILO): The HIV Infection, Aging and Immune Function Long-Term Observational Study

• 1035 Participants (81% male, 48% white)
  – Median age 51 years
  – Median CD4 ct at ART initiation: 228 c/mm3
  – Median CD4 ct at study entry: 621 c/mm3
  – HIV VL <50 cp/mL at study entry: 61%
  – Median years of ART: 7.2 years

• Many data elements/samples available
  – Labs (CD4, VL, CBC, CMP, lipids, urine)
  – Neurocognitive examination
  – Questionnaires/assessments
    • Smoking, frailty, substance use, medical insurance, behavioral data, physical activity, ADLs

1035 participants enrolled; observational follow-up ongoing; analysis ongoing
### A5322 Non-AIDS Events Through 2016

<table>
<thead>
<tr>
<th>Clinical Event Category</th>
<th>Observed event rate per 100 person-years since A5001 (#events/total person years)</th>
<th>Expected event rate per 100 person-years*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular Diseases</td>
<td>0.83 (19 / 2294.91)</td>
<td>0.48</td>
</tr>
<tr>
<td>Thrombosis/Embolism</td>
<td>0.39 (9 / 2302.35)</td>
<td>0.12</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.61 (53 / 2027.86)</td>
<td>1.10</td>
</tr>
<tr>
<td>Hepatobiliary Disorders</td>
<td>0.30 (7 / 2307.3)</td>
<td>0</td>
</tr>
<tr>
<td>Neoplastic Disease</td>
<td>0.52 (12 / 2301.64)</td>
<td>0.41</td>
</tr>
<tr>
<td>Renal Disorders</td>
<td>0.58 (12 / 2076.27)</td>
<td></td>
</tr>
<tr>
<td>Bone fractures due to falls</td>
<td>0.79 (18 / 2291.57)</td>
<td>0.15</td>
</tr>
<tr>
<td>Bone fractures due to trauma</td>
<td>0.44 (10 / 2297.81)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0.43 (10 / 2312.91)</td>
<td>0.88</td>
</tr>
</tbody>
</table>

**Creation of 5 Working Groups to Seek Independent Funding:**

- Cardiovascular Disease
- Kidney Disease
- Frailty/Physical Function
- Neuropsychiatric issues
- Cancer
A5355: Safety, Tolerability, Immunogenicity, and Virologic Efficacy of an anti-CMV Vaccine (Triplex®)
Protocol Co-Chairs: Sara Gianella-Weibel and Don Diamond

The trial will randomize 90 HIV-and CMV-infected adults 18-65 years of age, on suppressive ART with CD4 count >250 c/mm³

60 participants on ART + Triplex at weeks 2 and 6
30 participants on ART + placebo at weeks 2 and 6

Followed for an additional 90 weeks off study therapy after last vaccine/placebo

Rationale
- Persistent sub-clinical CMV replication in genital and oral secretions and urine is frequently found in HIV-infected individuals on ART and is associated with increased systemic immune activation, T cell proliferation and exhaustion, and larger HIV DNA reservoir

Primary Study Objective
- To evaluate safety and tolerability of Triplex in HIV-infected persons (Primary)
- To determine effects of Triplex on CMV DNA levels
A5363: Effects of Cenicriviroc on Arterial Inflammation in People Living with HIV
Protocol Chair: Janet Lo
Vice Chairs: Judith Currier & Ned Tawakol

The trial will randomize 93 HIV-infected adults ≥45 years of age on suppressive ART for ≥48 weeks with at least one cardiovascular disease risk factor.

- 62 participants on ART + Cenicriviroc x 24 weeks
- 31 participants on ART + Placebo x 24 weeks

Rationale

- Monocyte/macrophage activation is increased in HIV infection and plays a key role in cardiovascular events
- CCR2 and CCR5 mediate monocyte migration and are thought to contribute to atherosclerosis
- Cenicriviroc (CVC) is a CCR2/CCR5 antagonist

Primary Study Objective

- To assess whether CVC decreases arterial inflammation as measured by 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography (CT) imaging of the carotid arteries and aorta
A5371: Treatment of NAFLD: A Metabolic Syndrome
Protocol Chairs: Kristine Erlandson and Jordan Lake

The trial will randomize HIV-infected adults on suppressive ART for ≥24 weeks with central adiposity, indicator(s) of impaired insulin glucose homeostasis, and 5% steatosis on MRS.

34 Participants on ART + Sitagliptin x 36 weeks
34 Participants on ART + Liraglutide x 36 weeks

Lead-in (12 weeks)

Rationale
- Non-alcoholic fatty liver disease (NAFLD) is associated with cardiovascular events in the general population and affects 30-40% (or more) of HIV-infected adults.
- NAFLD may have unique origins in HIV infection

Primary Study Objective
- To assess whether sitagliptin or liraglutide for 36 weeks decreases MRI-quantified intrahepatic triglyceride deposition by proton MR spectroscopy (MRS)
What our current portfolio can teach us?

In the next few years, we should know more about

• Whether probiotics can facilitate gut healing, and if so, if this attenuates inflammation (A5350/52s)

• Relative contribution of CMV to systemic inflammation in chronic treated HIV infection (A5351s, A5355)

• Role of Jak/Stat signaling in driving chronic inflammation in treated HIV infection (A5336)

• Effects of systemic inflammation on HIV persistence and transcriptional activation (A5337, A5336, A5346)

• Role of macrophage recruitment via CCR2/CCR5 in vascular inflammation, neurocognitive function, liver steatosis (A5363)

• Drivers of hepatic steatosis in HIV infection (A5371)

• Specific mechanisms behind accelerated CVD in HIV (A5332/33s)

Ultimately, these studies will lead to a greater understanding of HIV pathogenesis in the next several years
Unanswered Questions to Address

- What are the drivers of persistent inflammation?
  - GI mucosal dysregulation/microbial translocation
  - Unhealthy fat accumulation, particularly NAFLD→NASH
  - HIV persistence
  - Other pathogens (Hepatitis and Herpes viruses)
  - Mitochondrial dysfunction
  - Severity of immune deficit

- Does sustained ART and virologic suppression reduce inflammation adequately?

- Can we do anything about it beyond ART to prevent diseases of interest?
  - Treating early has incomplete benefit
  - Various treatment strategies being evaluated

- What is the role in chronic inflammation in HIV persistence?

- If we effect a cure, what are the consequences on end organ disease/comorbidities?
  - Remains unknown with only 1 cure to date
  - Even if a cure is identified, roll-out to almost 37 million people will take time and money and
  - People have comorbidities now
Critical Neurological Topics Requiring Ongoing Investigation

- Optimal cART for the brain compartment (A5303, A5324)
- CNS compartment (A5321, A5341s, biorepository studies, biomarker development, viral escape characteristics)
- Impact of anti-inflammatory approaches on brain/csf inflammatory response (**needs better plans – 5332, 5336)
- Vascular disease (Stroke, brain perfusion as source and/or measure of HAND)
- Aging/Degenerative Dx (A5322 HAILO neurological component, frailty)
- Co-morbidity (CMV, HCV)

Current Red Line

- Psychiatric disease
- Sleep (glymphatics and degeneration)
- CNS opportunistic infections (crypto, TB, toxo, JC)
- Peripheral neuropathy

Slide courtesy of David Clifford.
Greater ART access with initiation at higher CD4 cell counts

BUT

Morbidity and Mortality remains higher in low and middle income countries
– TB - Bacterial infections
– Malnutrition - Non-AIDS diseases (CVD, obesity, DM, HTN)

A5175 secondary analyses (ART initiation)
– Baseline and persistently elevated inflammatory biomarkers associated with TB, AIDS, and Mortality
– Weight gain associated with increases in inflammatory biomarkers despite ART

Key questions for international studies:
– How will anti-inflammatory therapies work?
– Are drivers of persistent inflammation different?
– What is the role of late ART initiation, i.e. low CD4 count?
– CVD is a common comorbidity in these settings (A5332)?
Pathways Forward

• Utilize existing data and samples for secondary analyses
  – NWCS 329
  – A5224s/A5260s data
  – ALLRT/HAILO
  – Longitudinal follow up in 5320; A5321/41
  – REPRIEVE (*a treasure trove*)

• Systems Biology Approach to completed studies
  – Find the unexpected

• Select the appropriate study population
  – CD4 count
  – Evidence or risk factors for end organ disease

• Partner with experts within the ACTG
  – Hepatitis Committee: NAFLD/NASH working group
  – WHISC: the role of sex and sex hormones
  – Cure TSG: 5354, ATIs
  – TB: biomarker development
  – ARTS: long acting agents; studying hard to reach populations (A5359); metabolic consequences of bNAb
  – International sites and partners: different drivers in developing world

• Partnerships with NIH Institutes for Studies
  – A5224s: NIAID
  – A5260s: NHLBI
  – A5314: NHLBI
  – REPRIEVE: NHLBI, NIAID, NIDDK, NIA
  – NAFLD/NASH: NIDDK 10/20/17 meeting

• Partnerships with Industry
  – A5363: Allergan
  – A5346: Merck
  – A5371: Nordisk; Merck

• Engage experts from specific areas
  – NAFLD/NASH: Kara Chew
  – Frailty/Physical function: Marcus Bamman
  – Mucosal immunology: Jason Brenchley
Pathways Forward

- **What are the strengths of the ITSG?**
  - Investigators and Breadth of Knowledge
  - Diversity of areas of research
  - Collaborations between Clinicians and Laboratorians
  - Strong Statistical Support
  - Availability of large repository of samples and data

- **What are we not doing well?**
  - Soliciting studies from non-ACTG investigators
  - Difficult process getting protocols from genesis to enrollment
  - Utilizing existing samples/data
  - Engaging International investigators
  - Collaborating with TB investigators

- **Are there new opportunities in this field that the ITSG should pursue?**
  - Utilizing newer imaging techniques
  - Collaboration with industry and other groups
    - Example: NASH Clinical Research Network
  - Collaborating with NIH Institutes beyond NIAID
  - Identifying novel therapeutic agents
    - Example: IDO inhibitors, cancer therapeutics
  - Targeting endpoints beyond biomarkers
Our People Provide Our Expertise

- Turner Overton
- Netanya Utay
- Adriana Andrade
- Donald Anthony
- Roberto Arduino
- Francesca Aweeka
- Jason Baker
- David Clifford
- Robert Coombs
- Kristina Crothers
- Michael Dube
- Kristine Erlandson
- Nicholas Funderburg
- Sonya Heath
- Peter Hunt
- Nichole Klatt
- John Koethe
- Nagalingeswaran Kumarasamy
- Jordan Lake
- Alan Landay
- Bernard Macatangay

- Carlos Malvestutto
- Christina Marra
- Vidya Mave
- Grace McComsey
- Mosepele Mosepele
- Fred Sattler
- Thomas Uldrick
- Sara Weibel
- Michael Yin
- Doug Kitch (Statistical and Data Analysis Center)
- Carlee Moser (SDAC)
- Heather Ribaudo (SDAC)
- Baljinder Singh (SDAC)
- Karin Klingman (DAIDS representative)
- Dave Rusin (Data Management Center representative)
- Stanford Chimutimunzeve (Community Scientific Subcommittee)
- David Palm (CSS)
- Andrea White (Coordinator)
- Reena Masih (Coordinator)