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937. Virally Suppressed PLH Switching From Abacavir to Tenofovir Alafenamide Did Not Have Changes in Immune Activation or Inflammation
Nicholas Funderburg, PhD1; Grace McComsey, MD, FIDSA2; Manjusha Kulkarni, PhD3; Emily R. Bowman, PhD1; Janelle Gabriel, PhD1; Devi Sengupta, MD4; Patrick Mallon, MD, PhD5; Alan Winston, MD, PhD6; Brandon Snyder, BS7; Mingjin Yan, PhD8; Martin S Rhee, MD9; and Moupali Das, MD9, MPH9. The Ohio State University, Columbus, Ohio, 1Case Western Reserve University, Cleveland, Ohio, 2The Ohio State University College of Medicine, Columbus, Ohio, 3School of Medicine and Medical Science, University College Dublin, Dublin, Ireland, 4Imperial College London, London, UK and 5Gilead Sciences Inc., Foster City, California
Session: 115. HIV-Related Comorbidities and Complications
Friday, October 5, 2018: 8:45 AM

Background. Abacavir (ABC) use has been associated with increased risk of myocardial infarction in persons living with HIV (PLH). Its mechanism is unknown, but may involve immune activation inflammation, and/or altered platelet reactivity. In the current analysis, we compared changes in biomarkers of immune activation and inflammation associated with increased cardiovascular (CV) mortality in virally suppressed PLH who switched off ABC to tenofovir alafenamide (TAF) to those who remained on ABC.

Methods. In a randomized, double-blinded, active-controlled trial (GS US 311-1717), virally suppressed PLH on a stable regimen containing ABC plus lamivudine (3TC) were randomly assigned (1:1) to maintain therapy or to switch to TAF plus emtricitabine (FTC) while continuing their third agent. At baseline (BL) and weeks 4, 12, 24, and 48 plasma markers (IL-6, hsCRP, D-Dimer, sCD14, sCD163, sTNFR-1, and sTNFR-2) were measured by ELISA; PL-P LA2 levels were measured by the Plac assay. Differences between treatment groups overtime were assessed by 2-sided Wilcoxon rank-sum tests.

Results. Of 556 PLH randomized, 548 had samples available for biomarker assessments (TAF=274; ABC=274), both arms were of similar CD4 (median 671 cells/µL) age (median 52 years), race (73% white), but there were fewer women in the TAF arm (14% vs. 22%, P = 0.015) at baseline (BL). Mean BL ASCVD scores were 7.9 in both arms (>7.5 is increased CV risk); BL biomarker concentrations were similar between arms. Mean high concentrations of Lp-PLA2 ≥200 mg/mL (94%) and one-third had elevated hsCRP levels ≥3 mg/L (34%). After switching from ABC to TAF sCD14 had an early (W12) decrease (−3.4% vs. −0.1%, P = 0.023), while sCD163 increased at both W4 (2.5% vs. −1.1%, P = 0.02) and W24 (1.4% vs. −0.8%, P = 0.025) in the TAF arm; levels of sTNFR-1 also increased through W24 (3.2% vs. 0.2%, P = 0.003) (figure). There were no significant differences in percentage changes from BL between arms for levels of Lp-PLA2, hsCRP, IL-6, D-dimer, or sTNFR-2.

Conclusion. Prior to switching from ABC to TAF, virally suppressed PLH with mean ASCVD scores of 7.9 had elevated levels of CV risk markers (Lp-PLA2 and hsCRP). Switching off ABC to TAF was not associated with any meaningful change in markers of immune activation or inflammation, suggesting that the ABC-associated increased MI risk may involve an alternative etiology.

962. Cutaneous Leishmaniasis: Investigating Skin Drug Levels to Optimize Liposomal Amphotericin Dosing
Tobin E. Arenson, MD, Nancy Koles, MS, Sean Moran, PhD and Aibong Zhang, PhD, Uniformed Services University of the Health Sciences, Bethesda, Maryland
Session: 124. Adventures with Globally Acquired Infections
Friday, October 5, 2018: 10:30 AM

Background. Liposomal amphotericin B (L-AMB, AmBisome®) is popular for off-label use in the treatment of cutaneous leishmaniasis (CL) using dosing of 3 mg/ kg/day for days 1–5, 8, 9, or days 1–5, 10 with reported clinical cure rates of 46–84%.
In rodents, the skin concentration of L-amB is 40-fold less than that in visceral organs. We hypothesize that a specific L-amB regimen targeted to skin concentrations could maximize a beneficial treatment response in CL.

**Methods.** SKHI 477 Elite hairless mice (Charles River), 5 per group, received intravenous L-amB at doses of (A) 3 mg/kg/day for days 1–5, 8, 9, (B) 5 mg/kg/day for 4 days, (C) 10 mg/kg load than 5 mg/kg/day for 3 days, (D)10 mg/kg/day for 2 days, (E) 15 mg/kg/day for 2 days. Serum and skin (back) punch biopsies were collected on day 0, 2, 5, 14, and 21. Nasal mucosa was biopsied on day 21. Tissue samples were homogenized and L-amB was extracted with methanol and acetonitrile. Liquid chromatography–mass spectrometry (LC-MS) was performed using Ommic extracted samples on an Agilent 1200 series HPLC and an AB Sciex Q-Trap 4000 mass spectrometer. Experiment conducted twice for confirmation.

**Results.** L-amB doses were well tolerated by the mice; except weight loss was seen in groups E. Day 21 serum L-amB levels were 82 ± 3.3 (ng/mL) regimen A, 91 ± 4.2 in B, 89 ± 4 in C, 118 ± 3.7 in D, 98 ± 1.5 in E. Mean L-amB nasal tissue levels on day 21 were 1.33 ± 3.2 (mg/tissue) regimen A and 6.5 ± 3 in D (P = 0.031). Mean L-amB skin levels on day 14 were 8.4 ± 5.6 (ng/tissue) in regimen A, 4.0 ± 1.7 in B, 6.2 ± 3.3 in C, 13.9 ± 7.1 in D, 33.9 ± 24.7 in E. Skin L-amB levels at day 21 were less than 5 (ng/tissue) except for regimen D 9.3 ± 4.2 and regimen E 7.8 ± 2.6. SKHI 477 Elite mice did not permit an adequate *Leishmania* major infection (very tiny lesions when compared with other murine species) to correlate these results clinically in this specific murine model.

Conclusion. CL cases in Uganda and nasal mucosal levels were significantly higher in the short, high daily dose regimens compared with the L-amB regimen that is currently used in CL patients. This suggests that better clinical results might be seen by using a L-amB dosing regimen for CL of 10 mg/kg for 2 days, a dose regimen used in the treatment of visceral leishmanial leishmaniasis.

**Disclosures.** All authors: No reported disclosures.

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**963. Whole Blood Transcriptome Analysis Reveals Differences in Erythropoiesis and Neurologically Relevant Pathways Between Cerebral Malaria and Severe Malarial Anemia**

Srinivas Naanllahbighal, MS1; Gregory Park, PhD2; Yen Yi Ho, PhD2; Robert Opoka, MBCHB3; Chandie John, MD, MS4; and Tran Juan, MD, PhD5; 1Department of Medicine, Division of Infectious Diseases, Indiana University School of Medicine, Indianapolis, Indiana, 2Department of Pediatrics, Division of Global Pediatrics, University of Minnesota Medical School, Minneapolis, Minnesota, 3Department of Statistics, University of South Carolina College of Arts and Sciences, Columbia, South Carolina, 4Makerere University, Kampala, Uganda and 5Ryan White Center for Pediatric Infectious Disease and Global Health, Indiana University School of Medicine, Indianapolis, Indiana

**Session:** 124. Adventures with Globally Acquired Infections

**Friday, October 5, 2018: 10:30 AM**

**Background.** *Plasmodium falciparum* malaria can rapidly progress to severe disease that can lead to death if left untreated. Severe malaria cases commonly present as severe malarial anemia (SMA), defined in children as hemoglobin (Hb) <5 g/dL with signs of severe hypoperfusion, or neurologic symptoms such as altered consciousness and convulsions, or severe anemia without hypoperfusion or neurologic symptoms. SMA has a high case fatality ratio (6%–9%) and severe cerebral malaria (CM) has a case fatality ratio of 12%–47%.

**Methods.** In this study, we compared genome-wide transcription profiles of whole blood obtained from Ugandan children with acute CM (n = 17) or SMA (n = 17) and community children without P. falciparum infection (n = 12) who were enrolled in a parent cohort study of severe malaria. We determined the relationships between gene expression, hematological indices, and plasma biomarkers, including inflammatory cytokines, chemokines, and proteins.

**Results.** Both CM and SMA demonstrated enrichment of dendritic cell activation, inflammatory/TLR/chemokines, monocyte, and neutrophil modules but depletion of lymphocyte modules. Neuroinflammatory disease and neuroinflammation pathways were upregulated in CM. Increased NDR2 pathway gene expression corresponded with increased plasma heme oxygenase-1 and the heme catabolite bilirubin in a manner specific to children with both SMA and sickle cell disease. Reticuloocyte-specific gene expression was markedly decreased in CM relative to SMA despite higher Hb levels and appropriate increases in plasma erythropoietin, Viral sensing/interferon regulatory factor (IRF) 2 module (M111) expression and plasma IP-10 levels both negatively correlated with reticuloocyte-specific signatures, but only M111 expression independently predicted decreased reticuloocyte gene expression after controlling for leukocyte count, Hb level, and clinical syndrome by multiple regression.

**Conclusion.** Differences in the blood transcriptome of CM and SMA relate to neurologically relevant pathways and erythropoiesis. Erythropoietic suppression during severe malaria is more pronounced during CM versus SMA and is positively associated with IRF2 blood signatures. Future studies need to be validated to these findings.

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**965. Applying Clinical Prediction Tools to Patients with Lassa Fever**

John Chois1, MD; Jeffrey Shaffer, PhD2; and John Schieffelin, MD1; 1Pediatric Infectious Disease and Global Medicine, Tulane University School of Medicine, New Orleans, Louisiana, 2Tulane School of Public Health and Tropical Medicine, New Orleans, Louisiana and Tulane University Health Sciences Center, New Orleans, Louisiana

**Session:** 124. Adventures with Globally Acquired Infections

**Friday, October 5, 2018: 10:30 AM**

**Background.** Clinical prediction tools such as the Quick Sequential Organ Failure Assessment (qSOFA) and the Modified Early Warning Score (MEWS) have been used to predict mortality from sepsis in high-income countries, but their application to low- and middle-income countries have been limited. Lassa fever is a viral hemorrhagic fever endemic to West Africa with a case fatality ratio for hospitalized patients of up to 69%. The purpose of this study was to evaluate existing clinical prediction tools for critical illness in predicting adverse outcomes in patients with Lassa fever.**

**Methods.** We conducted a retrospective cohort study of patients admitted to the Kenema Government Hospital Lassa ward in Sierra Leone between 2012 and 2017. Patients were required to meet the World Health Organization case definition for suspected Lassa Fever to be admitted to the ward. We included patients who had laboratory-confirmed Lassa fever or IgM. Control samples were included with negative ELISA tests for Lassa Ag and IgM. We compared criteria for qSOFA, MEWS, Systemic Inflammatory Response Syndrome (SIRS), and Universal Vital Assessment (UVA) among the Lassa Ag+ (patients with acute viremia), Ag+ IgM+ (patients who cleared the virus and developed an immune response), and Ag-/IgM– (control) groups.

**Results.** There were 157 patients included in this preliminary analysis. Of patients in the Ag+ group, the mean age was 20.2 years and 40.8% were female. Patient demographics were similar among all groups. Clinical outcomes significantly differed among the groups with mortality at 62.5% in the Ag+ group, 31% in the Ag+ IgM+ group, 25% in the Ag-/IgM– group and the lowest in the Ag+ IgM– group (P < 0.05; see table). The highest scores were consistently seen in the Ag+ group.

**Conclusion.** Patients with acute viremia for Lassa fever had higher scores for clinical prediction tools compared with controls, which imply a higher risk of mortality. Additional research is needed on the sensitivity and specificity of these tools for mortality due to Lassa fever.

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**Table:** Mean Score of Clinical Prediction Tools in Patients With Lassa Fever and Controls

|                     | Ag+ | Ag+/IgM+ | Ag-/IgM– |
|---------------------|-----|----------|----------|
| qSOFA (out of 3)    | 2.0 | 1.7      | 1.6      |
| SIRS (out of 4)     | 3.0 | 2.1      | 1.9      |
| MEWS (out of 11)    | 7.6 | 6.8      | 5.2      |
| UVA (out of 9)      | 3.8 | 2.1      | 1.4      |

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