RESEARCH STRATEGY

SPECIFIC AIMS

Cancer is an increasing cause of morbidity and mortality among patients with HIV living in sub-Saharan Africa (SSA)[1]. As access to cancer treatment in SSA has improved, infection-related complications, particularly infections with multi-drug-resistant (MDR) bacteria such as extended-spectrum beta-lactamases (ESBLs) and carbapenem-resistant Enterobacterales (CREs), are a growing concern.[2-6] For patients with cancer who are being treated with chemotherapy, gastrointestinal colonization with these multi-drug-resistant organisms (MDROs) can result in the development of bloodstream infections, resulting in increased mortality.[7-10] While antibiotic use and exposure to the healthcare system are established risk factors for MDRO colonization, it is unclear whether HIV is also a risk factor.[11-14] Since those with HIV experience chronic gastrointestinal inflammation[15] and have relatively high rates of antibiotic use[16], HIV status may well be associated with MDRO colonization. In SSA, 30-40% of individuals with cancer are also HIV-seropositive[17] and ESBL- and CRE-related infections are common.[18-20] For example, in our group's studies at the Uganda Cancer Institute (UCI), we found that more than 50% of bloodstream infections were caused by ESBL or CRE.[3] Resource constraints and limited access to effective broad-spectrum antibiotics pose a significant challenge when managing these infections in resource-limited settings. Understanding the association between HIV and MDRO colonization could allow us to develop tailored antibiotic treatment protocols for patients with HIV who are being treated for cancer. This would avoid unnecessary use of broad-spectrum antibiotics, which is a driving factor in the development of further antimicrobial resistance, while ensuring that that those who would benefit continue to receive them. Thus, strategies to inform rational antibiotic use within cancer programs in SSA could improve patient outcomes and would also be beneficial on a healthcare systems level. In this study, we will explore the association between HIV-status and MDRO colonization among patients with cancer. Our central hypothesis is that ***HIV serostatus is associated with increased rates of gastrointestinal colonization with MDROs in patients with cancer living in Uganda.*** To test this hypothesis, we will pursue the following aims:

Aim I: Define the association between HIV-status and prevalence of MDRO gastrointestinal colonization among patients with cancer in Uganda. Patients with newly diagnosed cancer who are scheduled to receive chemotherapy will be eligible for the study. We will enroll an equal number of HIV-positive and HIV-negative patients matched to tumor type (solid tumor vs. hematologic malignancy). Prior to the initiation of chemotherapy, we will screen participants for colonization with ESBL and CRE by collecting perirectal swabs and plating them onto selective media[16]. Our primary outcome will be prevalence of MDRO colonization based on HIV-serostatus. Our secondary outcome will be prevalence of MDRO colonization in those who are HIV-positive based on CD4 count and HIV viral load.

Aim 2: Assess the factors associated with incident MDRO colonization in the first 30-days after initiation of chemotherapy. Participants will be prospectively followed for 30 days after their first dose of chemotherapy. Those who were not colonized with an MDRO at study enrollment will undergo repeat screening for ESBL and CRE using perirectal swabs. We will then compare 30-day incidence of MDRO colonization based on HIV-serostatus. In participants who are HIV-positive, we will also evaluate the association between baseline CD4 count and HIV viral load with incident MDRO colonization.

Aim 3: Investigate whether gastrointestinal colonization with an MDRO is associated with an increased risk of developing a bacterial bloodstream infection with that organism. We will follow patients prospectively for 30-days after they receive their first dose of chemotherapy to determine whether they developed a bacterial bloodstream infection. We will then compare the incidence of infection in participants who were colonized with MDROs prior to initiation of chemotherapy and those who were not.

SIGNIFICANCE

MDROs are a growing cause of bloodstream infections in patients with cancer and are associated with high rates of morbidity and mortality.[21,22] For those receiving cancer treatment, the cytotoxic effects of radiation and chemotherapy disrupt the gastrointestinal mucosa, resulting in bacterial translocation and development of bacterial bloodstream infections.[23] Studies from high-income countries have demonstrated that patients with cancer who are colonized with ESBL or CRE are at increased risk of developing bacterial bloodstream infections with these organisms.[7-10] MDROs can also be transmitted from one patient to another through direct contact, making robust infection control measures critical to preventing outbreaks within the healthcare setting. In low-resource settings, the limited availability and the high cost of broad-spectrum antibiotics make it especially

difficult to treat infections with MDROs. Understanding which patients are likely to be colonized with ESBL or CRE can inform appropriate empiric antibiotic selection and improve infection prevention strategies.

In SSA, the high rate of HIV-related malignancies and growing prevalence of MDROs pose a unique challenge. In a 2019 meta-analysis, pooled data from 32 studies across SSA showed a high prevalence of ESBL colonization, ranging from 18% among community members to 55% among hospitalized patients.[24] However, the role that HIV plays in colonization has not been well-established. There is a known association between HIV infection, chronic gastrointestinal mucosal inflammation, and dysregulation of the gut microbiome, even among those with well-controlled HIV.[15] Those with HIV also have relatively high rates of antibiotic exposure[15,16] and are at higher risk of developing infections with methicillin-resistant strains of *Staphylococcus aureus* and penicillin-resistant strains of *Streptococcus pneumoniae*.[16,25] However, few studies have evaluated the interaction between HIV and gastrointestinal colonization with resistant enteric organisms.[13,26] Only three studies in the meta-analysis included the participant's HIV serostatus.[12] Two pediatric studies found an association between HIV infection and ESBL colonization.[11,13] Studies in the adult population showed higher,[27] lower,[22] and no difference[12] in the prevalence of ESBL colonization when comparing HIV-positive and HIV-negative individuals. While the two studies that evaluated HIV immune status found no association between CD4 count or HIV viral load and ESBL colonization, it is important to note that >90% of those studied had CD4 counts >350.[11,26] This is not reflective of the cancer population, as those with poorly-controlled HIV are at higher risk of developing cancer.[28]

Management of bloodstream infections with MDROs is a significant challenge for patients receiving cancer treatment at the UCI in Kampala, Uganda. The UCI is a major cancer referral center for patients throughout East Africa and is the designated East African Center of Excellence in Oncology. More than 5,000 patients with newly diagnosed cancer are treated at UCI annually; 35% of these are HIV-positive.[17] To date, our group has enrolled more than 500 participants in two ongoing studies investigating the microbiology of febrile illness among patients receiving cancer treatment. In our studies, we observed that 33% of those with hematologic malignancies developed neutropenic fever. Of these, 1/3 had a bacterial bloodstream infection, 56% of which were caused by ESBL or CRE. For those with bacteremia, 30-day mortality rates approached 44%[3] (Figure 1). Similarly, 50% of patients with solid tumors who had a bloodstream infection had an ESBL-producing organism (unpublished data).

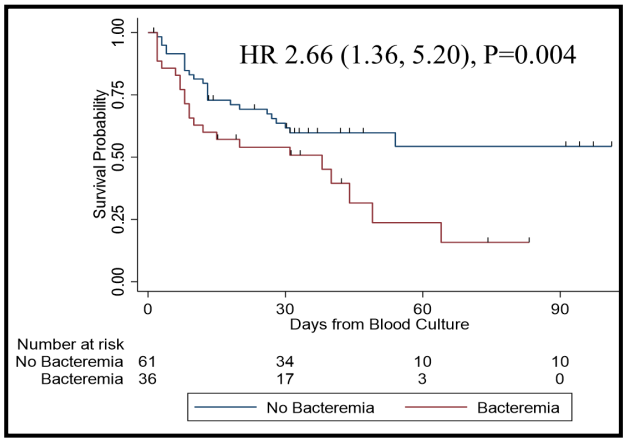

Figure 1. Probability of survival in hematologic malignancy patients with neutropenic fever based on the presence of bacteremia at the Uganda Cancer Institute[3]

The high prevalence of MDRO bloodstream infections is especially concerning, given the limited availability of broad-spectrum antibiotics in SSA. Available antibiotics are often prohibitively expensive (e.g., carbapenems, colistin) and/or associated with significant toxicities (e.g., permanent bone-marrow suppression with chloramphenicol, renal toxicity with colistin) and are therefore often reserved for patients with proven MDRO infections. Understanding which patients are at highest risk for developing these infections can allow us to create targeted antibiotic management strategies for judicious use of these limited resources. Since 35% of patients at UCI have concurrent HIV infection,[17] determining whether HIV status is associated with MDRO colonization is an important step to developing targeted antimicrobial treatment algorithms, optimizing the use of limited resources, and improving patient outcomes.

Innovation

Our study will:

- Be one of the first to compare gastrointestinal colonization with MDROs in adults who are HIV-positive and those who are HIV-negative in SSA.
- Be the first to characterize the ESBL and CRE colonization rates in patients who are being treated for cancer in SSA, many of whom have high rates of antibiotic exposure.
- Generate data that can contribute to novel approaches for antimicrobial stewardship and infection control (e.g., use of rapid diagnostic tests to detect MDRO colonization, development of HIV-specific infection treatment guidelines), particularly in hospitals located in low-resource settings with high HIV prevalence.

- Assist in local capacity-building by partnering with Makerere Microbiology Laboratory to create local protocols for screening of rectal carriage with MDROs.

APPROACH

Our overarching goal is to characterize the relationship between HIV-status, gastrointestinal colonization with MDROs, and the development of MDRO bloodstream infections in patients who are receiving treatment for cancer in Uganda. To do this, we will conduct a prospective cohort study of 150 HIV-seronegative and 150 HIV-seropositive patients with newly diagnosed cancer who are initiating chemotherapy at the UCI (Figure 1). We will first determine the prevalence of MDRO colonization prior to chemotherapy initiation (Aim 1). We will then follow the participants prospectively for 30 days after the first dose of chemotherapy is administered to determine the 30-day incidence of MDRO colonization (Aim 2). Finally, we will explore whether participants who are colonized with MDROs are more likely to develop bacterial bloodstream infections with these organisms (Aim 3).

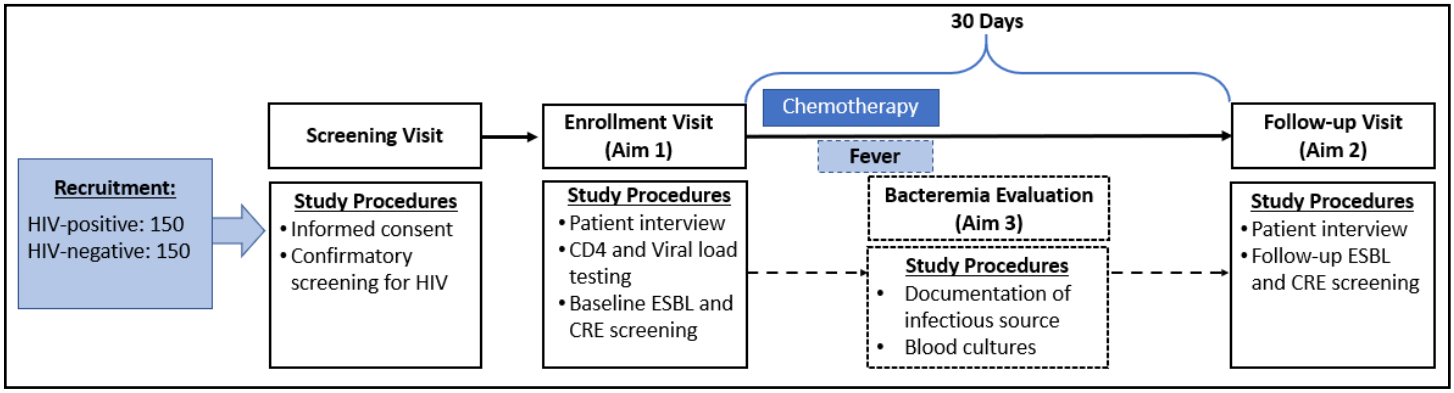

Figure 1. Flow diagram of study procedures by research aim. All participants will complete three visits: screening, recruitment, and enrollment. Only participants who develop fever will be complete the infectious evaluation.

Aim I: Define the association between HIV-status and prevalence of MDRO gastrointestinal colonization among patients with cancer in Uganda.

Participant Recruitment and Eligibility: Participants will be recruited from the UCI outpatient clinics and the adult oncology wards using established recruitment procedures. For outpatients, study staff will work directly with UCI physicians to identify eligible patients. For inpatients, study staff will work directly with the ward charge nurse to identify eligible patients. Table 1 shows details regarding inclusion and exclusion criteria.

Over a 12-month period, we will enroll a convenience sample of 300 participants. Since our exposure of interest is HIV-seropositivity, we aim to enroll 150 HIV-positive and 150 HIV-negative participants. To ensure a representative sampling of tumor types, we will divide enrollment between those with solid tumors and hematologic malignancies (See Statistical Considerations).

Table 1. Inclusion and exclusion criteria for study enrollment

Inclusion Criteria
• Adult patients*
• New diagnosis of cancer
• First dose of chemotherapy prescribed
Exclusion Criteria
• Already receiving chemotherapy
• On hormonal therapy alone (e.g., tamoxifen for breast cancer, flutamide for prostate cancer)¥

*At UCI, adults are considered those 18 years or older.
¥Regimens with low risk of chemotherapy-related infection.

Study Procedures:

a) *Screening Visit:* After obtaining informed consent, we will review the participant's medical records to confirm their HIV serostatus. If a participant is reported to be HIV-negative, we will review their medical record to ensure there is a negative HIV test within the past 30 days. If test results cannot be found, we will screen the participant for HIV using the HIV 1/2 immunoassay. For participants with hematologic malignancies, we will leverage our ongoing study *Hematologic Cancer Patients with Febrile Neutropenia in Uganda* to provide HIV screening; for participants with solid tumors, we will provide resources for screening through this study.

b) *Enrollment Visit:* This visit will occur immediately before chemotherapy is initiated. Study staff will interview the participant and review medical records to obtain baseline demographics, including age, medical comorbidities, cancer type, and planned treatment regimen. We will also document any antibiotic exposure and hospital admissions within the past 30 days. For those who are HIV-positive, we will record the date of diagnosis, current antiretroviral therapy (ART), prior ART regimens, current use of prophylactic antibiotics, and history of opportunistic infections. We will also obtain baseline CD4 count and HIV viral load testing.

To determine the baseline prevalence of MDRO colonization, we will screen participants for ESBL and CRE using a self-administered perirectal swab. The swabs will be placed in Aimes media and transported to the Makerere University Clinical Microbiology Laboratory. The samples will be vortexed and 100 µL of the fluid inoculated onto selective chromogenic agar plates to detect MDROs (Figure 3).[29] We will use HardyChrome ESBL media to detect ESBL and HardyChrome CRE media to detect CRE. The colonies identified on the selective media will be subcultured for bacterial identification and antimicrobial susceptibility testing using disk diffusion as per the Clinical and Laboratory Standards Institute criteria.[30] These isolates will be cryopreserved for future sequencing to detect molecular mechanisms of resistance.

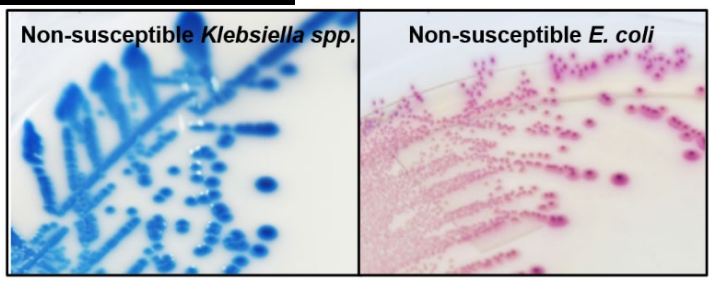

Figure 3. HardyChrome selective and differential chromogenic agar showing growth of carbapenem-resistant *Klebsiella* spp (left) and carbapenem-resistant *Escherichia coli* (right).

Statistical Considerations and Sample Size: To obtain a representative distribution of cancer-types, we will divide the enrollment between those with solid tumors and hematologic malignancies. Approximately 200 patients with newly diagnosed hematologic malignancies present to the UCI annually, 40-50 of which are HIV-positive. Since we anticipate a 75% recruitment rate, we expect to enroll 35 participants with hematologic malignancies who are HIV-positive along with 35 participants who are HIV-negative. We will recruit the remaining 230 participants from those with solid tumors, 115 of which will be HIV-positive and 115 HIV-negative. To account for temporal trends that may occur in MDRO colonization, we will use frequency matching to enroll an equal number of HIV-positive and HIV-negative participants each month.

The primary outcome will be prevalence of MDRO (ESBL or CRE) gastrointestinal colonization prior to treatment initiation, and the primary exposure will be HIV serostatus. Table 2 shows the minimum detectable prevalence ratio (PR) for colonization comparing HIV-positive to HIV-negative participants for a range of colonization rates among HIV-seronegative participants.[24] We will use Poisson regression with robust standard errors to test whether HIV serostatus is associated with colonization after adjusting for important demographic and clinical characteristics.

Table 2. Minimum detectable prevalence ratio (PR) for gastrointestinal colonization with multidrug-resistant organisms*

Frequency of Colonization Among HIV-negative participants	Minimum Detectable PR
15%	1.9
25%	1.6
35%	1.5

*Given 150 HIV-positive and 150 HIV-negative patients and assuming 80% power and two-sided type I error rate of 0.05.

The secondary outcome will be the prevalence of MDRO gastrointestinal colonization prior to treatment initiation in HIV-positive participants only. Similar Poisson regression models will be used to test for associations between uncontrolled versus well-controlled HIV disease, as determined by CD4 count and HIV viral suppression. We will consider an HIV viral load of <1000 copies/mL to be a suppressed viral load.

Aim 2: Assess the factors associated with incident MDRO colonization in the first 30-days after initiation of chemotherapy.

For participants who were not colonized with MDROs at the time of study enrollment, we will evaluate the factors associated with incident MDRO colonization within 30 days after chemotherapy is initiated.

Study Procedures:

c. *Follow-up Visit:* We will prospectively follow the participants for 30 days after the first dose of chemotherapy has been administered. Participants will attend a final study visit to assess 30-day MDRO colonization status. Study staff will interview the participant and review the medical record. We will record any chemotherapy that is received, hospital admissions that occurred, and antibiotics that were used in the past 30-days. At this visit, participants will undergo repeat testing for gastrointestinal colonization with ESBL and CRE using a perirectal swab as described in Aim 1.

Statistical Considerations and Sample Size: The primary outcome will be incidence of MDRO colonization during the first 30-days following chemotherapy initiation, and the primary exposure will be HIV status. We will assume that 65-85% of the HIV-negative participants and 50-72% of the HIV-positive participants will not be colonized with MDROs at baseline. Consequently, we anticipate that 98-128 HIV-negative participants and 75-

108 HIV-positive participants will be available for incidence analysis. Table 3 shows the relative risk for incidence of colonization comparing HIV-positive to HIV-negative participants, for a range of assumed colonization incidence rates among HIV-negative participants.[24] As in Aim 1, we will use Poisson regression with robust standard errors to test whether HIV serostatus is associated with incident colonization after adjusting for important demographic and clinical characteristics. While we do not expect many participants to die during the study period, we will consider using time-to-event analysis methods that accommodate death as a competing risk for colonization if there is higher than expected mortality among participants during the follow-up period.

Table 3. Minimum detectable relative risk (RR) for incidence of gastrointestinal colonization with multi-drug resistant organisms comparing HIV-seropositive to HIV-seronegative patients.

Incidence of colonization among HIV-negative participants	Minimum detectable RR
10%	2.6
15%	2.2
20%	2.0

*Given 75 HIV-positive and 100 HIV-negative patients and assuming 80% power and two-sided type I error rate of 0.05.

Secondary analyses will include identification of additional factors that are associated with increased risk of MDRO colonization during the study time period. For participants with HIV, Poisson regression models will be used to test for associations between uncontrolled versus well-controlled HIV disease, as determined by CD4 count and HIV viral suppression.

Aim 3. Investigate whether gastrointestinal colonization with an MDRO is associated with an increased risk of developing a bacterial bloodstream infection with that organism.

We will examine whether participants who are colonized with MDROs at the time of chemotherapy initiation are at higher risk of developing a subsequent bacterial bloodstream infection with that organism.

Study Procedures We will prospectively follow the participants for 30-days after chemotherapy is initiated and monitor for development of bacterial bloodstream infections. Patients who develop fever and present to the UCI will receive blood cultures as part of our ongoing prospective cohort studies: *Hematologic Cancer Patients with Febrile Neutropenia in Uganda* and *Post-Chemotherapy Febrile Illness in Patients with Solid Tumors*. In these study protocols, participants who develop fever as an outpatient, present to the UCI, and are admitted to the hospital have blood cultures drawn at the time of hospital admission. For participants who develop fever while admitted to the hospital, blood cultures are drawn at the time that fever is detected.

If a participant is admitted to the hospital for fever evaluation, our study staff will record the date of hospital admission and the suspected source of infection. They will then follow the participant through the hospital stay and record all blood culture results, antibiotics used, and date of hospital discharge.

Statistical Considerations and Sample Size: Our primary outcome will be development of an MDRO bloodstream infection, and our primary exposure will be MDRO colonization at the initiation of chemotherapy. Based on previous studies, we anticipate that 30-40% of those with hematologic malignancy will develop fever, and 30-40% of these will have bacteremia. Thus, of the 70 participants with hematologic malignancies, we anticipate that 21-28 will develop fever, and 6-11 of these will have a bacterial bloodstream infection. For those with solid tumors, we anticipate that 20-30% will develop fever, and 15-20% will have bacteremia. Thus, of the 230 participants with solid tumors, we anticipate that 46-69 will develop fever and 7-14 will have a bacterial bloodstream infection. Of the 13-25 total participants expected to have bloodstream infections, we anticipate that 50-60% (7-15) will have an infection with an MDRO. Due to the few expected events, this aim will be exploratory. We will use time-to-event analysis methods to test for an association between baseline MDRO colonization and incidence of MDRO bloodstream infection, treating deaths without infection as a competing risk. We will analyze colonization and infection events as ESBL and CRE combined as well as each individually.

FUTURE DIRECTIONS

The proposed studies will provide foundational data for my career as a physician-scientist who designs and tests evidence-based strategies to implement antimicrobial stewardship programs in low-resource settings. The proposed CFAR NIA award will serve as an excellent complement to my recently submitted NIH K08 mentored research award, in which I plan to use principles of implementation science to identify barriers to initiating guideline-recommended antibiotics at UCI and address these barriers using implementation strategies. Understanding how HIV-status affects treatment-related infections is critical to developing rational guidelines for antibiotic use in patients with cancer who live in HIV-endemic settings. I hope to use the results of the CFAR NIA to develop a multi-site prospective cohort study to determine whether empiric antibiotic therapy selection guided by MDRO colonization status improves outcomes among patients with cancer who have HIV.

BIBLIOGRAPHY & REFERENCES

1. Sasco AJ, Jaquet A, Boidin E, et al. The challenge of AIDS-related malignancies in sub-Saharan Africa. PloS one 2010;5:e8621-e.

2. Arega B, Woldeamanuel Y, Adane K, Sherif AA, Asrat D. Microbial spectrum and drug-resistance profile of isolates causing bloodstream infections in febrile cancer patients at a referral hospital in Addis Ababa, Ethiopia. Infect Drug Resist 2018;11:1511-9.

3. Lubwama M, Adams S, Muwonge C, et al. 169. Multidrug-Resistant Bacteria Are Common Cause of Neutropenic Fever and Increase Mortality Among Patients with Hematologic Malignancies in Uganda. Open Forum Infectious Diseases; 2019: Oxford University Press US. p. S108-S9.

4. Mohammed HB, Yismaw MB, Fentie AM, Tadesse TA. Febrile neutropenia management in pediatric cancer patients at Ethiopian Tertiary Care Teaching Hospital. BMC Res Notes 2019;12:528.

5. Mvalo T, Eley B, Bamford C, et al. Bloodstream infections in oncology patients at Red Cross War Memorial Children's Hospital, Cape Town, from 2012 to 2014. Int J Infect Dis 2018;77:40-7.

6. von Knorring N, Nana T, Chibabhai V. Cumulative antimicrobial susceptibility data for a tertiary-level paediatric oncology unit in Johannesburg, South Africa. South African Journal of Oncology 2019;3:8.

7. Cornejo-Juárez P, Pérez-Jiménez C, Silva-Sánchez J, et al. Molecular analysis and risk factors for Escherichia coli producing extended-spectrum β-lactamase bloodstream infection in hematological malignancies. PLoS One 2012;7.

8. Cornejo-Juárez P, Suárez-Cuenca JA, Volkow-Fernández P, et al. Fecal ESBL Escherichia coli carriage as a risk factor for bacteremia in patients with hematological malignancies. Supportive Care in Cancer 2016;24:253-9.

9. Woerther P-L, Micol J-B, Angebault C, et al. Monitoring antibiotic-resistant enterobacteria faecal levels is helpful in predicting antibiotic susceptibility of bacteraemia isolates in patients with haematological malignancies. Journal of medical microbiology 2015;64:676-81.

10. Liss B, Vehreschild J, Cornely O, et al. Intestinal colonisation and blood stream infections due to vancomycin-resistant enterococci (VRE) and extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBLE) in patients with haematological and oncological malignancies. Infection 2012;40:613-9.

11. Wilmore SMS, Kranzer K, Williams A, et al. Carriage of extended-spectrum beta-lactamase-producing Enterobacteriaceae in HIV-infected children in Zimbabwe. Journal of medical microbiology 2017;66:609-15.

12. Nelson E, Kayega J, Seni J, et al. Evaluation of existence and transmission of extended spectrum beta lactamase producing bacteria from post-delivery women to neonates at Bugando Medical Center, Mwanza-Tanzania. BMC research notes 2014;7:279.

13. Tellevik MG, Blomberg B, Kommedal Ø, Maselle SY, Langeland N, Moyo SJ. High prevalence of faecal carriage of ESBL-producing Enterobacteriaceae among children in Dar es Salaam, Tanzania. PloS one 2016;11.

14. Reinheimer C, Keppler OT, Stephan C, Wichelhaus TA, Friedrichs I, Kempf VA. Elevated prevalence of multidrug-resistant gram-negative organisms in HIV positive men. BMC infectious diseases 2017;17:206.

15. Nwosu FC, Avershina E, Wilson R, Rudi K. Gut microbiota in HIV infection: implication for disease progression and management. Gastroenterology research and practice 2014;2014.

16. Gaskell KM, Feasey NA, Heyderman RS. Management of severe non-TB bacterial infection in HIV-infected adults. Expert review of anti-infective therapy 2015;13:183-95.

17. Bender Ignacio R, Ghadrshenas M, Low D, Orem J, Casper C, Phipps WJJogo. HIV Status and Associated Clinical Characteristics Among Adult Patients With Cancer at the Uganda Cancer Institute. 2017;4:1-10.

18. Sangare S, Maiga A, Guindo I, et al. Prevalence of extended-spectrum beta-lactamase-producing Enterobacteriaceae isolated from blood cultures in Africa. Medecine et maladies infectieuses 2015;45:374-82.

19. Saravanan M, Ramachandran B, Barabadi H. The prevalence and drug resistance pattern of extended spectrum β–lactamases (ESBLs) producing Enterobacteriaceae in Africa. Microbial pathogenesis 2018;114:180-92.

20. Storberg V. ESBL-producing Enterobacteriaceae in Africa–a non-systematic literature review of research published 2008–2012. Infection ecology & epidemiology 2014;4:20342.

21. Garcia-Vidal C, Cardozo-Espinola C, Puerta-Alcalde P, et al. Risk factors for mortality in patients with acute leukemia and bloodstream infections in the era of multiresistance. PloS one 2018;13:e0199531.

22. Scheich S, Weber S, Reinheimer C, et al. Bloodstream infections with gram-negative organisms and the impact of multidrug resistance in patients with hematological malignancies. Annals of hematology 2018;97:2225-34.

23. Lalla RV, Bowen J, Barasch A, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer 2014;120:1453-61.

24. Lewis JM, Lester R, Garner P, Feasey NA. Gut mucosal colonisation with extended-spectrum beta-lactamase producing Enterobacteriaceae in sub-Saharan Africa: a systematic review and meta-analysis. Wellcome Open Research 2019;4:160.

25. Mulu W, Yizengaw E, Alemu M, et al. Pharyngeal colonization and drug resistance profiles of Morraxella catarrrhalis, Streptococcus pneumoniae, Staphylococcus aureus, and Haemophilus influenzae among HIV infected children attending ART Clinic of Felegehiwot Referral Hospital, Ethiopia. PloS one 2018;13.

26. Hosuru Subramanya S, Bairy I, Nayak N, Padukone S, Sathian B, Gokhale S. Low rate of gut colonization by extended-spectrum β-lactamase producing Enterobacteriaceae in HIV infected persons as compared to healthy individuals in Nepal. PloS one 2019;14:e0212042-e.

27. Marbou WJT, Kuete V. Bacterial resistance and immunological profiles in HIV-infected and non-infected patients at Mbouda AD LUCEM Hospital in Cameroon. Journal of Infection and Public Health 2017;10:269-76.

28. Park LS, Tate JP, Sigel K, et al. Association of viral suppression with lower AIDS-defining and non–AIDS-defining cancer incidence in HIV-infected veterans: a prospective cohort study. Annals of internal medicine 2018;169:87-96.

29. Satlin MJ, Chavda KD, Baker TM, et al. Colonization with levofloxacin-resistant extended-spectrum β-lactamase-producing enterobacteriaceae and risk of bacteremia in hematopoietic stem cell transplant recipients. Clinical Infectious Diseases 2018;67:1720-8.

30. Clinical, Institute LS. Performance standards for antimicrobial susceptibility testing of anaerobic bacteria: informational supplement: Clinical and Laboratory Standards Institute (CLSI); 2009.

A. Protection of Human Subjects

A.1. Human subjects involvement and characteristics. Specimens and clinical data will be collected from participants who have consented to enroll in our study. All adults >18 years of age who present to the Uganda Cancer Institute (UCI) with a newly diagnosed solid tumor or hematologic malignancy and who receive a prescription for their first dose of chemotherapy will be eligible for enrollment. We will collect samples and clinical data from 300 participants, of whom 150 are HIV-positive and 150 are HIV-negative. We anticipate that 70 patients with hematologic malignancies and 130 patients with solid tumors will be included. No vulnerable or special populations will be included in the study. Written informed consent will be obtained from all participants.

A.2. Source of Materials. All procedures will be completed over the course of three visits. At the *screening visit*, participants will be screened for HIV using the HIV 1/2 immunoassay. At the *enrollment visit*, participants will be screened for gastrointestinal carriage of multidrug-resistant organisms using a perirectal swab. The cultured bacteria will be frozen and stored for future analysis. Data obtained from enrolled subjects includes demographic characteristics, oncologic and medical history, HIV history, and history of prior infections. For those who are HIV-positive, we will obtain a baseline CD4 count and HIV viral load. We will then follow the participants prospectively for 30-days. Participants who develop fa ever will have blood cultures drawn to test for bacterial infections. All participants will complete a *follow-up visit* where they will be screened for MDRO gastrointestinal colonization using a perirectal swab. All samples and data will be collected in coded identifiers and access to identifiable participant information will be protected and limited to the principal investigator (PI) and study coordinator.

A.3. Potential risks. Risks associated with blood draws include pain, hematoma, and excess bleeding. Since blood draws could also worsen pre-existing anemia, blood collection will be limited to those with hemoglobin >8. Learning HIV testing results may cause stress. Risks associated with perianal swabs include discomfort or embarrassment during collection. Any anti-retroviral therapy or chemotherapy administered during the study will be given and patients will be monitored by UCI physicians independent of study procedures. All samples will be de-identified to maintain participant confidentiality and potential identifying sequence information will not be made public without informed consent.

B. Adequacy of protection against risks.

B.1. Recruitment and informed consent. Participant enrollment will follow well-established protocols for patient recruitment and enrollment for UCI-Fred Hutch studies. IRB-approved consent forms are reviewed with patients, including the purpose of the study, study procedures, risks and benefits, and alternatives to participation. All consent forms are printed in English (the official language of Uganda) and Luganda (the most common tribal dialect in Kampala). For those with limited literacy, provisions are made to have the script read to them in English or Luganda. Potential participants and family members will have adequate time to review consent forms and provided with the entire copy of the consent documents to keep. Original signed consent forms are maintained in a secured designated location at UCI. Participants have an opportunity to agree to future use of any specimens collected by signing a future use of specimens consent form; only participants who sign this form will have their samples stored for future analysis.

B.2. Protection against risk. Confidentiality will be protected by the following mechanisms: 1) All study staff at the UCI and Fred Hutch are trained in Good Clinical Practices and practices to protect confidentiality; 2) Access to UCI-Fred Hutch study databases is password protected; 3) All participants are assigned a unique study number, which uses an indirect identifier in databases and communications; and 4) Study numbers are kept in a secured location accessible only by designated study staff. The study PI, [redacted], will be available to answer questions. There will also be a study clinician on call 24-hours a day, 365 days per year, who can be reached by calling a mobile study phone carried by the clinician. Participants will be given clear instructions for reaching the study clinician in the event of an emergency or question. Participants may refuse to answer any questions and may refuse to complete any study procedure at any time without penalty.

B.3. Potential benefits of the proposed research to the subjects and others. Individual participants may benefit from learning their HIV-serostatus, which will allow them to be enrolled in HIV care. Participant CD4 count and viral load can inform their HIV control and these results will be provided to their HIV care provider on request. Participants will be screened for gastrointestinal carriage of MDROs, which could guide choices of antimicrobial regimens in patients who go on to develop fever during the course of their cancer treatment.

B.4. Importance of knowledge to be gained. The proposed study seeks to define the way in which HIV-status affects gastrointestinal colonization with MDR bacteria in patients with cancer. This will serve as the basis to build antimicrobial stewardship and infection-control practices. It will also help us identify risk factors for developing MDR bacterial bloodstream infections in patients with HIV who are being treated for cancer.