# SEMI ANNUAL RESEARCH REPORT

January – July 2015

**Acknowledgements**

This report would not be possible without the hard work and dedication of the investigators, research coordinators, and administrative support staff who make up AMPATH's research community. We appreciate all their contributions to this report. AMPATH's co-directors of research, Professors Winstone Nyandiko and Rachel Vreeman deserve special recognition for their constant support in the development of this report. Their leadership continues to strengthen the Research Program.

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*www.medicine.iu.edu/ampathresearch*

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# OVERVIEW

The start of 2015 has brought some positive developments for the AMPATH Research Program. In April, the Chandaria Cancer and Chronic Disease building opened its doors along with a new floor dedicated to research and clinical trials. This allowed us to consolidate a number of our research projects into one location from our two research compounds and other locations around Eldoret. This new facility will provide a strong foundation for the future growth of the AMPATH research program and provides plenty of room to grow. Centrally located in the heart of the Moi medical campus, the CCCDC building is an ideal home for research. It offers 4 new conference rooms that will be equipped with dedicated conferencing equipment, secure storage space, project offices, and plenty of room for trainings and other research related activities.

Along with the new building, the AMPATH Program has continued to strengthen its global research collaborations. Since the start of the year, AMPATH's research working groups have reviewed more than 50 new study proposals – a slightly higher number of studies than had been reviewed at the same point in the previous year.

During the same period the number of publications from AMPATH investigators increased dramatically. Since the start of the year, AMPATH investigators have more than 40 manuscripts published in peer reviewed journals – nearly the same number of published articles in all of 2014. In addition, 32 posters and abstracts were presented at professional conferences and meetings by AMPATH investigators.

Despite these strong gains, overall funding for new research continued to be slow in the first half of 2015. In the first 6 months of this year, investigators reported only 4 new research and training awards totaling just under US$1 million. While it is not uncommon for awards to be underreported at the start of the year, this amount is lower than in previous periods.

The following report includes updates from 44 active AMPATH research studies along with brief updates on the status of funding for research and publications produced in 2015. It was compiled with the assistance of AMPATH investigators, research coordinators, and assistants from more than 15 institutions in Kenya and North America. We begin the report with a brief summary of AMPATH research funding awarded in 2014 and continue with a description of the publications produced during the year. We conclude with brief project updates provided by AMPATH investigators listed alphabetically by the study title.

*Please visit the AMPATH Research Network Website to download a copy of this and past reports, www.medicine.iu.edu/ampathresearch.*

# GRANTS

The number of new awards for AMPATH research projects remained low in the first half of 2015 continuing trends from the previous 6 months. Investigators reported only 4 new awards from January to July 2015. While it is not unusual for new awards to be under reported in the first 6 months of the year, there are signs that the second half of the year will provide more positive growth. The number of new study proposals submitted to external funders continued to increase from the previous 6 months and it was reported that several new awards would likely be received in the second half of 2015. New awards in 2015 brought the total level of program direct awards to nearly US$ 90 million since the program received its first research award in 1998 (See Figure 1).

Funding from the National Institutes of Health (NIH) remains the largest source of funding for AMPATH's research projects. All of the new research awards during this period were from the NIH.

# PUBLICATIONS

AMPATH investigators were publishing at a faster rate than in same period last year. More than 40 manuscripts from AMPATH investigators appeared in peer reviewed journals – the same number that appeared in all of 2015 (See Figure 4). A bibliography of publications from the first half of 2015 is included at the end of this report.

In addition, AMPATH investigators were actively involved in preparing publications for submission to a wide range of professional conferences and journals. The AMPATH Publications Committee, which reviews all publications produced from AMPATH research projects, reviewed a total of 86 draft publications during this period this is up from 79 during the same period last year. Around 61 percent of the publications reviewed were abstracts and nearly 11 percent were poster presentations presented at professional conferences (See Figure 5).

# STUDY REPORTS

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| **Study Title** | **A Formative Study to Develop Culturally Valid Psychosocial Assessment Tools and Interventions to Promote Family Well-Being in Kenya** |
| **Principal Investigator(s)** | Eve Puffer, Duke University<br>David Ayuku, Moi University |
| **Co-Investigator(s)** | |
| **Working Group(s)** | Behavioral and Social Sciences |
| **Description** | The purpose of this study is to assess family functioning and children's psychosocial well-being in a Kenyan context in order to develop culturally tailored measures and family-based intervention approaches. Many measures of child well-being, mental health, and behavior were developed in the West and are inappropriate or insufficient for use in Kenya. The same is true for measures of family well-being. Culturally tailored measures are needed to assess important aspects of family relationships, such as communication, conflict, and parenting. Such measures will be useful in identifying children and families who are in need of treatment and in measuring the impact of interventions for children and families to identify which treatments work best. We will use a variety of methods to develop assessment tools to measure family functioning and mental health. These will include focus groups with community members (both youth and adults), community leaders, and people already working in the field of mental health in the communities. Methods will also involve questionnaires and observational measures, in which family and child behaviors are directly observed and assessed. A family-based intervention to address psychosocial concerns will be developed using a community-based participatory approach. |
| **Site(s)** | |
| **Project Period** | 5/28/2013 – 4/16/2016 |
| **Funding Status** | Funded – Grand Challenges Canada |
| **Direct Award (USD)** | $129,000 |
| **Update** | We completed pilot testing of the family functioning measure in Pioneer and Webuye communities. In addition, observational measures and in-depth interviews were piloted in Pioneer as part of the process to create and validate family functioning ratings scales within these measures. The formulation and piloting of these three measures prepares us for the quantitative validation of the survey in the future. |
| **Future Plans** | The validity portion of the study will include both survey administration as well as in-depth interviews and observations with families in these areas. The validity study will be done in order to determine whether the survey measure which is currently being pilot tested accurately predicts diagnosis of both family functioning issues and mental health status of individuals within a family. Concurrently, we will begin the family therapy |

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| | intervention pilot informed by community advisory committees. The family therapy intervention will address issues raised in the focus group qualitative data in order to make the intervention culturally relevant for peri-urban and rural communities in Kenya. A technology tool will be created to assist lay counselors in conducting family therapy in the community. Thus, the study will evaluate both the family therapy intervention itself as well as the technology tool's efficacy to assist lay counselors. |
| **Publication(s)** | |

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|---|---|
| **Study Title** | **A Stage 2 Cognitive Behavioral Trial, Reduce Alcohol First in Kenya Intervention (RAFIKI)** |
| **Principal Investigator(s)** | Rebecca Papas, Brown University<br>B. Gakinya, Moi University |
| **Co-Investigator(s)** | Maisto, S. Martino, S. Baliddawa, J. Sidle, J. Hogan, J. Carroll, K. |
| **Working Group(s)** | Adult Medicine, Behavioral and Social Sciences |
| **Description** | This study will determine whether a group cognitive-behavioral therapy intervention that demonstrates preliminary evidence of reducing alcohol use among HIV-infected outpatients in western Kenya is effective when compared against a group health education intervention in a large sample over a longer period of time. It will be delivered by paraprofessionals, individuals with limited professional training. This approach is consistent with successful cost-effective models of service delivery in resource-limited settings in which paraprofessionals (e.g. clinical officers, traditional birth attendants and peer counselors) are trained. |
| **Site(s)** | Iten District Hospital, Moi Teaching and Referral Hospital , Turbo Health Centre, Webuye District Hospital |
| **Project Period** | 11/1/2011 – 8/31/2016 |
| **Funding Status** | Funded – NIH - National Institute on Alcohol Abuse and Alcoholism (NIAAA) |
| **Direct Award (USD)** | $2,268,832 |
| **Update** | The 5-year RAFIKI RCT, which examines the efficacy of a group Cognitive Behavioural Therapy (CBT) intervention to reduce alcohol use when compared against a group health education intervention, is halfway through its fourth year of recruitment. We have randomized 563 total participants, and have completed recruitment and intervention for cohorts 1-19. In the January-June 2015 reporting period, we recruited and randomized 115 participants. Recruitment and retention are progressing within expectations according to our NIH specific aims. We have had no immediately reportable serious adverse events during the course of this study. |
| **Future Plans** | Build on progress made so far and reach our recruitment target. |
| **Publication(s)** | |

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| **Study Title** | **A5225/HiFLAC Protocol - A Phase I/II Dose-Finding Study of High-Dose Fluconazole Treatment in AIDS-Associated Cryptococcal Meningitis** |
| **Principal Investigator(s)** | John Sidle, Indiana University<br>Abraham Siika, Moi University |
| **Co-Investigator(s)** | Lagat, D. |
| **Working Group(s)** | Adult Medicine, Behavioral and Social Sciences |
| **Description** | A5225/HiFLAC is a phase I/II dose escalation and validation study of the safety, tolerability, and therapeutic effect of an induction-consolidation strategy of high-dose fluconazole alone for the treatment of cryptococcal meningitis (CM) in HIV-infected participants. The study will proceed in two stages. In Stage 1, Dose Escalation, up to three induction doses of fluconazole will be tested in sequentially enrolled cohorts. Stage 2, Dose Validation, will not open until the maximum tolerated dose (MTD) of fluconazole has been identified in Stage 1. In Stage 2, induction doses of fluconazole that are found to be safe in Stage 1 will be tested in simultaneously enrolled cohorts. In each stage, participants will be randomized at entry into Step 1. Over the course of the study, participants will register to subsequents steps (Steps 2-4) based on their initial randomization and/or their response to treatment. The study steps are: Step 1: Induction therapy with either high dose fluconazole or ampho B; Step 2: Induction following early ampho B intolerance (only for participants randomized to ampho B treatment in Step 1) (fluconazole at 400-800 mg daily); Step 3: Consolidation therapy (fluconazole 400 mg daily); and Step 4: Maintenance therapy (fluconazole 200 mg daily). |
| **Site(s)** | Moi Teaching and Referral Hospital |
| **Project Period** | 5/18/2011 – 12/31/2013 |
| **Funding Status** | Funded – NIH - National Institute of Allergy and Infectious Diseases (NIAID) |
| **Direct Award (USD)** | Not Reported |
| **Update** | The site has enrolled 5 participants into stage 2 ( Version 3.0 ) of the protocol and follow up is going on well. In total, 22 participants have been enrolled into the study, this is out of the site target of 30. Globally, accrual is 122 out of the protocol sample size of 168. |
| **Future Plans** | The site plans to continue enrolling participants and hopefully attain accrual target of 30 participants. |
| **Publication(s)** | |

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| **Study Title** | **A5263 'A Randomized Comparison of Three Regimens of Chemotherapy with Compatible Antiretroviral Therapy for Treatment of Advanced AIDS-KS in Resource-Limited Settings'** |

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| **Principal Investigator(s)** | Abraham Siika, Moi University |
| **Co-Investigator(s)** | |
| **Working Group(s)** | |
| **Description** | This is an ACTG prospective, randomized, active-controlled clinical trial in which participants will be randomized 1:1:1 to oral etoposide (ET) plus antiretroviral therapy (ART), bleomycin and vincristine (BV) plus ART, or paclitaxel (PTX) plus ART. The primary objective will be to compare the clinical efficacy of two regimens, oral ET plus ART and BV plus ART, to PTX plus ART for initial treatment of advanced stage AIDS-KS. |
| **Site(s)** | |
| **Project Period** | 4/1/2014 – 2/28/2021 |
| **Funding Status** | Funded – NIH - AIDS Clinical Trials Group (ACTG) |
| **Direct Award (USD)** | unknown |
| **Update** | The Moi University Clinical Research Center has recently commenced recruitment for this study. There are 2 participants already enrolled against a target of 100 for the Eldoret site. There are currently 110 participants enrolled into this multi-centre, multi-national clinical trial. |
| **Future Plans** | The site will continue screening and enrolling eligible participants into the study. |
| **Publication(s)** | |

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| **Study Title** | **A5264/AMC067 A Randomized Evaluation of Antiretroviral Therapy Alone or with Delayed Chemotherapy versus Antiretroviral Therapy with Immediate Adjunctive Chemotherapy for Treatment of Limited Stage AIDS-KS in Resource-Limited Settings (REACT-KS)** |
| **Principal Investigator(s)** | Abraham Siika, Moi University |
| **Co-Investigator(s)** | Busakhala, N. Njiru, E. |
| **Working Group(s)** | Adult Medicine, Behavioral and Social Sciences |
| **Description** | A5264/AMC 067 is a phase III, open-label, prospective, randomized study stratified by CD4+ lymphocyte cell count and antiretroviral therapy (ART) history. The study will compare the KS tumor outcomes of ART alone or with delayed Etoposide (ET) to ART with immediate ET, for initial treatment of limited stage AIDS-KS in chemotherapy and radiation treatment na- HIV-1 infected participants who are currently not receiving ART |
| **Site(s)** | Moi Teaching and Referral Hospital |
| **Project Period** | 11/28/2012 – 6/30/2014 |
| **Funding Status** | Funded – NIH - National Institute of Allergy and Infectious Diseases (NIAID) |

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| **Direct Award (USD)** | Not Reported |
| **Update** | There are currently 171 participants enrolled into this multi-center clinical trial. Of these, 16 are from the Eldoret site. Enrollment into this protocol has been very slow both globally and at our site, in the last 6 months we managed to enroll 3 participants. The participants on follow up are doing well. |
| **Future Plans** | The site plans to continue screening and enrolling participants into the study. |
| **Publication(s)** | |

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| **Study Title** | **A5273 'Multicenter Study of Options for Second-Line Effective Combination Therapy (SELECT)'** |
| **Principal Investigator(s)** | Abraham Siika, Moi University |
| **Co-Investigator(s)** | Dr Faraj Some |
| **Working Group(s)** | Adult Medicine, Behavioral and Social Sciences |
| **Description** | A5273 is a phase III, dual-arm, open-label, randomized, non-inferiority study for participants who are on a failing non-nucleoside reverse transcriptase inhibitor (NNRTI)-containing first-line regimen. The study will evaluate the difference in virologic failure rate between two treatment arms: lopinavir/ritonavir plus raltegravir (LPV/r + RAL) and LPV/r plus best available nucleos(t)ide reverse transcriptase inhibitors (NRTIs).The NRTIs to be used will be specified by the site prior to randomization. The primary objective for this study will be to determine whether the combination of LPV/r + RAL is associated with virologic efficacy that is non-inferior to that achieved with LPV/r + best-available NRTIs by 48 weeks of follow-up. |
| **Site(s)** | Moi Teaching and Referral Hospital |
| **Project Period** | 1/22/2013 – 10/3/2016 |
| **Funding Status** | Funded – NIH - AIDS Clinical Trials Group (ACTG) |
| **Direct Award (USD)** | unspecified |
| **Update** | The study is closed to follow up, all participants exited the study and were transitioned back to primary care provider, AMPATH. Data analysis is ongoing. |
| **Future Plans** | Data analysis is expected to continue. |
| **Publication(s)** | |

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| **Study Title** | **A5274/REMEMBER Reducing Early Mortality and Early Morbidity by Empiric Tuberculosis Treatment Regimens '** |

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| **Principal Investigator(s)** | Abraham Siika, Moi University |
| **Co-Investigator(s)** | Dr David K Lagat |
| **Working Group(s)** | Adult Medicine, Behavioral and Social Sciences |
| **Description** | In this randomized, open-label, phase IV strategy trial, participants from resource-limited settings (RLS) who present with advanced HIV disease and no probable or confirmed tuberculosis (TB), as defined in the current ACTG diagnosis appendix, and who are initiating antiretroviral treatment (ART) will be randomized to one of two strategy arms: immediate, empiric TB treatment (public health approach) or local standard of care TB treatment (individualized approach). The primary endpoint is survival status in the two arms 24 weeks after randomization. AIDS progression (any new WHO Stage 3 or 4 condition), virologic and CD4+ cell response, HIV and TB drug resistance, AND safety and tolerability of, and adherence to HIV and TB drugs will be evaluated, as will the cost-effectiveness of the two strategies. The primary objective is to compare survival probabilities between the two study arms 24 weeks after randomization. |
| **Site(s)** | Moi Teaching and Referral Hospital |
| **Project Period** | 10/10/2012 – 12/31/2016 |
| **Funding Status** | Funded – NIH - AIDS Clinical Trials Group (ACTG) |
| **Direct Award (USD)** | Unspecified |
| **Update** | The study is closed to accrual. The site enrolled a total of 70 participants(out of 851 participants enrolled globally). Follow up is going on well and participants have completed 48 weeks of active follow up and are currently on telephone/chart review follow up every three months. |
| **Future Plans** | The plan is to continue with telephone/chart review follow up every three months. |
| **Publication(s)** | |

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| **Study Title** | **A5288 'Management Using the Latest Technologies in Resource-limited Settings to Optimize Combination Therapy After Viral Failure (MULTI-OCTAVE)'** |
| **Principal Investigator(s)** | Abraham Siika, Moi University |
| **Co-Investigator(s)** | Dr Beatrice Wangari Ndege |
| **Working Group(s)** | Adult Medicine, Behavioral and Social Sciences |
| **Description** | A5288 is an open-label phase IV, prospective interventional, strategy study in resource-limited settings (RLS) for HIV-infected participants with triple-class experience or resistance to [nucleoside reverse transcriptase inhibitors (NRTIs), non-NRTIs (NNRTIs), and protease inhibitors (PIs)] and who are failing their current regimen. The use of novel agents and contemporary management tools that include standard genotyping, plasma viral load (VL) monitoring will be evaluated. The screening genotype results and |

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| | antiretroviral (ARV) history will be used to allocate potential participants to one of the four cohorts and for selection of ARV regimen for each potential participant. At sites where feasible and relevant(including MTRH) the study will also conduct an adherence study. This will be a randomized comparison of cell phone-based adherence intervention plus local standard-of-care adherence procedures (CPI+SOC) versus the SOC adherence procedures. The primary objective of the study is to use novel agents and contemporary management tools, including standard genotyping to select an appropriate third-line regimen, interventions to improve adherence and plasma viral load (VL) monitoring, in order to achieve a ? 65% rate of virologic control at 48 weeks of follow-up |
| **Site(s)** | Moi Teaching and Referral Hospital |
| **Project Period** | 12/18/2013 – 12/31/2015 |
| **Funding Status** | Funded – NIH - AIDS Clinical Trials Group (ACTG) |
| **Direct Award (USD)** | Unspecified |
| **Update** | A total of 319 participants have been enrolled globally in this multi center trial, this is out of the protocol sample size of 500. At Moi University Clinical Research Centre, a total of 21 participants have been enrolled. The site has a target of enrolling 60 participants into this study. |
| **Future Plans** | The site continues to screen potential participants to be enrolled into this study. |
| **Publication(s)** | |

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| **Study Title** | **A5290 A Randomized, Phase 2b Study of a Double-Dose Lopinavir/Ritonavir-Based Antiretroviral Regimen with Rifampin-Based Tuberculosis Treatment versus a Standard-Dose Lopinavir/Ritonavir-Based Antiretroviral Regimen with Rifabutin-Based Tuberculosis Tre** |
| **Principal Investigator(s)** | Abraham Siika, Moi University |
| **Co-Investigator(s)** | Dr. Faraj Some |
| **Working Group(s)** | None |
| **Description** | A5290 is a prospective, randomized (1:1:1), open-label, phase 2b study comparing three lopinavir/ritonavir (LPV/r)-based antiretroviral (ARV) regimens among participants in high tuberculosis (TB) endemic resource-constrained settings undergoing treatment for confirmed or probable TB and requiring protease inhibitor (PI)-based antiretroviral therapy (ART). A two accrual period design will be used, including a full pharmacokinetic (PK) and safety evaluation to be conducted when 54-60 participants enrolled during the accrual period 1 have completed 28 days of ARV treatment and day 12 Â± 2 (after initiation of ART) drug levels are available (an early interim PK and safety evaluation will also be completed when 10-12 participants per arm have completed 28 days of ARV treatment and day 12 Â± 2 drug levels are available). Primary Objective: To compare rates of virologic suppression to < 400 copies/mL at 48 weeks for the two standard dose |

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| | LPV/r and RBT arms versus the double-dose LPV/r and RIF arm. |
| **Site(s)** | Moi Teaching and Referral Hospital |
| **Project Period** | 5/13/2015 – 11/30/2018 |
| **Funding Status** | Funded – NIH - AIDS Clinical Trials Group (ACTG) |
| **Direct Award (USD)** | Unknown |
| **Update** | |
| **Future Plans** | |
| **Publication(s)** | |

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| **Study Title** | **A5297 'An Open-Label, Proof of Concept, Randomized Trial Comparing a LPV/r-Based to an nNRTI-Based Antiretroviral Therapy Regimen for Clearance of Plasmodium falciparum Subclinical Parasitemia in HIV-infected Adults with CD4+ Counts >200 and <500 cells/m** |
| **Principal Investigator(s)** | Abraham Siika, Moi University |
| **Co-Investigator(s)** | Dr. Ronald Tonui |
| **Working Group(s)** | None |
| **Description** | A5297 is a phase I/II, open-label, proof of concept, two-step, two-arm, controlled randomized clinical trial (RCT) to test the superiority of lopinavir/ritonavir (LPV/r)-based antiretroviral therapy (ART) to non-nucleoside reverse transcriptase (nNRTI)-based ART for clearance of Plasmodium falciparum (Pf) subclinical parasitemia (SCP). Participants will be followed for 30 days in order to evaluate parasitemia clearance, Pf parasitemia, gametocytemia, and plasmepsin sequencing. Participants will have blood collected twice at entry, day 3, 6, 9, 12, 20, and 25 and three times for day 15 and day 30. Therefore, on most study days, participants will need to either remain at the clinic for an extended period of time or be willing to return two or three times at approximately 8-hour intervals (see section 6.2 for details). The hypothesis is that in HIV-infected participants with CD4+ counts >200 and <350 cells/mm3, lopinavir/ritonavir (LPV/r)-based ART will be superior to nNRTI-based ART in PCR-defined Plasmodium falciparum (Pf) subclinical parasitemia (SCP) clearance after 15 days of therapy. The primary objective is to compare the proportions of Pf SCP clearance between LPV/r-based and nNRTI based ART in participants after 15 days of therapy (Step 1). |
| **Site(s)** | Moi Teaching and Referral Hospital |
| **Project Period** | 2/27/2014 – 6/1/2016 |
| **Funding Status** | Funded – NIH - AIDS Clinical Trials Group (ACTG) |
| **Direct Award (USD)** | Unknown |

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| **Update** | |
| **Future Plans** | |
| **Publication(s)** | |

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| **Study Title** | **AMPATH - Oncology Institute: HPV and Cervical Cancer in Kenyan Women with HIV/AIDS** |
| **Principal Investigator(s)** | Patrick Loehrer, Indiana University - Purdue University in Indianapolis (IUPUI)<br>Darron Brown, Indiana University - Purdue University in Indianapolis (IUPUI) |
| **Co-Investigator(s)** | Omenge, Orango - C0-Principal Investigator MTRH Kaaria, Alice - Project 1 MTRH Cu-Uvin, Susan - Project 2 Brown |
| **Working Group(s)** | Oncology |
| **Description** | The core objective of this project is to better understand the natural history of oncogenic HPV infections in HIV-infected Kenyan women, and to identify potentially modifiable (and non-modifiable) factors that are associated with progression of oncogenic HPV infection to clinical disease, including cervical cancer. Our central hypothesis is that the incidence, persistence, and spectrum of HPV are all substantially greater in HIV-infected versus non-HIV-infected Kenyan women, and that this explains a higher incidence of cervical neoplasia in HIV-infected populations. We further hypothesize that these and other modifiable factors (such as concurrent STIs, sexual behaviors, nutrition, and environment) disproportionately and adversely impact outcomes of local therapies such as cryotherapy and Loop Electrosurgical Excision Procedure (LEEP) in HIV- infected women. The specific aims of this AMPATH-Oncology Institute are to: 1. Expand the capabilities and expertise of the current laboratories and biobanking capabilities in Kenya through AMPATH and the Kenya Medical Research Institute (KEMRI) 2. Identify potentially modifiable behavioral and biological factors that are associated with the duration of infection with oncogenic HPV and cervical dysplasia in HIV-infected and non-HIV-infected women from western Kenya 3. Assess the risk factors associated with the short and long term results of cryotherapy and LEEP in VIA- positive (including LEEP-eligible) HIV-infected and non-HIV-infected women in western Kenya. 4. Provide biostatistical and data management support for proposed projects in this application and for future pilot projects, and 5. To establish a sustainable, multi-institutional and transdisciplinary mentoring program fostering the development of new cancer researchers in Kenya |
| **Site(s)** | Moi Teaching and Referral Hospital, Center for Global Health Research - KEMRI at Kisumu City, Kenya |
| **Project Period** | 9/19/2014 – 8/31/2019 |
| **Funding Status** | Funded – NIH - National Cancer Institute (NCI) |
| **Direct Award (USD)** | $2,132,402 |

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| **Update** | In February, 2015 a face to face meeting with key stakeholders involved with the U54 met in Eldoret. Pat Loehrer, Darron Brown, Aaron Ermel, Neil Flick, and Susan Cu-Uvin traveled from the US to discuss the grant and plan its Project 1 and 2 commencement. The baseline questionnaires for patients entered onto projects 1 and 2 were evaluated and suggested changes were made to simplify and clarify key components regarding modifiable behaviors. These changes were then submitted to the appropriate IRBs and were approved. The Biostatistics and Data Management Core has completed the construction of the study database and lab supplies for the Translational Core at KEMRI have been sourced. The Mentoring Core has approved four mentees who are currently completing AMPATH new study forms for projects that will be initiated upon the enrollment of patients. Additionally, the Administrative Core has implemented regularly scheduled meetings with each project and core and has established data sharing for the U54. |
| **Future Plans** | Over the next 6 months, we hope to begin enrolling patients into Projects 1 and 2 and to officially establish our External Advisory board and plan their first meeting. We also hope to begin our mentee projects in Eldoret and Kisumu and will be seeking new mentees for the following year. Currently, we are working on establishing a new vendor relationship for the continued procurement of supplies at Kisumu and are currently in the process of obtaining a new study freezer for the AMPATH lab in Eldoret. |
| **Publication(s)** | |

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| **Study Title** | **Biomarkers of Vincristine Toxicity in Kenyan Children** |
| **Principal Investigator(s)** | Jodi Skiles, Indiana University<br>F. Njuguna, Moi University |
| **Co-Investigator(s)** | Skiles, J. |
| **Working Group(s)** | Oncology, Pediatrics |
| **Description** | This study evaluates the presence of peripheral neuropathy induced by Vincristine in Kenyan children receiving chemotherapy. The main purpose is to assess whether the genetic makeup of each child (particular the genotype of CYP3A5) influences drug exposure and subsequent vincristine toxicity. |
| **Site(s)** | Moi Teaching and Referral Hospital |
| **Project Period** | 6/23/2011 – 6/30/2014 |
| **Funding Status** | Funded – NIH |
| **Direct Award (USD)** | $8,743 |
| **Update** | The first of the manuscripts that will result from this work was submitted to NEJM in May 2014. It received good comments, but was ultimately rejected. It was then resubmitted to Journal of Clinical Oncology where it received constructive feedback and the request for the planned 2nd manuscript to be submitted to support the methodology used in this |

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| | paper. The 2nd manuscript was completed and submitted to Journal of Chromatography B where it received constructive feedback and we are in the process of responding to reviewer comments. Once it is accepted for publication, the original manuscript will be re-submitted to Clinical Cancer Research. |
| **Future Plans** | submission/acceptance of 2 additional manuscripts |
| **Publication(s)** | |

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| **Study Title** | **Bridging Income Generation with Gruop Interated Care(BIGPIC)** |
| **Principal Investigator(s)** | Rajesh Vedanthan, Mount Sinai School of Medicine |
| **Co-Investigator(s)** | Dr. Jemimah Kamano |
| **Working Group(s)** | AMWG and CVMD |
| **Description** | The objective of this proposal is to utilize a trans disciplinary implementation research approach to address the challenge of reducing CVD risk in low-resource settings. The research aims at integration of group medical visits and microfinance with the additional social network characteristics.Aim 1: Identify the contextual factors, facilitators, and barriers that may impact integration of group medical visits and microfinance for CVD risk reduction, using a combination of qualitative research methods: 1) baraza; and 2) focus group discussions among individuals with diabetes or at increased risk for diabetes, microfinance group members, and rural health workers. Then develop a contextually and culturally appropriate integrated group medical visit-microfinance model. Aim 2:Evaluate the effectiveness of group medical visits and microfinance groups for CVD risk reduction among individuals with diabetes or at increased risk for diabetes, by conducting a four-arm cluster randomized trial comparing: 1) usual clinical care; 2) usual clinical care plus microfinance groups only; 3) group medical visits only (no microfinance); and 4) group medical visits integrated into microfinance groups. Aim 3: Evaluate the incremental cost-effectiveness of each intervention arm of the trial. |
| **Site(s)** | Bumala A Health Centre, Bumala B Health Centre, Chulaimbo Sub-District Hospital, Endebess Sub-District Hospital, Kapsara District Hospital, Khunyangu Sub-District Hospital, Matayos Health Centre, Mois Bridge Health Centre, Saboti Sub-District Hospital, An |
| **Project Period** | 4/1/2015 – 4/1/2015 |
| **Funding Status** | Funded |
| **Direct Award (USD)** | $2,478,465 |
| **Update** | No update |
| **Future Plans** | |
| **Publication(s)** | |

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| **Study Title** | **Building Competencies through Bilateral International Exchanges-Using Qualitative Methods to Measure the Impact on Pediatric Residents from Host and Visiting Countries in Professionalism, Communication and Systems-Based Care** |
| **Principal Investigator(s)** | Debra Litzelman, Indiana University<br>Samuel Ayaya, Moi University |
| **Co-Investigator(s)** | Umoren, R. Woodward, J. Vreeman, R. Palmer, M. Stelzner, S. Lorant, D. Riner, M. |
| **Working Group(s)** | Pediatrics |
| **Description** | This study uses focus groups to assess the impact of resident exchange project on participating residents from Indiana University School of Medicine (IUSOM), Moi University School of Medicine (MUSM), and Universidad Autonoma del Estado de Hidalgo Health Sciences Campus (UAEH) particularly related competencies in professionalism, communication, systems based practice, and practice based learning and improvement. |
| **Site(s)** | Moi Teaching and Referral Hospital |
| **Project Period** | 11/27/2007 – 6/30/2014 |
| **Funding Status** | Unfunded |
| **Direct Award (USD)** | |
| **Update** | No additional study data collected. Analysis of study data in progress. |
| **Future Plans** | Completion of data analysis and preparation of manuscript for publication |
| **Publication(s)** | |

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| **Study Title** | **Can integration of effective family planning services into Anticoagulation Management Services (AMS) improve uptake?** |
| **Principal Investigator(s)** | Astrid Christoffersen-Deb, University of Toronto |
| **Co-Investigator(s)** | |
| **Working Group(s)** | Reproductive Health, CVMD |
| **Description** | The purpose of the study is to evaluate whether integration of family planning education and free, on-site provision of all reversible family planning methods in Anticoagulation Monitoring Service (AMS) Clinic can improve uptake of long-acting reversible contraception (LARC; specifically intrauterine contraceptive devices (IUCDs) and contraceptive implants) in this high-risk population. Our hypothesis is that implementation of an educational intervention emphasizing long-acting reversible contraception (LARC) combined with free on-site provision of LARC within Anticoagulation |

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| | Monitoring Service (AMS) can improve uptake of these methods by 250% in this population. Our objectives are to: 1) Determine whether integration of education about and free provision of highly effective long-acting reversible contraceptive methods within Anticoagulation Monitoring Services (AMS) is feasible. 2) Determine whether integration of education about and free provision of highly effective long-acting reversible contraceptive methods within Anticoagulation Monitoring Services (AMS) can improve uptake of long-acting reversible contraceptive methods (IUCDs and contraceptive implants). 3) Determine whether integration of education about and free provision of highly effective long-acting reversible contraceptive methods within an Anticoagulation Monitoring Services (AMS) Clinic can prevent unplanned pregnancies. In order to evaluate these objectives we will provide the intervention and follow the participants for the following 1 year time period. At 3-month, 6-month, and 12-month follow-up we will evaluate whether they are using any method of family planning and whether they have experienced subsequent unplanned pregnancies. This data will be compared to the same group of women prior to implementation of the education intervention and free, on-site provision of all reversible contraceptive methods. |
| **Site(s)** | Moi Teaching and Referral Hospital |
| **Project Period** | 4/20/2015 – 8/31/2016 |
| **Funding Status** | Unfunded |
| **Direct Award (USD)** | |
| **Update** | |
| **Future Plans** | |
| **Publication(s)** | |

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| **Study Title** | **Childhood Leukemia in Kenya Identified Through Malaria Slide Review** |
| **Principal Investigator(s)** | Terry Vik, Indiana University<br>F. Njuguna, Moi University |
| **Co-Investigator(s)** | Skiles, J. Moormann, A. |
| **Working Group(s)** | Oncology, Pediatrics |
| **Description** | The aim of this study is to improve the case detection rate of leukemia by retrospectively reviewing blood smears done for malaria screening to identify children with leukemia in defined population cohorts. If the case detection rate can be improved by utilizing a common and well established procedure, then there is potential to identify children, refer them earlier for treatment and save lives. |
| **Site(s)** | Kitale District Hospital, Moi Teaching and Referral Hospital |
| **Project Period** | 7/1/2012 – 6/30/2015 |

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| **Funding Status** | Funded – Alex's Lemonade Stand Foundation |
| **Direct Award (USD)** | $200,000 |
| **Update** | We have completed the third aim of our study by reviewing a collection of 6000 malaria slides. We found 3 slides with high white blood cell count and likely leukemia. We will report those 3 slides as a separate paper to show the feasibility of our approach. |
| **Future Plans** | Our original 36,000 slide review is now the basis for a project we will start in the coming year to analyze the DNA content of the white cells on the slides and determine if we can prove the presence of leukemia in a subset of our possible positive leukemia slides, about 200 of the 36,000 we examined. |
| **Publication(s)** | |

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| **Study Title** | **Developing and Assessing a Community-Based Model of Antiretroviral Care** |
| **Principal Investigator(s)** | Abraham Siika, Moi University<br>Kara Wools-Kaloustian, Indiana University |
| **Co-Investigator(s)** | Suzanne Goodrich |
| **Working Group(s)** | AMWG |
| **Description** | ART Co-ops study will develop and assess an alternative care model that is established on the platform of a HIV-infected peer-group (ART Co-op) and facilitated by community health workers (CHWs). This model of care is intended to decentralize ART services and bring them closer to the patients. Specifically, we will: 1. Develop an acceptable and sustainable model for extending HIV care and treatment into the community.<br>2. Perform a pilot study comparing the outcomes of patients enrolled in the ART Co-ops program to those receiving standard of care. 3. Determine the cost savings and cost effectiveness of ART Co-ops. |
| **Site(s)** | Kitale District Hospital |
| **Project Period** | 2/9/2015 – 2/9/2017 |
| **Funding Status** | Funded – Centers for Disease Control and Prevention (CDC) |
| **Direct Award (USD)** | $924,042 |
| **Update** | Site activation for the study was officially carried out by the study sponsor,CDC on the 3rd - 5th of February,2015.The CDC team had a chance to go through study source documents,SOP's and study protocol.They came up with recommendations which have since |
| **Future Plans** | Purchase of equipment and supplies. - Carry out mapping of the patient catchment area in preparation for specific aim 1. - Execute specific aim 1 of the study. - Complete specific aim 1 of the study and use the findings to make changes on the proto |

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| **Publication(s)** | |
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| **Study Title** | **Drug Resistance in HIV Infected Children after Failure of Prevention of Mother to Child Transmission in Western Kenya** |
| **Principal Investigator(s)** | Winstone Nyandiko, Moi University<br>Rami Kantor, Brown University |
| **Co-Investigator(s)** | Vreeman, R. Songok, J. Diero, L. Kosgei, R. Ayaya, S. |
| **Working Group(s)** | Pediatrics, Reproductive Health |
| **Description** | The project seeks to determine the proportion of children getting HIV infected despite interventions of pMTCT, and the type, if any, of antiretroviral drug resistance in those children who get HIV infected after failure of pMTCT. |
| **Site(s)** | Kitale District Hospital, Moi Teaching and Referral Hospital, Turbo Health Centre |
| **Project Period** | 5/3/2011 – 4/10/2015 |
| **Funding Status** | Funded – Other |
| **Direct Award (USD)** | $20,000 |
| **Update** | We have not enrolled any study participant since the last update .We have had challenges in getting eligible patients to be recruited. This is due to few children turning positive after undergoing the PMTCT intervention within AMPATH.This is as a result of a vibrant PMTCT program within AMPATH. We have so far enrolled a total of fourteen patients into the study up to date. None of the study participants has either withdrawn or defaulted. The study is now closed. |
| **Future Plans** | A manuscript is under development otherwise the study has been closed. |
| **Publication(s)** | Manuscript is under development. Abstract submitted to AIDS conference in Australia last year. |
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| **Study Title** | **Enhancing Training for Implementation Research in Chronic Disease: CITE/Kenya** |
| **Principal Investigator(s)** | Tom Inui, Indiana University<br>Paul Ayuo, Moi University |
| **Co-Investigator(s)** | Siika, A. Litzelman, D. |
| **Working Group(s)** | Adult Medicine |
| **Description** | An innovative clinical and implementation research training program for Kenyan investigators, one built on the foundation of the highly successful and mature clinical and implementation research core curriculum for young investigators within our IUSM CTSI, |

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| | will be developed. This program will attract graduate trainees nominated by faculty at Moi University schools of medicine, public health, dentistry, nursing, and possibly young faculty from health-related behavioral and social science programs at Moi. This curriculum will be presided over by seasoned Eldoret-based investigators from the AMPATH research network (especially Dr. Thomas Inui and his 5 co-directors of the AMPATH Field Research program). Trainees who complete the core curriculum will be eligible to compete for resources to propose and conduct research in an implementation research practicum under the supervision of a tailored mentorship panel populated by Moi and international faculty. This research will focus upon a chronic disease of importance to the health of the populations in Western Kenya and will contribute to the improvement of health care processes, including village-based processes, medical and psycho-social services, and integration of care for chronic conditions within the MOH delivery system. The 'laboratory' for this research will be the AMPATH-MOH chronic disease program. The training program will build on the successful AMPATH multi-disciplinary and multi-institutional research foundation already in place, supported by AMPATH's remarkable e-Health infrastructure. This program's graduate training will enable Kenyans to acquire knowledge and skills in health systems and implementation research, enhance their capacity to promote continuous improvement of health care, inform health policy, and acquire leadership and management skills needed to develop, manage and improve chronic disease control programs. The ultimate aim of this proposal is to prepare Moi health professionals to serve as effective change agents and scientific leaders in Kenya's evolving system of care. |
| **Site(s)** | Moi Teaching and Referral Hospital |
| **Project Period** | 10/1/2012 – 9/30/2016 |
| **Funding Status** | Funded – NIH - Fogarty International Center (FIC) |
| **Direct Award (USD)** | $862,970 |
| **Update** | Cohort 3 completed all 22 of the D43 seminars. Seminar attendance was variable, in response to the attractiveness of the topic, but overall more than 40 individuals have participated in the training the seminars provided to young investigators and research coordinators. All fellows in the 3 cohorts have now named members of their mentor committees and produced protocols for their practicum research that are in various stages of review, peer review in the AMPATH research working groups and human subjects review in IREC. The June 2015 D43 oral abstract presentation session was well-attended and provided useful feedback to all presenters. |
| **Future Plans** | The principal activities of the next six months will be implementation of practicum research projects. Dr. Inui will travel to Kenya to review fellow progress in October 2015. |
| **Publication(s)** | |
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| **Study Title** | **Epidemiology, Acute Management, and Outcomes of Patients with Sepsis Presenting to a Referral Hospital in western Kenya before and after** |

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| | **implementation of a World Health Organization sepsis management algorithm** |
| **Principal Investigator(s)** | Wangari Siika, Moi Teaching and Referral Hospital |
| **Co-Investigator(s)** | |
| **Working Group(s)** | Adult Medicine |
| **Description** | This study will describe the epidemiology of patients presenting with severe sepsis, to examine the microbiology causing severe sepsis, to describe current management and outcomes for severe sepsis, and to test the effect of implementation of the WHO resuscitation algorithm at MTRH. The study design is a prospective before and after clinical trial. In an initial observational phase, adult patients presenting to the MTRH Casualty Department with sepsis and severe sepsis (the latter of which will be defined by elevated lactate) will be enrolled into a prospective observational cohort. Demographic data, medical characteristics, and microbiological studies will be obtained, then the management and outcomes of these patients will be observed. In a second phase, patients with sepsis will continue to be enrolled into a prospective observational cohort, while patients with severe sepsis will be enrolled into an intervention group. Patients in the intervention group will be managed according to the WHO resuscitation algorithm. Specifically, the WHO algorithm involves fluid boluses guided by vital signs and physical exam findings, rapid and early administration of empiric antibiotics, and frequent patient monitoring. The outcomes of interest are achievement of lactate clearance, which is a correlate of tissue perfusion, as well as 24-hour, in-hospital, and 30-day mortality. Specific Aims: 1. To describe the characteristics, including demographics, medical co-morbidities, and acute health status of patients presenting to MTRH with sepsis. 2. To describe the microbiological epidemiology of community-acquired sepsis at MTRH. 3. To understand the fraction of patients with severe sepsis who achieve adequate tissue perfusion as measured by 24-hour lactate clearance within current practices, and to determine the short-term (48-hour) and long-term (30-day) outcomes of these patients. 4. To analyze the WHO algorithm's effect on clinical outcomes (lactate clearance, mortality) of patients with severe sepsis. 5. To determine whether there are any physical exam-based markers of volume status and/or perfusion which reliably predict fluid responsiveness or lactate clearance. |
| **Site(s)** | Moi Teaching and Referral Hospital |
| **Project Period** | 1/12/2015 – 12/31/2015 |
| **Funding Status** | Funded – NIH - Fogarty International Center (FIC) |
| **Direct Award (USD)** | $22,038 |
| **Update** | |
| **Future Plans** | |
| **Publication(s)** | |

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| **Study Title** | **Evaluation of A Comprehensive Strategy to Measure Pediatric Adherence to Antiretroviral Therapy (CAMP study)** |
| **Principal Investigator(s)** | Rachel Vreeman, Indiana University<br>Winstone Nyandiko, Moi University |
| **Co-Investigator(s)** | Inui, T. Tierney, W. Tu, W. Marrero, D. Ayaya, S. Blaschke, T. Arpadi, S. Caroll, A. Bell, D. |
| **Working Group(s)** | Pediatrics |
| **Description** | The primary objective of this study is to develop and test a reliable, valid instrument to measure pediatric ART adherence for children ages 0 to 14 years in western Kenya and to evaluate which administration strategy yields the most accurate information about children's ART adherence. We will pursue the following four specific aims: Aim 1: Develop a reliable, valid comprehensive pediatric ART adherence measurement questionnaire (CAMP - Comprehensive ART Measure for Pediatrics); Aim 2: Develop a reliable, valid, short-form version of the pediatric ART adherence measurement tool (SF-CAMP) for use as an adherence screening measure in busy clinical care environments; Aim 3: Evaluate the field readiness, implementation feasibility, and clinical utility of CAMP and SF-CAMP within the AMPATH HIV clinical care system in western Kenya; and Aim 4: Evaluate the reliability and validity of this measurement tool in a clinic-based care setting compared to a home?based care setting. |
| **Site(s)** | Moi Teaching and Referral Hospital |
| **Project Period** | 9/11/2009 – 2/28/2014 |
| **Funding Status** | Funded – NIH - National Institute of Mental Health (NIMH) |
| **Direct Award (USD)** | $1,336,011 |
| **Update** | Over the last 6 months, we continue to make progress in data analysis and dissemination. We published the results of an important part of analysis using our Phase 2 data, which resulted in a validated, 10-item adherence questionnaire. These results were published in January 2015 in AIDS and Behavior under the title, 'Comprehensive Evaluation of Caregiver-Reported Antiretroviral Therapy for HIV-Infected Children.' We have completed data analysis on Phase 3 of the CAMP study and are now writing up the results of that analysis, which investigated the validity of the 10-item adherence questionnaire created as part of Phase 2 but this time with the questionnaire being administered by the child's routine clinical officer (versus a research team). We found that the adherence questionnaire remained valid. Data analysis on Phase 5 to investigate the validity of adherence questionnaires administered in a clinic versus home setting are ongoing. This analysis has been delayed due to extraction of data from the study database but this issue has been resolved and analysis is progressing well. Finally, we have finished the first round of analyses related to our pharmacokinetic modeling using the Phase 2 data. We have a draft manuscript circulating for comments. To summarize the results, we created a valid adherence measure that used PK drug properties and dose timing data using electronic dose monitors (MEMS) that captures drug exposure over time. The abstract describing these results was presented at the International AIDS Society meeting in July |

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| | 2015. |
| **Future Plans** | Over the next 6 months, we aim to achieve the following: 1.) Finishing drafting a manuscript describing Phase 3 findings and submit the manuscript for publication 2.) Complete data analysis on Phase 5 data and begin to draft a manuscript 3.) Finalize the writing of the PK manuscript and submit the manuscript for publication |
| **Publication(s)** | Vreeman, RC; Nyandik, WM; Liu, H; Tu, W; Scanlon, ML; Slaven, JE; Ayaya, SO; Inui, TS 'Comprehensive evaluation of caregiver-reported antiretroviral therapy adherence for HIV-infected children' AIDS Behavior (Jan 2015) 19:626-634. |
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| **Study Title** | **Evaluation of the growth and development of young children of HIV-infected mothers in western Kenya.** |
| **Principal Investigator(s)** | Megan McHenry (maiden name: Uhl), Indiana University |
| **Co-Investigator(s)** | Apondi, Edith Vreeman, Rachel Ayaya, Samuel |
| **Working Group(s)** | Pediatrics |
| **Description** | Children under five years of age are at significant risk for mortality in resource-limited settings. One in nine children in sub-Saharan Africa die before they reach five years of age. Approximately 45% of child deaths are related to poor growth and malnutrition. Children born to HIV-infected mothers are at increased risk for stunting, wasting, and being underweight, and children with HIV and AIDS are even more likely to be malnourished. Without treatment, 50% of HIV-infected and 7% of HIV-exposed, but uninfected infants will die before two years of age. My long-term research goal is to provide evidence to improve the nutritional status and, in turn, decrease under-5 mortality for children born to HIV-infected women in resource-limited settings. As access to HIV care expands and we push towards the Millennium Development Goal of reducing child mortality, we must address the risks faced by young children exposed to or infected with HIV. The Academic Model Providing Access To Healthcare (AMPATH) in Kenya provides an ideal setting in which to evaluate the growth and development of this vulnerable population, and to explore effective interventions to improve their health. AMPATH is a long-standing, academic partnership, created between the Moi University School of Medicine, Moi Teaching and Referral Hospital, and the Indiana University School of Medicine, that provides care for over 15,000 HIV-infected and HIV-exposed children, one of the world's largest pediatric HIV cohorts. Few current data focus on the best strategies to foster the growth and development of HIV-exposed and HIV-infected children under five years of age and living in resource-limited settings. The objective of this study is to evaluate the growth and development of young children of HIV-infected mothers in western Kenya, with attention to identifying areas to target for future interventions. We plan to accomplish our research objective by pursuing the following four specific aims: Aim 1: Evaluate the changes in anthropometrics over time for children under the age of five who are born to HIV-infected mothers enrolled in AMPATH clinics. Hypothesis: Among those enrolled in AMPATH, HIV-infected children will have lower Z-scores for measured anthropometrics (WAZ, HAZ, WHZ) than HIV-exposed |

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| | children. Aim 2: Determine factors associated with poor weight gain in this population of children. Hypothesis: Factors such as being orphaned, being HIV-infected, having developmental delays, having been hospitalized, and lower immunization rates will be associated with lower Z-scores for measured anthropometrics in both HIV-exposed and HIV-infected children under 5. . Aim 3: Evaluate the rates at which clinical providers detect failure-to-thrive in children under 5 years during routine AMPATH clinic visits. Hypothesis: Clinical providers will have low rates of identifying failure-to-thrive as a problem for children under-five requiring follow-up. Aim 4: Describe the mortality rates and rates of losses to follow-up in this population. Hypothesis4a: Mortality rates will be higher among those children who are HIV-infected and malnourished. Hypothesis 4b: Losses to follow-up are more common among HIV-exposed children compared to HIV-infected children. Rates of those lost to follow-up for both groups will be <20%, which is generally considered acceptable in research studies. |
| **Site(s)** | |
| **Project Period** | 7/1/2015 – 6/30/2017 |
| **Funding Status** | Unfunded |
| **Direct Award (USD)** | |
| **Update** | This study is a retrospective chart review of data from the AMPATH Medical Record System. We received the data from Edwin Sang in June, and we will start analysis of the data in the upcoming months. |
| **Future Plans** | We hope to complete the analysis of this data. |
| **Publication(s)** | |

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| **Study Title** | **Exploring the Role of Faith Leaders Towards Promotion of Home Based HIV Testing and Treatment Program Around Kisumu, Kenya** |
| **Principal Investigator(s)** | Eunice Kamaara, Moi University |
| **Co-Investigator(s)** | |
| **Working Group(s)** | Behavioral and Social Sciences |
| **Description** | This proposed exploratory study about the attitudes of faith leaders towards home based HIV testing around Kisumu, Kenya draws on the aforementioned home-based testing studies which found that home-based testing programs enhance HIV/AIDS cascade outcomes. Study Aims The specific aims include: 1. To explore the beliefs and knowledge of faith leaders in Nyanza about HIV/AIDS and attitudes about home-based HIV testing and linkage to care programs. 2. To explore the role of faith leaders in patients' clinical practices related to HIV/AIDS, including presentation for HIV testing, treatment and retention in care; and 3.To explore the perspectives of AMPATH and other outreach workers on if and how partnering with faith leaders could enhance current home-based HIV testing, treatment and retention in care. |

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| **Site(s)** | Chulaimbo Sub-District Hospital, Mukhobola Health Centre, Port Victoria Sub-District Hospital |
| **Project Period** | 7/1/2015 – 10/30/2015 |
| **Funding Status** | Funded – Brown University - Center For AIDS Research |
| **Direct Award (USD)** | $25,300 |
| **Update** | No Update Provided |
| **Future Plans** | |
| **Publication(s)** | |

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| **Study Title** | **Group B streptococcus colonization among antenatal women: Prevalence and Antibiotic Susceptibility at Moi Teaching and Referral Hospital** |
| **Principal Investigator(s)** | Saudah Farooqui, Moi University |
| **Co-Investigator(s)** | |
| **Working Group(s)** | Reproductive Health |
| **Description** | This project is being done in Moi Teaching and Referral Hospital in the antenatal clinic. Based on studies performed in developed countries, approximately 10%-30% of pregnant women are colonized with GBS (Group B Streptococcus) in the vagina or rectum. GBS sepsis is a leading cause of maternal and perinatal morbidity and mortality and one of the most common causes of neonatal sepsis throughout the world. A rectovaginal swab is done on all pregnant women who fit our inclusion criteria and the culture is done in Lancet lab. Our main objectives are: 1. To determine the prevalence of GBS colonization among pregnant women seeking antenatal care in MCH at MTRH. 2. To determine the antibiotic susceptibility profile in pregnant women attending antenatal clinic at MTRH. 3. To determine feasibility of a screen and treat program at MTRH. |
| **Site(s)** | Moi Teaching and Referral Hospital |
| **Project Period** | 5/5/2015 – 10/30/2015 |
| **Funding Status** | Unfunded |
| **Direct Award (USD)** | |
| **Update** | |
| **Future Plans** | |
| **Publication(s)** | |

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| **Study Title** | **HI-Train: Health Informatics Training and Research in East Africa for Improved Health Care** |
| **Principal Investigator(s)** | Abraham Siika, Moi University<br>Martin Were, Indiana University |
| **Co-Investigator(s)** | Ayuo, Paul Nabukenya, Josephine Mughal, Khalid Tylleskar, Thorkild |
| **Working Group(s)** | None |
| **Description** | With increased deployment of eHealth systems, comes the need for an appropriate health information technology workforce. This workforce includes: (a) Local level: Health IT professionals, eHealth specialized programmers, data managers, implementation managers, support specialists and reporting personnel; (b) Institutional level: chief medical information officers; and health information management specialists, (c) administrative: regional and national eHealth coordinators and eHealth monitoring and evaluation specialists, and (d) Other: health information privacy and security specialists and HI researchers. End users, institutional managers and policy makers also need to be appropriately trained on the relevant eHealth systems. Alarmingly, most sub-Saharan countries remain woefully unprepared to systematically train an adequate workforce to support the eHealth systems already being deployed. Countries like Uganda and Kenya recognize an emergent need for national strategies to build health informatics human capacity. These countries have appropriately developed national eHealth capacity-building strategies Implementing the strategies however requires direct leadership by Higher Education Institutions in the relevant countries. The urgency for sustainable mechanisms to increase HI workforce and research capacity in developing countries is self-evident. This goal can only be realized by having enough faculty members from developing countries fully trained in Health Informatics. These staff faculty can then be part of a well-functioning and high quality HI program moving forward. Recognizing this need, and the multidisciplinary competencies needed for HI training and research, our team identified partner institutions with complementary capabilities to support advanced Health Informatics training in East Africa for our project. Aims 1) Provide post-graduate (Masters and PhD) level training in Health Informatics and research. The focus will be on post-graduate training for health professionals and computer science personnel to help them become HI faculty at their institutions. 2) Increase number of women and marginalized populations in faculty-level training in Health In-formatics and research at the LMIC higher education institutions. 3) Improve the quality and quantity of Health Informatics research conducted primarily by re-searchers based in the LMIC countries in collaboration with our Northern partners. 4) Provide model curricula, educational programs and approaches for faculty-level health informatics training that can be emulated by regional higher education institutions. |
| **Site(s)** | Moi University, Makerere University, University of Bergen |
| **Project Period** | 12/5/2013 – 6/30/2019 |
| **Funding Status** | Funded – Other |
| **Direct Award (USD)** | $2,757,830 |

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| **Update** | 5 PhD candidates(1 Moi, 4 Makerere) were accepted into the programme and will be starting their PhD studies at University of Bergen Two draft curricula for PhD program to be approved at LMIC institutions were drafted in a workshop in February 2015 at Kampala. Moi and Makerere university are yet to start the university adoption process. Leadership and gender sensitization workshops were held in February 2015 at Kampala with participants from Moi, Makerere and University of Bergen. MSc. Health Informatics advert went out in March 2015 and 53 applications were received. Shortlisting and interviews were done. The 2015/2016 project budget and work plan was approved by NORAD |
| **Future Plans** | PhD students to commence studies at UiB in August 2015, travel plans have been set. The drafted PhD curriculum to begin university adoption process within Moi and Makerere universities. MSc. Health Informatics program to commence in September 2015 where accepted candidates will be notified and admitted. 1 semester exams will take place in December and the 2nd semester to start in January 2016. Mentorship and gender workshop will take place within the first semester of the MSc HI program. Project Annual meeting with Norad will take place in Norway between October and November 2015 |
| **Publication(s)** | Presentations at the Kenya Medical Association Conference were presented by; 1. Computerized Clinical Decision support for HIV care in Kenya by Dr. Aggrey Kenya 2. Health Informatics Capacity Building in Kenya, a case study of Moi University by Prof. Pa |

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| **Study Title** | **HIV-1 Drug Resistance in Different Subtypes** |
| **Principal Investigator(s)** | Rami Kantor, Brown University<br>Lameck Diero, Moi University |
| **Co-Investigator(s)** | Nathan Buziba Wilfred Emonyi |
| **Working Group(s)** | |
| **Description** | Examine drug resistance upon tenofovir-containing first line antiretroviral therapy in multiple subtypes in western Kenya using different analyates. |
| **Site(s)** | |
| **Project Period** | 5/12/2012 – 2/20/2014 |
| **Funding Status** | Funded – NIH - National Institute of Allergy and Infectious Diseases (NIAID) |
| **Direct Award (USD)** | $98,168 |
| **Update** | Work presented in CROI and resistance workshop 2015. Manuscript under review. Second manuscript in preparation. |
| **Future Plans** | Finalize publication. |
| **Publication(s)** | 1. K Brooks, L Diero, A Delong, M Balamane, M Reitsma, E Kemboi, M Orido, M Coetzer, J Hogan, R Kantor. Viral Failure and High K65R in Kenyan Patients on Tenofovir-Based 1st- |

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| | Line Therapy (under review; Clinical Infectious Diseases). 2. K Brooks, L Diero |
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| **Study Title** | **IeDEA Comprehensive Adherence Measure for Pediatrics (ICAMP)** |
| **Principal Investigator(s)** | Rachel Vreeman, Indiana University<br>Winstone Nyandiko, Moi University |
| **Co-Investigator(s)** | |
| **Working Group(s)** | Pediatrics |
| **Description** | The primary objective of the proposed study is to validate an adherence questionnaire for pediatric and adolescent patients at 3 IeDEA sites using electronic dose monitors (Medication Event Monitoring Systems®, or 'MEMS', MWV/AARDEX, Switzerland) as external criterion for adherence. While the adherence questionnaire (known as the Comprehensive Adherence Measure for Pediatrics - Short Form, or 'CAMP-SF') has been previously validated in a large, urban referral site at AMPATH in the East Africa IeDEA region, re-validation is warranted to ensure external and internal validity is upheld across resource-limited sites. In conducting this validation study, we will also collect valuable, detailed prospective data on adherence to ART among this sample of HIV-infected children and adolescents using electronic dose monitoring. The study has the following specific aims and hypotheses: Specific Aim 1: Validate a 10-item adherence questionnaire for routine use as an adherence measurement tool in resource-limited settings. Hypothesis 1a: Adherence estimates from the CAMP-SF will be reliable and valid across 3 IeDEA sites in East Africa, Southern Africa and Asia-Pacific when compared with MEMS electronic dosing data. Specific Aim 2: Describe pediatric adherence to ART prospectively over 6 months using electronic dose monitoring (i.e., MEMS) and the CAMP-SF among a sample of HIV-infected children and adolescents at 3 IeDEA sites. Hypothesis 2a: Rates of adherence to ART will be similar for children across different IeDEA sites. Hypothesis 2b: More pediatric non-adherence will be reported during prospective evaluation using the CAMP-SF than in existing rates reported in IeDEA datasets for children. Specific Aim 3: Evaluate factors associated with adherence among a sample of HIV-infected children and adolescents at 3 IeDEA sites. Hypothesis 3a: Risk of medication non-adherence is increased among older children, children with lower disease stages, children with higher CD4 counts, children with a higher medication burden, and orphaned children. Hypothesis 3b: Sites will differ in factors that may influence adherence, including number of children initiating ART; availability of nutritional support, adherence support, disclosure support, and pediatric formulations; and routine use of standardized adherence measures. Specific Aim 4: Assess evidence of the impact of ART non-adherence on clinical outcomes such as treatment failure and mortality, and programmatic factors such as loss-to-follow up. Hypothesis 4a: Medication non-adherence by MEMS is associated with increased risk of changing to second-line antiretroviral medications. Hypothesis 4b: Medication non-adherence by MEMS is associated with increased risk of mortality. Hypothesis 4c: Medication non-adherence by MEMS is associated with high risk of loss to follow-up. |
| **Site(s)** | Busia District Hospital, HIV-NAT Clinic, Bangkok, Thailand; Rahima Moosa Mother and |

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| | Child Hospital, Johannesburg, South Africa |
| **Project Period** | 8/1/2014 – 7/31/2016 |
| **Funding Status** | Funded – NIH - National Institute of Allergy and Infectious Diseases (NIAID) |
| **Direct Award (USD)** | $171,257 |
| **Update** | Over the last 6 months, we obtained IRB approval from all 3 study sites, hired and trained research teams at all sites, created and launched a multi-site REDCap database, and began recruited participants for prospective monitoring of their adherence. As of July 1, we have recruited 92 (out of 110) participants at the Thailand site, 29 (out of 110) participants at the South Africa site, and 40 (out of 110) participants at the Kenya site. Data collection and entry is progressing well and we are on target with our enrollment targets. |
| **Future Plans** | Over the next 6 months, we aim to: 1. Complete enrollment of study participants at all sites. 2. Continue with data collection and entry across all sites. 3. Complete study follow-up for at least 50 study participants at the Thailand site (study follow-up for the majority of participants will be ongoing at the South Africa and Kenya sites due to delayed IRB approval and thus delayed enrollment). |
| **Publication(s)** | |

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| **Study Title** | **Indiana University-Moi University Academic Research Ethics Partnership** |
| **Principal Investigator(s)** | Eric Meslin, Indiana University<br>David Ayuku, Moi University |
| **Co-Investigator(s)** | Were, E. |
| **Working Group(s)** | Adult Medicine |
| **Description** | The IU-Moi AREP is funded for five years with a $1.25 million grant from the Fogarty International Center at the National Institutes of Health to establish a new research ethics training partnership with colleagues at Moi University in Eldoret, Kenya. IU-Moi AREP is a curriculum development and training initiative that builds on longlasting partnerships and collaborations in East Africa. IU-Moi AREP has developed two Masters' degree programs:one at Indiana University-Purdue University Indianapolis and one at Moi University in Eldoret, Kenya.These graduate programs have common overlapping components,joint advisory committes,shared dissemination plans and harmonized evaluation strategies. Both programs include a curriculum involving required core courses, electives and a practicum experience, part of which is taken at the counterpart university. Besides, each IU-Moi AREP partner convenes an annual Teaching Skills in International Research Ethics(TaSkR) workshop to provide training to approximately 40 faculty and students each year. |
| **Site(s)** | Moi Teaching and Referral Hospital |

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| **Project Period** | 5/31/2012 – 1/31/2017 |
| **Funding Status** | Funded – NIH - Fogarty International Center (FIC) |
| **Direct Award (USD)** | $1,250,000 |
| **Update** | Summary of progress made between January 1 and June 30, 2015 1. Student Progress towards Completion of Training At Moi: a. Reverend Katwa has successfully defended his thesis and is expected to graduate soon. He will be the second student to graduate from the Moi program. Five other students are scheduled for their thesis defense. b. Three students were enrolled in the fifth cohort (2014/2015) and will be planning their Practicum Visit to Indianapolis for September/October 2015. At IU: a. Of the two students currently enrolled, Avril Rua Pitt completed her research titled Biobanking in Kenya: Challenges for Policy and Governance, and graduated with her MA May 2015. Dr. Scott Saxman completed his coursework , and is working on preparations for his practicum experience in Eldoret. Nairobi location as satellite for Moi program Due to increased interest in research ethics programs expressed by Nairobi-based professionals, the Msc. in International Health Research Ethics is now being offered in Nairobi. The Moi University Nairobi campus serves as the satellite site for this evening program. Classes are held from 5:00 pm - 10:00 p.m. EAT weekdays on Monday to Friday, and including weekends. 2. Short courses and training programs. Global Bioethics Seminar Series: The IU Center for Bioethics, in partnership with the IUPUI Medical Humanities and Health Studies Program, the IU Hall Center for Law and Health, the IUPUI Office of International Affairs, the IU Center for Global Health convened a 7-part seminar series in spring 2015 (January-April) on Global Bioethics as part of its ongoing commitment to studying ethical issues in international health and research. The goals were: (1) to provide a venue for in-depth discussion of emerging (and persistent) ethical issues in global health, (2) identify gaps in knowledge and practice that present research and collaboration opportunities; and (3) develop and expand local capacity. The topics have been selected from current developments in the academic literature, on the ground, and in the media, including epidemic preparedness and response, international clinical trials, humanitarian intervention, and the use of new technologies to support global health. The seminars were moderated discussions using cases, pre-circulated readings, and other relevant information.. Session leaders included Eric M. Meslin, Ph.D., Fran Quigley, JD, MA; William H. Schneider, Ph.D., Nic Terry, LLM; Ian McIntosh, Ph.D. Ross D. Silverman, Jd, MPH, Thomas S. Inui, MD, and David Plater, MPA. Topics included: Introduction to Global Bioethics; Population Health Ethics; Research Ethics Across Cultures; International Humanitarian Assistance; Privacy Regulation of the Health Data Stack and Is There a Human Right to Health? Seminar coordinators were Christopher Carter and Josh Rager. The seminars were moderated discussion using cases, pre-circulated readings and other relevant information. The seminars were accessible via Skype for those who were unable to attend in person. Participants included faculty and affiliates of AMPATH and the IU Center for Global Health; faculty & staff of the Office of International Affairs, IRB and Research Administration as well as faculty and students with an interest in international health ethics. An evaluation is underway. Short Course in Health Research Ethics: Moi University held a short-course February 16 - February 27. This short-course aims at building capacity in the area of international research ethics. This capacity will assure ethical and a scientific review of research protocols developed by local and international |

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| | scientists. The course covered topics in: Metaphysics & Theories of Knowledge; Research Methods; Contemporary Issues in International Research; Management of International Research Ethics, Research Ethics Committees & Consultation; Gender Issues in Research Ethics; Principles of Healthcare and Health Research Ethics; Qualitative and Quantitative Data Analysis; Ethical Theories; and Culture, Policy and Ethical Issues in International Research. The learning methods utilized were lectures, small group discussions, case studies, group-work, self-directed learning and written and oral presentations. Facilitators were drawn from varied backgrounds and included: Professor Joseph Kahiga; Dr. Joice Baliddawa, Professor Paul Omondi, Professor David Ayuku, Professor Edwin Were; Dr. Juddy Wachira, Professor Omar Egesa and Dr. Ann Mwangi. There were 15 participants: 7 from Moi University; 5 from AMPATH; 1 from Kisii Referral & Teaching Hospital; 1 from Moi Teaching and Referral Hospital; and 1 from the University of Eastern Africa-Baraton. Seventh Annual Teaching Skills in International Research Ethics (TaSkR VII) Workshop: The IU-Moi AREP convened a TaSkR workshop in Indianapolis April 15 - 17, 2015. The theme for the workshop was Epidemic Ethics. The recent Ebola outbreak has brought to the fore ethical issues in epidemics, and it is hoped that the workshop will extend beyond Ebola to other epidemics. The workshop was organized into panels and round-table sessions on humanitarian action, clinical trial design, ethics review, regulatory issues and scientific communication. A 'House-of-Commons' style debate and a session on information sources for International Research Ethics were highlights of the workshop. Now in its seventh year, the TaSkR workshop series attracts local, regional and international experts from Indiana University, Moi University and the community. The workshop was held in room 1110, Health Information and Translational Sciences Building (HITS). More information about the workshop can be found at http://bioethics.iu.edu/programs/arep/taskr/. Total workshop registration was 77. New Collaborations The TaSkR Workshop was also an opportune occasion for a meeting of many African-based Fogarty bioethics program directors: Richard Waddell (Dartmouth-Tanzania); Troy Moon (Vanderbilt-Mozambique); Clement Adebemowo (Nigeria), as well as representatives from NACOSTI (Simon Langat) and KEMRI (Elizabeth Bukusi). This meeting resulted in several positive collaborative plans including: agreement to invite Bukusi and Langat onto IU Mio AREP Advisory Committee; agreement for Meslin, Were, and Ayuku to join the advisory committee for a new Fogarty Bioethics Program, submitted by KEMRI; and plans for a new grant submission (see below). |
| **Future Plans** | Planned Activities for the Next Six Months a. TaSkR VIII - Elboret. Based on discussions from the recent Fogarty PI meeting which was held before TaSkR VII on April 15 in Indianapolis, TaSkR VIII may need to be a larger meeting which would include all Africa-based Fogarty directors including local site. The focus would be more than Moi University. Typically, TaSkR in Eldoret is held in February. b. Practicum Experience, Fall 2015 Practicum Experience for Moi MSc. Students: IU-Moi AREP his planning to host and support three students from the MSc. in International Health Research Ethics at Moi University for six weeks beginning in September 2015. Students will be selected from their cohort to complete their practicum experience in Indianapolis. The remaining students will complete their practicum experience in Eldoret at AMPATH, at the Moi/MTRH Institutional Ethics Review Committee, and in Nairobi at the Kenya Medical Research Institute (KEMRI). The three students will be paired with mentors from the IU |

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| | campus who are experts in the student's research area. They will attendcore lectures as per the NIH requirements for Responsible Conduct of Research as well as other interests. This includes conflict of interest, research with animals, history of research with human subjects, policies concerning research with human subjects, peer review, data acquisition and management and safe laboratory practices. They will audit three IUPUI research ethics courses: GRAD-G 504 Introduction to Research Ethics (Instructor: Prof. Kimberly Quaid) ; PHIL-P547 Foundations of Bioethics (Instructor: Prof. Peter Schwartz); PHIL 555: Ethical and Policy Issues in International Research (Instructor: Prof. Eric Meslin) and participate in a two-day intensive Research Coordinator Education Program. They will visit the IU Simon Cancer Center, the Regenstrief Institute, the IU - Kenya Partnership, the Indiana Biobank, the IU Animal Labs, the Hall Center for Law and Health at the McKinney School of Law, and had a day-long visit to Eli Lilly and Company where they were hosted by the Lilly Bioethics program. The students will also have an opportunity to interact with the School of Medicine Global Health Track for IU Residents and presented on their research projects. c. HIV Supplement Grant Application On June 15 an HIV Fogarty Grant Supplement was submitted entitled 'Enhancing Ethics Capacity in Kenyan Ethics Review Committees'. This $50,000 supplement would support 'Summit of Kenyan Ethics Review Committees' held in conjunction with the Bioethics Society of Kenya (BSK) meeting in November in collaboration with KEMRI and NACOSTI. Dates of the meeting are November 25-27, 2015 at the Kenyatta Conference Centre. One day will be devoted to a summit of Ethics Review Committees (ERCs) in Kenya. The grant supplement will be used to support travel and some logistics of this summit, and both pre- and post-Summit surveys, plus online for a to discuss ethics issues in HIV research. d. Collaboration with Other Programs Dr. Meslin has joined the advisory committee of Vanderbilt University's Fogarty-funded bioethics program in Mozambique. Both activities will ensure greater outreach of our program. In March, Eunice Kamaara facilitated a session on research ethics for postgraduate research supervisors from the College of Health Sciences, School of Law, and School of Tourism and hotel Management (all of Moi University) at Sirikwa hotel. The invitation to facilitate came from the director of postgraduate studies at Moi. e. Renewal of R25 Grant Even though the renewal is not due until 2017, planning has already begun. Needs assessment for the program are planned for the program. |
| **Publication(s)** | |

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| **Study Title** | **IU Health Cardiovascular Research Biobanking Project** |
| **Principal Investigator(s)** | Tom Inui, Indiana University<br>Sylvester Kimaiyo, Moi University |
| **Co-Investigator(s)** | Bloomfield, G. |
| **Working Group(s)** | Adult Medicine, Cardiovascular and Metabolic Disease |
| **Description** | Atrial fibrillation is the most common sustained arrhythmia in high-income countries. Recent insights have been made with regard to the genetic variations that may predispose an individual to developing atrial fibrillation. There has long been observed a |

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| | disproportionately low prevalence of atrial fibrillation among Africans and African-American compared to people of European descent. Whether mutations in the genes known to cause atrial fibrillation are also causing AF among Kenyan patients with this disorder is unknown. Identification of the frequency of mutations in these genes in patients with atrial fibrillation in Kenya may shed light into the causal pathways of atrial fibrillation in this population. Using a case-control (1:2) research design in a Kenyan population with atrial fibrillation, we propose to perform mutational analysis of the coding sequence and flanking splice sites of the KCNQ1, KCNJ2, KCNE2 and KCNA5 genes known to be mutated in familial and lone atrial fibrillation in patients from high-income countries. A thorough phenotyping protocol will be employed which will include clinical assessment, a medical history, echocardiography and electrocardiography. Genetic material will be collected, stored and processed in Eldoret as the first initiative of the Genetic Biorepository Initiative (PI: Inui, Co-PI: Emonyi) and subsequently shipped for analysis of specific alleles at Indiana University. Using a convenience sample of approximately 140 patients with atrial fibrillation and 140 controls, we will demonstrate the frequency of pathological mutations in the aforementioned genes and provide a thorough clinical description of patients with atrial fibrillation including echocardiographic descriptions and the burden of other comorbid illnesses. |
| **Site(s)** | Moi Teaching and Referral Hospital |
| **Project Period** | 4/30/2012 – 4/28/2017 |
| **Funding Status** | Funded – IU Health |
| **Direct Award (USD)** | $1,060,000 |
| **Update** | During this last six-month interval collection of data from the original cohort of AF patients and their controls was concluded, closing the original study to new enrollment. Packed white blood cell pellets for the 292 enrollees were shipped to the IU Biobank, where 7% of the specimens were (for various reasons) found to be deficient. Work commenced to re-consent those patients with deficient PBMCs to redraw their blood specimens for processing. Cardiovascular echo recordings were transported to Duke. A data manager was hired and began entering all study data into a RedCap database, including clinical data, EKG interpretations, and lab data. A second protocol for the one-year followup of original cohort patients was submitted to IREC, Duke and IU IRBs and approved. A methods paper was written and submitted to review at the American Hearth Journal. |
| **Future Plans** | We hope to finish clinical followup at one year of the AF and control patients. Echos should be read by September and genomic analysis (NexGen) by October. |
| **Publication(s)** | Bloomfield G, Temu T, Akwanalo CO, Binanay C, Chen PS, Emonyi W, Heckbert SR, Koech MM, Manji I, Shen C, Vatta M, Velazquez EJ, Wessel J, Sylvester Kimaiyo S, Inui TS. Genetic Mutations in African Patients with Atrial Fibrillation: Rationale and Design of |
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| **Study Title** | **Knowledge, Attitudes and Practices of Sepsis Management at Moi Teaching and** |

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| | **Referral Hospital, Kenya** |
| **Principal Investigator(s)** | Elizabeth Mathenge, Duke University |
| **Co-Investigator(s)** | Elizabeth Mathenge, Duke University |
| **Working Group(s)** | Adult Medicine |
| **Description** | Study objectives: Sepsis is the presence of suspected or confirmed infection, in addition to systemic manifestations of infection. In many developing countries the data on sepsis - causes, prevalence, morbidity, mortality and current practices - is sparse. This study aims to understand sepsis related intervention practices among health care providers within a referral center in Kenya. This study will also look at the main attitudinal and health system barriers to adequate care for patients with sepsis. Methods: This is an analytical cross-sectional study. Knowledge Attitude and Practice (KAP) questionnaires will be distributed to health care providers at the Moi Teaching and Referral hospital in Eldoret, Kenya. The target population is physicians, clinical officers, and senior nurse practitioners working at the ICU, casualty and Nyayo wards between June 2014 and August 2014. Data analysis: Data will be presented using descriptive statistics in the form of frequencies and percentages for similar open form questions, and standard deviations for quantitative variables. Chi-square and fisher's exact test will be used for categorical variables and the level of significance will be set at 0.05. Open format responses will be analyzed qualitatively into nominal categories using NVIVO. Certain themes that represent the objectives of the study will be identified. |
| **Site(s)** | Moi Teaching and Referral Hospital) |
| **Project Period** | 7/13/2014 – 3/31/2015 |
| **Funding Status** | Funded – Duke Global Health Institute |
| **Direct Award (USD)** | $1,000 |
| **Update** | Progress Report. We performed data analysis for the initial phase of the study. The study has now been extended to the pediatrics department. Once data has been analyzed, we will commence working on a manuscript for publication. |
| **Future Plans** | In the next 6 months, we are hoping to continue data analysis. This will be mainly centered around the pediatric department. |
| **Publication(s)** | |

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| **Study Title** | **Linkage and Retention to Care in Western Kenya Following HIV Testing** |
| **Principal Investigator(s)** | Becky Genberg, Brown University<br>Juddy Wachira, Moi University |
| **Co-Investigator(s)** | Paula Braitstein Violet Naanyu Beth Rachlis Hana Lee Joseph Hogan |
| **Working Group(s)** | Adult Medicine |

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| **Description** | This project is focused on identifying the individual, psychosocial, and structural barriers to timely linkage and retention. This project has three specific aims: 1. To comprehensively describe linkage and retention to HIV care following home-based counseling and testing by examining time from testing to linkage and the socioeconomic, demographic and structural determinants of linking to care. We will conduct retrospective and multilevel analyses using existing de-identified clinical and facility-level data collected within AMPATH, defining linkage to care as the completion of an initial HIV clinical encounter with a provider following testing. We will also examine factors that predict retention in HIV care over time. 2. To characterize the psychosocial and structural facilitators and barriers to linkage and retention to care following positive HIV diagnosis through HBCT and PITC. We will conduct a qualitative study to examine the psychosocial factors inhibiting or motivating linkage to care, experiences in accessing care, and factors that promote or interrupt retention among those who tested positive via HBCT or PITC. We will also collect data from clinicians and community health workers to examine how features of the healthcare system facilitate or constrain linkage and retention to care. 3. To develop and implement a feasibility study of a pilot psychosocial intervention aimed at increasing linkage to care among individuals testing positive for HIV. The content of this intervention pilot will be informed by the results of Aims 1 and 2. The first aim of this study involves secondary analysis of data collected during home-based counseling and testing linked to medical records data. This data will include information collected as part of routine testing procedures and care, for those who successfully linked to care. AIM 2 will employ qualitative approaches to identify barrier and facilitators to linkage and retention. AIM 3 will include information collected as part of routine care, for those who successfully linked to care. Specifically, medical record reviews at baseline and post-intervention. |
| **Site(s)** | Other |
| **Project Period** | 6/4/2012 – 12/20/2013 |
| **Funding Status** | Funded – NIH - National Institute of Mental Health (NIMH) |
| **Direct Award (USD)** | $152,806 |
| **Update** | During the last 6 months of the project, we conducted qualitative research to characterize the barriers and facilitators of linkage and retention in care from the perspective of health care professionals and community members. 60 in-depth interviews were carried out between the months of September - October 2014, in three different AMPATH sites (2 rural sites and 1 urban site), with different carders of health care providers, including clinical officers, nurses, nutritionists, social workers, outreach workers, etc. Transcription and data collection phases ran concurrently; that is, every evening after data collection, the audio files were sent out to a team of transcribers. The transcription phase took place for a period of four months: from September 2014 to December 2014. We have completed data quality monitoring and the development of the codebook. Open coding began immediately after the development of the codebook. This began in mid-March 2015 and it is ongoing. 57 transcripts have been coded to date. We also conducted 30 in-depth interviews in Burnt Forest with adult community members between the months of October and November 2014 and this included 10 men and 20 women. The purpose of |

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| | this data collection was to understand community perceptions of HCT and to examine how gender influences seeking testing and care in this region. Transcription was completed in December 2014. Data Quality Monitoring is complete. Coding and analysis of this data is in progress. We continue to make progress on quantitative analyses of linkage and retention in HIV care cascade, including analyses designed to: 1) determine the impact of point of entry (testing program) on retention; 2) analyze gaps and interruptions in HIV care over time; 3) develop novel methods (state-space models) to examine transitions in and out of HIV care over time; 4) determine the impact of care navigators on linkage and retention in HIV care; and 5) examine spatial patterns of linkage to care. |
| **Future Plans** | In the next phase of the project, we will continue the analysis of the qualitative data that has been collected from key informant health care providers and adult community members. We will also collect additional data from n=60 adults who did and did not engage with care following an HIV-positive test result through home-based counseling and testing, i.e., 30 adults who linked to care and 30 adults who did not link to care. For the 30 adults who linked to care, data will be collected in 3 AMPATH sites (1 rural, 1 semi-urban and 1 urban). We are currently working in Busia County to collect this data. Finally we will continue to make progress with quantitative analyses of AMRS data to examine linkage and retention in HIV care within AMPATH. |
| **Publication(s)** | 1. Genberg BL, Naanyu V, Wachira J, Hogan JW, Sang E, Nyambura M, Odawa M, Duefield C, Braitstein P. Linkage to and engagement in HIV care in western Kenya: An observational study using population-based estimates from home-based counseling and testing. La |
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| **Study Title** | **National Cancer Institute Supplement to East African IeDEA: Improving Kaposi's Sarcoma, Lymphoma Diagnostics, and Assessing Kaposi's Sarcoma Incidence in Western Kenya** |
| **Principal Investigator(s)** | Kara Wools-Kaloustian, Indiana University<br>Nafthali Busakhala, Moi University |
| **Co-Investigator(s)** | |
| **Working Group(s)** | Oncology |
| **Description** | The toxicity and potential side effects of therapy for malignancy justify a standard of care in cancer medicine of tissue biopsy. Further, an accurate assessment of the epidemiology of HIV-related malignancy requires reliable pathologic diagnosis. This study will help validate local pathology for the diagnosis of Kaposi Sarcoma (KS). The limited resources available to local pathology mandate that most diagnoses are made via H&E staining and immunohistochemistry which are techniques, like many pathology diagnostic tools, open to inter-observer variability in interpretation. Thus the experience of the pathologist is a major determinant in diagnostic accuracy. Quality assurance efforts and continuing evaluation of diagnostic skills are routine practices in the United States to help ensure ongoing reproducibility between pathologists. The present effort will facilitate similar |

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| | ongoing quality checks and thus increase the reliability of a biopsy based diagnosis of KS and lymphoma at the selected sites. |
| **Site(s)** | |
| **Project Period** | 7/1/2012 – 7/31/2014 |
| **Funding Status** | Funded – NIH - National Cancer Institute (NCI) |
| **Direct Award (USD)** | Not Reported |
| **Update** | Punch biopsy services continue at AMPATH sites. As of 31st June 2015 we had done 1690 biopsies of which 1358 are AMPATH patients and 332 were non-AMPATH. The last shipment was at the end of July 2015 to USCF. Results of several samples have been updated and disseminated to the Kenyan pathologist and oncologist. Challenges: Disruption and delayed punch biopsy results have been hindered by as the Tissue Processing machine was faulty and hence the need to procure a new. The Machine has been bought and tissue processing will commence in several weeks. Testing of the Machine is ongoing. |
| **Future Plans** | The study continues to do punch biopsy, send shipment to UCSF for over reads every 2-3 months and continuous data entry and cleaning is ongoing. |
| **Publication(s)** | |

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| **Study Title** | **Nurse Management of Hypertension Care in Rural Western Kenya** |
| **Principal Investigator(s)** | Rajesh Vedanthan, Mount Sinai School of Medicine<br>Sylvester Kimaiyo, Moi University |
| **Co-Investigator(s)** | |
| **Working Group(s)** | Adult Medicine, Cardiovascular and Metabolic Disease |
| **Description** | This project aims to evaluate barriers and facilitators to nurse management of hypertensive patients in rural western Kenya, using a qualitative research approach. The four specific aims for attaining this objective are: Aim 1: To evaluate facilitators and barriers to nurse-based management of hypertensive patients in rural western Kenya. This will be accomplished by conducting a rapid assessment procedure involving key informant interviews, focus group discussions, and field observations. Aim 2: To develop and evaluate an innovative smartphone-based DEcision Support and Integrated REcord-keeping (DESIRE) tool utilizing a participatory, iterative, human-centered design process, to assist nurses taking care of hypertensive patients. We will evaluate the usability and feasibility of the DESIRE tool using qualitative methods (e.g. think-aloud, mock patient encounters, semi-structured interviews, and focus groups). Aim 3: To conduct an impact evaluation of a pilot program for nurse-based management of hypertension to be implemented by AMPATH, by performing secondary analysis of routine clinical data collected by AMPATH. The primary outcome measure will be change in systolic blood pressure in hypertensive patients assigned to nurse-based management after one year. |

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| | Aim 4: To estimate the nurse workforce requirements for stable, long-term treatment of hypertension throughout western Kenya, using a needs-based workforce estimation model. |
| **Site(s)** | Mosoriot Rural Health Training Centre, Turbo Health Centre |
| **Project Period** | 9/17/2011 – 7/30/2016 |
| **Funding Status** | Funded – NIH - Fogarty International Center (FIC) |
| **Direct Award (USD)** | $675,543 |
| **Update** | For Aim 1: All data collection and qualitative analyses complete,manuscript in preparation. For Aim 2: Data collection and qualitative analyses complete and Manuscript published in International Journal of Medical Informatics, Consultative feedback provided to AMPATH Chronic Disease Management and Informatics Teams. For aim3:Aim 3: Data entry complete, Data cleaning on-going, Study Oversight Committee convened and Preliminary statistical analyses on-going. Aim 4: Data collection activities completed, data analysis on-going and workforce estimation model development on-going |
| **Future Plans** | We hope to complete the following activities pertaining to each study aim: Aim 1: Complete qualitative manuscript. Aim 2: collect data on assessing patient perceptions of the mHealth interventions in the CDM program. Aim 3: complete preliminary and final data analyses, submit abstracts to professional conferences. Aim 4: Complete data analysis and , estimation model and submit abstracts to professional |
| **Publication(s)** | |

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| **Study Title** | **Optimizing Linkage and Retention to Hypertension Care in Rural Kenya** |
| **Principal Investigator(s)** | Valentin Fuster, Mount Sinai School of Medicine<br>Jemima Kamano, Moi University |
| **Co-Investigator(s)** | Fuster, V. Horowitz, C. Were, M. Inui, T. Hogan, J. Velazquez, E. Bloomfield, G. Naanyu, V. Menya, D. Kimaiyo, S. Akwanalo, C. |
| **Working Group(s)** | Adult Medicine, Cardiovascular and Metabolic Disease |
| **Description** | Hypertension awareness, treatment, and control rates are low in most regions of the world. A critical component of hypertension management is to facilitate sustained access of affected individuals to effective clinical services. In partnership with the Government of Kenya, the Academic Model Providing Access to Healthcare (AMPATH) Partnership is expanding its clinical scope of work in rural western Kenya to include hypertension and other chronic diseases. However, linking and retaining individuals with elevated blood pressure to the clinical care program has been difficult. To address this challenge, we propose to develop and evaluate innovative community-based strategies and initiatives supported by mobile technology. The objective of this project is to utilize a multi-disciplinary implementation research approach to address the challenge of linking and retaining hypertensive individuals to a hypertension management program. The central |

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| | hypothesis is: community health workers (CHWs), equipped with a tailored behavioral communication strategy and a smartphone-based tool linked to an electronic health record, can increase linkage and retention of hypertensive individuals to a hypertension care program and thereby significantly reduce blood pressure among these patients. We further hypothesize that these interventions will be cost-effective. To test these hypotheses and achieve the overall objectives, we will pursue the following specific aims: Aim 1: Identify the facilitators and barriers to linking and retaining individuals with high blood pressure to a hypertension care delivery program, using a combination of qualitative research methods: 1) baraza (traditional community gathering) form of inquiry; 2) focus group discussions among individuals with elevated blood pressure during home-based testing; and 3) focus group discussions among CHWs. Subsidiary Aim 1.1: Using identified facilitators and barriers, develop a tailored behavioral communication strategy guided by the Health Belief Model modified by incorporating emotional elements for the CHWs to use with hypertensive patients, focusing on regular and timely attendance at hypertension clinic. We will test the communication strategy for face and content validity using focus group discussions with CHWs and individuals with elevated blood pressure. Subsidiary Aim 1.2: Using identified facilitators and barriers, develop a smartphone-based tool linked to the AMPATH Medical Record System (AMRS) to be used by CHWs to optimize linkage and retention of hypertensive patients to the care program, and evaluate the usability and feasibility of this tool using think-aloud technique, mock patient encounters, focus group discussions, and participant observation. Aim 2: Evaluate the effectiveness of CHWs equipped with a tailored behavioral communication strategy and a smartphone-based tool in improving linkage and reducing blood pressure among hypertensive patients, by conducting a cluster randomized trial comparing: 1) usual care (CHWs with standard training on recruitment of individuals with any chronic condition); 2) CHWs with an additional tailored behavioral communication strategy; and 3) CHWs with a tailored behavioral communication strategy an also equipped with smartphone-based tool linked to the AMRS. The co-primary outcome measures will be: 1) documented linkage to care following home-based testing, and 2) one year change in systolic blood pressure among hypertensive individuals. Aim 3: Evaluate the incremental cost-effectiveness of each intervention arm of the cluster randomized trial. Cost effectiveness will be presented both in terms of costs per unit decrease in blood pressure and in terms of costs per reductions in cardiovascular disease (CVD) risk by extrapolating one-year blood pressure reductions to CVD risk reductions based on the QRISK2-2011 CVD risk calculator specific for Black African populations. This research will generate innovative and productive solutions to the expanding global problem of hypertension, and will add to existing knowledge on scalable and sustainable strategies for effectively managing hypertension and other chronic diseases in low- and middle-income countries. |
| **Site(s)** | Mosoriot Rural Health Training Centre, Turbo Health Centre |
| **Project Period** | 5/4/2012 – 3/31/2017 |
| **Funding Status** | Funded – NIH - National Heart, Lung, and Blood Institute (NHLBI) |
| **Direct Award (USD)** | $2,104,519 |

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| **Update** | Aimed at realizing the study deliverable, noted progress has been made from Jan 1 to June 30, 2015, these entails; Aligning LARK study with Process Evaluation: to ascertain the fidelity of the study protocol, various tools to be utilized in the exercise have been developed which include, Objective Structured Clinical Examinations (OSCEs), CHWs' Written Tests, Focus Group Discussion (FGD) Guide for both Community Health Workers (CHWs) & Hypertensive patients as well as System Usability Testing aligned with subsequent development of Redcap databases where applicable. IREC approval too to partake the exercise was obtained on April 14, 2015. Roll-out/Participant enrollment, by end of June, 15, we had roll-out the study in 20 Community Units (CUs) out of a total of 24 CUs. The total enrollment was 991, this was coupled too with 12 Month follow-up for the costing questionnaire. Programming Function. Programming of the study behavioral Assessment questionnaires were accomplished which paved way for roll-out of the study in smartphone arm. Year Four study IREC approval was obtained.<br>Personnel Capacity Building: three of the study personnel underwent a short course on Health Research Ethics. Faculty (PIs/Co-PIs) Visits (to Eldoret), we have had several visits by Faculty. Challenges 1) Ministry of Health Activities that are done concurrently with the study activities have impacted on study deliverable 2) Study Data Manager did resign 3) Pronounced delays in programming function 4) Delays in store requisitions and procurement functions coupled with ATPs initial slowness. 5) Low monthly enrollment (as low as 50% of the monthly targets) |
| **Future Plans** | Next Steps/Six Months: Scale up the roll-out process to the of the study to the four remaining CUs. Continue with the participants enrollment aligned with Data Entry (both real-time & manual for both Costing & BA) Pursue Process Evaluation: Data Management Protocol Development: generated a protocol detailing periodic updates with respect to query of AMRS, VM server using IDs, Data Dictionary, Integrity checks.<br>Hire Data Manager and a Research Assistant. Pursue Error Resolution/Prevention. Finalize on qualitative paper due for publication by JGIM. |
| **Publication(s)** | |

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| **Study Title** | **Patient-Centered Disclosure Intervention for HIV-Infected Children, Helping AMPATH Disclose Information and Talk about HIV Infection (HADITHI)** |
| **Principal Investigator(s)** | Rachel Vreeman, Indiana University<br>W. Nyandiko, Moi University |
| **Co-Investigator(s)** | Marete, I. Inui, T. Mwangi, A. Hogan, J. MC Henry, M. |
| **Working Group(s)** | Behavioral and Social Sciences, Pediatrics |
| **Description** | The purpose of this study is to assess the effect of a patient- and family-centered intervention guiding disclosure to HIV-infected Kenyan children using a randomized trial comparing the intervention to routine care. The primary endpoint will be probability of disclosure among children, with secondary endpoints of adherence, clinical outcomes, psychological distress and social outcomes. Phase One, which will last 6 months, focuses on cultural adaptation of the intervention materials through intensive patient |

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| | participation, including focus groups and cognitive interviewing; selecting narrative components; and training dedicated disclosure counselors. Phase Two consists of a randomized design to examine whether the culturally adapted, multi-component HADITHI intervention increases the prevalence of disclosure to HIV-infected children in western Kenya compared to children receiving usual care. HIV-infected children ages 10-15 years who are enrolled in HIV care within the eight selected AMPATH clinics in western Kenya will be eligible for study enrollment and have a comprehensive patient assessment every 6 months for 2 years. |
| **Site(s)** | Burnt Forest Sub-District Hospital, Chulaimbo Sub-District Hospital, Khunyangu Sub-District Hospital, Kitale District Hospital, Moi Teaching and Referral Hospital , Mosoriot Rural Health Training Centre, Turbo Health Centre, Webuye District Hospital |
| **Project Period** | 9/1/2012 – 9/1/2016 |
| **Funding Status** | Funded – NIH - National Institute of Mental Health (NIMH) |
| **Direct Award (USD)** | $1,886,804 |
| **Update** | Phase 1: The first phase of the HADITHI study was a qualitative inquiry into the experiences of HIV-infected adolescents and caregivers of HIV-infected children with HIV disclosure to children in terms of their beliefs, practices and preferences. Dissemination of early findings are proceeding. In the past 6 months, these results were presented at the 2015 International AIDS Society meeting and the International Workshop on HIV Pediatrics. In addition, a manuscript describing the findings, entitled ''Why did you not tell me?': perspectives of caregivers and children on the social environment surrounding child HIV disclosure in Kenya' was published in AIDS. Phase 2: Phase 2 of the HADITHI study aims to evaluate the impact of a clinic-level disclosure intervention that involves multiple counseling components, including peer support groups and individual counseling. All 276 patients have been recruited for Phase 2, and data collection is ongoing and the 24 months of patient follow-up should be completed by end of October 2015. Data collection is complete for most active participants up to Month 24. Month 24 assessments include blood samples for viral load testing and hair sampling for ARV concentrations, in addition to the multiple measures of adherence, depresison, behavioral symptoms, stigma, quality of life, and social functioning. Data entry and cleaning is ongoing for these evaluations in preparation for analysis. For the counseling intervention in Phase 2, the HADITHI counselors have been using computer tablets that are loaded with the HADITHI application, which displays the HADITHI disclosure videos for individual and group counseling sessions with the HADITHI participants. In addition, using a community participatory process and cross-cultural adaptation techniques, we created a HADITHI animation, which displays an animated narrative describing the effects of HIV in a young boy's body. The HADITHI animation is used in post-disclosure counseling with caregivers and children to explain HIV physiology and its treatment. The development and content of this animation were also presented at the 2015 International Workshop on HIV Pediatrics. Counselors have also been using the computer tablets to record audio counseling reflections, which helps identify counseling issues within this cohort and aids in self-reflection of the counselors. These counseling tools have been useful to the counselors in the implementation of our counseling intervention to the HADITHI cohort at |

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| | intervention clinics. In addition, we have launched a stigma narrative film project, filming dramatic short films created from our broad qualitative work and from stigma interviews with adolescents, community members, and caregivers.. Utilizing transcripts from stigma interviews and input from a participatory advisory team, the stigma narratives and scripts for this project were created by a multinational, multidisciplinary team. The short films will be utilized in individual and group counseling by the HADITHI counselors. Funding for this work was achieve through an IU New Frontiers award to C. Thomas Lewis. |
| **Future Plans** | Over the next 6 months, we plan to: • Complete Phase Two 24-month evaluations of our disclosure and stigma cohort of HIV-infected adolescents. Collect blood samples for viral load tests. •Collect hair samples to evaluate drug level concentrations in hair samples, as well as to assess the feasibility and validity of this evaluation form in our population. •Continue to implement the use of Google Nexus tablets at intervention clinics for: 1) showing HADITHI disclosure videos and for accessing other disclosure-related materials; and, 2) weekly audio reflections from counselors that document counseling sessions •Conduct more group counseling sessions at all of the intervention clinics •Complete data cleaning, preparation of datasets, and begin key analyses. |
| **Publication(s)** | Presentations and Publications in the last 6 months: 'Perspectives of HIV-Infected Adolescents on Disclosure of HIV Status in Western Kenya.' McAteer CI, Fischer LJ, Nyandiko WM, Scanlon ML, Marete I, Vreeman RC. Poster Presentation at 8th International |

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| **Study Title** | **'Point of Care CD4 testing for people who fail to engage in care after testing HIV positive'.** |
| **Principal Investigator(s)** | Paula Braitstein,<br>Samson Ndege, Moi University |
| **Co-Investigator(s)** | |
| **Working Group(s)** | Adult Medicine |
| **Description** | This supplement responds to unique aspects of Specific Aim 1 of the East Africa-International epidemiological Databases to Evaluate AIDS (IeDEA) grant, which seeks to 'Determine the short and long-term outcomes of adults and children along the entire spectrum of HIV care.' Our broad aim is to inform and evaluate the implementation of AMPATH's HIV treatment and prevention work by fully characterizing the cascade of HIV care in population-based settings and identifying gaps and opportunities for improvement. The primary objective of this study is to characterize the outcomes of HIV-positive adults who did not engage with HIV care following the catchment-wide HBCT campaign held from Dec 2009-Feb 2011 in Bunyala. |
| **Site(s)** | Bunyala Sub-county, could be others as well |
| **Project Period** | 2/2/2015 – 2/1/2016 |

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| **Funding Status** | Funded – NIH |
| **Direct Award (USD)** | $62,432 |
| **Update** | Outcomes Study proposal approved by IREC on 23rd March 2015. Requests, getting specifications and procurement procedures for PIMA Machines done in March 2015. Request for approval of amendment to IREC to include verbal consent and two additional co-investigators done and approved on 11th May 2015. Approval of protocol by University of Toronto HIV Research Ethics Board on 2nd June 2015. Letter dated 28th May 2015 from IREC received asking for justification of using verbal consent. PIMA Machines received in June 2015 and validated by the AMPATH Lab and found to be in good working condition. IRB approval of protocol on 30th June 2015. Training for PHCT Counselors and Supervisors done on 29th and 30th June 2015. Training included research protocol, data collection, CITI and CD4 testing using PIMA machine. |
| **Future Plans** | The Study is in it first steps logistically and in enrollment. The plan is to start and continue enrollment for the study in the next 6 months to meet the Study objectives. The study has ordered for the 3rd PIMA CD4 machine which we hope to receive in the next coming weeks. |
| **Publication(s)** | |

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| **Study Title** | **Prevalence and Impact of Alcohol Use in Patients Enrolling in HIV Care** |
| **Principal Investigator(s)** | Kara Wools-Kaloustian, Indiana University<br>Lameck Diero, Moi University |
| **Co-Investigator(s)** | Judith Hahn, Jayne Kulzer, Suzanne Goodrich, Mswebesa Bosco Bwana, Patrick Oyaro, Maurice Aluda |
| **Working Group(s)** | Adult Medicine, Behavioral and Social Sciences |
| **Description** | Though drug use (including inhalant use) is an increasing problem in East Africa, alcohol remains the most common substance of abuse in our populations. There are limited data on the impact of alcohol use on immune reconstitution, adherence and retention in care within sub-Saharan African HIV- infected populations. Given the high rates of food insecurity and resulting malnutrition, the impact of alcohol use on clinical outcomes in HIV-infected individuals in East Africa may be more profound than that seen in North America. Further exploration of the prevalence of and impact of alcohol use on the outcomes of HIV-infected individuals in sub-Saharan Africa is needed in order to inform HIV-care and treatment programs and assess the need for systems adaptation targeted towards identifying and intervening in individuals with alcohol addiction issues. |
| **Site(s)** | Moi Teaching and Referral Hospital |
| **Project Period** | 6/3/2013 – 7/31/2014 |
| **Funding Status** | Funded – NIH - National Institute on Drug Abuse (NIDA) |

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| **Direct Award (USD)** | $36,000 |
| **Update** | The Study is closed to enrollment. |
| **Future Plans** | Data Analysis is ongoing and manuscripts on the same will follow in the coming months. |
| **Publication(s)** | |
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| **Study Title** | **REALITY 'Reduction of EArly mortaLITY in HIV-infected adults and children starting antiretroviral therapy'** |
| **Principal Investigator(s)** | Kara Wools-Kaloustian, Indiana University<br>Abraham Siika, Moi University |
| **Co-Investigator(s)** | |
| **Working Group(s)** | AMWG, PRWG |
| **Description** | A 2x2x2 open-label factorial multi-centre trial, conducted in 9 centres in 4 countries (Kenya, Malawi, Uganda, Zimbawe). Study participants will be1800 HIV-infected patients including adults, adolescents and children aged 5 years or older with low CD4 counts about to initiate combination antiretroviral therapy (ART). There will be Three methods to reduce early mortality following ART initiation (i) increasing the potency of ART with a 12 week induction period using 4 antiretroviral drugs from 3 classes (ii) augmented prophylaxis against opportunistic/bacterial infections and helminths for 12 weeks (iii) macronutrient intervention using ready-to-use supplementary food for 12 weeks. Each intervention will be compared with standard of care, which in previously untreated patients presenting late with very low CD4 counts is to initiate ART with 3 drugs from 2 classes, together with cotrimoxazole prophylaxis and macronutrient intervention only for those with low BMI (or low weight-for-height/mid-upper arm circumference in children). The primary objective of the trial is to identify effective, safe and acceptable interventions to reduce early mortality (all-cause) in HIV-infected adults, adolescents, and older children (5 years or more) initiating ART. |
| **Site(s)** | Moi Teaching and Referral Hospital |
| **Project Period** | 8/1/2013 – 8/1/2017 |
| **Funding Status** | Funded – Medical Research Council |
| **Direct Award (USD)** | |
| **Update** | REALITY Trial was closed to accrual in April 2015 after attaining the set target of 1800 participants across all sites. At Eldoret site 208 (195 adults and 13 children) participants were enrolled. Approximately 100 participants have exited the study after completing 48 weeks of follow up and were transitioned back to respective AMPATH Clinics where they were before joining the study. Follow up is going on well for the active participants. |
| **Future Plans** | The site will continue follow up of active participants. |

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| **Publication(s)** | |
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| **Study Title** | **SAFI (Stigma in AIDS Family Inventory) Validation Study** |
| **Principal Investigator(s)** | Rachel Vreeman, Indiana University<br>Winstone Nyandiko, Moi University |
| **Co-Investigator(s)** | Irene Marete, Hai Liu, Violet Naanyu |
| **Working Group(s)** | Pediatrics |
| **Description** | For families raising HIV-infected children in resource-limited settings, HIV/AIDS-related stigma shapes every aspect of the children's HIV management, from daily adherence to medication to decisions about pediatric HIV disclosure. We do not know the most effective strategies to reduce stigma for HIV-infected children and their families in resource-limited settings nor how to measure its effects on physical, emotional, or social outcomes. We want to learn more about how stigma affects families. As part of the HADITHI study, SAFI aims to develop and test a reliable, valid instrument to measure HIV/AIDS stigma as perceived, enacted, and internalized by Kenyan families with HIV-infected children. The specific aims for the SAFI validation study are to: Aim 1: Identify and modify H/A stigma questionnaire items for maximum reliability and content validity to measure perceived, enacted and internalized H/A stigma among Kenyan families with HIV-infected children. Aim 2: Assess the validity of the measures of perceived, enacted and internalized H/A stigma compared to independent construct measures including pediatric adherence to therapy and children's physical, psychological and social outcomes. Aim 3: Examine whether disclosure of a child's HIV status to the child reduces perceived, enacted, or internalized stigma for families with disclosed children compared to families with non-disclosed children. We thus propose assembling, adapting, and then validating measurement items for assessing the relevant domains of H/A stigma experienced by HIV-infected children and their caregivers in sub-Saharan Africa. |
| **Site(s)** | Burnt Forest Sub-District Hospital, Chulaimbo Sub-District Hospital, Khunyangu Sub-District Hospital, Kitale District Hospital, Moi Teaching and Referral Hospital , Mosoriot Rural Health Training Centre, Turbo Health Centre, Webuye District Hospital |
| **Project Period** | 12/17/2013 – 11/30/2015 |
| **Funding Status** | Funded – NIH - National Institute of Mental Health (NIMH) |
| **Direct Award (USD)** | $567,828 |
| **Update** | Aim 1: Identify and modify H/A stigma questionnaire items for maximum reliability and content validity to measure perceived, enacted and internalized H/A stigma among Kenyan families with HIV-infected children. Aim 2: Assess the validity of the measures of perceived, enacted and internalized H/A stigma compared to independent construct measures including pediatric adherence to therapy and children's physical, psychological and social outcomes. Aim 3: Examine whether disclosure of a child's HIV status reduces |

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| | perceived, enacted, or internalized stigma for families with disclosed children compared to families with non-disclosed children. No modifications have been made to the specific aims as stated in the original proposals. We have ongoing Institutional Review Board and local ethics committee approval for the aims. In the last 6 months: The data collected through the SAFI study will provide a comprehensive and validated family HIV/AIDS-related stigma measure for assessing HIV/AIDS (H/A) stigma in western Kenya, including perceived, enacted and internalized stigma. Using qualitative data gathered in our initial focus group discussions, as well as an extensive systematic review of pediatric HIV-related stigma measures, we developed a new candidate H/A stigma measurement tool. This stigma tool was incorporated into evaluations with study participants who were enrolled in the ongoing 2-year parent study on disclosure of HIV status to children, called the Helping AMPATH Disclose Information and Talk about HIV Infection (HADITHI Study) to test the reliability and validity of the stigma items in this setting. The H/A stigma measurement tool was utilized at 18-month evaluations for HADITHI study participants. Next, the H/A stigma measurement tool will be administered to all study participants at their final 24-month evaluations that started in May 2015. We continue the reliability and validity testing of the H/A stigma scale we constructed, utilizing the existing HADITHI cohort of families and administering the stigma measurement items during evaluations at months 18 and months 24 of HADITHI follow-up. We continue to complete a systematic review compiling items used to measure pediatric and caregiver H/A stigma in other settings. The review is well underway, with data now being extracted from the systematically identified studies. |
| **Future Plans** | For the SAFI revision, in the next 6 months, we will complete the systematic review and submit this manuscript for peer review. We will use the final data, once data collection from the HADITHI cohort of families is completed and data are cleaned, to assess the validity of the questionnaire measures of family stigma compared to independent construct measures including medication adherence, and children's clinical, psychological, and social outcomes. The data collected through the SAFI revision will enable us to assemble a comprehensive family HIV/AIDS-related stigma measure with maximum reliability and validity for assessing all relevant domains of stigma, including perceived, enacted and internalized stigma, and for use with all members of the family unit. |
| **Publication(s)** | 'HIV-Infected Adolescent and Caregiver Experiences of HIV Stigma and Discrimination in Kenya.' Fischer L, Nyandiko WM, Scanlon ML, McHenry M, Naanyu VM, R. Vreeman. Poster Presentation at 8th International AIDS Society Conference on HIV Pathogenesis, Trea |
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| **Study Title** | **Tablet Computer-Based Disclosure Counseling for HIV-Infected Adolescents and their Families: A Pilot Study of Perspectives from Providers** |
| **Principal Investigator(s)** | Megan McHenry (maiden: Uhl), Indiana University |
| **Co-Investigator(s)** | Vreeman, Rachel Apondi, Edith Nyandiko, Winstone McAteer, Carole Scanlon, Michael Fischer, Lydia |
| **Working Group(s)** | Pediatrics |

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| **Description** | The objective of this study is to evaluate a pilot project using Google tablet computers for disclosure-related counseling with HIV-infected children and their caregivers in three AMPATH clinics. Google Nexus 7 Android tablets donated to the IU-AMPATH Android Program will be loaded with materials developed as part of the ongoing HADITHI disclosure intervention trial (PIs: Nyandiko and Vreeman) and includes educational materials on HIV and disclosure, counseling-based activities, and video narratives sharing experiences of HIV and disclosure. A plan was in place prior to this proposal of this study to implement the tablet computers in these clinic sites regardless of whether the benefits or hindrances of these devices are measured. This study is focused on understanding how this implementation affects the healthcare provider's disclosure practice or perspectives. The healthcare providers (HCPs) targeted in this study will include all healthcare workers who handle children in the clinics of study. This would include a clinical officer, nurse, counselor, social worker, or other similar position. Our central hypothesis is that AMPATH HCPs will find these tablet computers usable and helpful as a tool in disclosure counseling. The long-term goal of this study is to provide evidence to better support adolescents through the disclosure process and increase the number of adolescents who know their HIV status. We plan to accomplish our research objective by achieving the following specific aims: Aim 1: Describe current disclosure practices and barriers to disclosure at three clinics (Bumala, Busia, and Port Victoria) in Western Kenya through interviews with key clinic staff. Aim 2: Compare the prevalence of disclosure at these clinics for HIV-infected adolescents (10 to 14 years) before and after the introduction of the tablet computers using disclosure status data collected through AMRS. Aim 3: Evaluate provider acceptability and usability of the tablet computers for disclosure counseling through surveys, cognitive interviews, and focus group discussions. Sub-aim 3a: Describe any changes in providers' knowledge, comfort, and attitudes regarding disclosure after the introduction of the tablet computers. |
| **Site(s)** | Bumala A Health Centre, Bumala B Health Centre, Busia District Hospital, Port Victoria Sub-District Hospital |
| **Project Period** | 2/23/2015 – 2/1/2016 |
| **Funding Status** | Unfunded – |
| **Direct Award (USD)** | |
| **Update** | This study has had a very successful start. Phase One had a total of 37 participants completing the survey and/or the semi-structure interview regarding how disclosure was taking place in their clinic. We went to all three clinic sites: Port Victoria, Bumala, and Busia for Phase One. This Phase is now complete. We are entering the data from those initial surveys into a REDCap. We also had the semi-structured interviews transcribed and we are currently coding them. In June 2015, we started Phase Two. This phase involved participants identified by that clinic's CO in charge as being involved in the disclosure process. These participants were trained on how to use a Google Tablet and how to access specific resources related to disclosure on them. These participants are to use the tablets for the patients they're helping with disclosure and track their use of the tablets on a survey. At the end of each month, they are to complete the survey and have it sent to Eldoret. After they do this, they will receive 200ksh via MPESA as compensation for |

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| | their time. The first surveys are expected in July. |
| **Future Plans** | We hope to receive all 6 monthly surveys back from all Phase Two participants at each site. We also hope to finished out coding and analysis of the semi-structured interviews. At the end of 6 months, we will hold focus groups at each of the clinic sites to explore the providers experiences with the tablet. |
| **Publication(s)** | |

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| **Study Title** | **Taking to the Streets: a Mixed-Methods Systematic Review of the Reasons Children and Youth Become Street-Involved** |
| **Principal Investigator(s)** | Lonnie Embleton, Moi University<br>Paula Braitstein, Indiana University |
| **Co-Investigator(s)** | Ayuku David |
| **Working Group(s)** | Pediatrics |
| **Description** | A wide variety of reasons children take to the streets to work or live have been cited in the literature; yet there lacks any compiled data on this topic by geographic region. It is suspected the dynamics that drive children to the streets are quite diverse and vary between high income and low-to-middle income countries. This systematic review aims to identify similarities and differences internationally for children living or working on the streets. In turn this literature should help identify future research needs as well as policy changes to best suit the needs for the millions of children worldwide before or after they turn to the streets as a way of survival. Overall objective To compile and critically analyze the literature regarding reasons why children and youth, aged <1-24, turn to the streets as a way to survive in order inform public health research and policy, while identifying gaps in knowledge and evaluating the strength of existing evidence. Specific Aim To describe the reasons children and youth become street-involved in both high and low to middle income countries including but not limited to: differences between street connected children in resource-constrained and very-high income settings, children on and of the street and males and females for street-involvement and the age they start living on the streets. Specific Questions: 1. What are the reasons children and youth come to the street both from quantitative and qualitative literature and are the reasons between the two methodologies similar or different? 2. What are the differences in reasons between children on the street versus of the street for coming to the streets? (if able to distinguish based on reporting) 3. What are the differences between children/ youth in high versus low/middle income countries? 4. What are the differences between genders? |
| **Site(s)** | Moi Teaching and Referral Hospital |
| **Project Period** | 8/1/2013 – 5/1/2014 |
| **Funding Status** | Unfunded |

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| **Direct Award (USD)** | $0 |
| **Update** | The meta-analyses for this study are complete and a manuscript has been drafted and will be submitted for publication by September 2015. |
| **Future Plans** | We aim to submit this manuscript for publication. |
| **Publication(s)** | |
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| **Study Title** | **The IU Simon Cancer Center (IUSCC) AMPATH-Oncology Institute (AOI): An Exemplar of Care for the Developing World and a Population-Based Research Environment for IUSCC** |
| **Principal Investigator(s)** | Tom Inui, Indiana University<br>Naftali Busakhala, Moi University |
| **Co-Investigator(s)** | Asirwa, C. |
| **Working Group(s)** | Oncology |
| **Description** | Kenya, like much of the developing world, is rapidly undergoing an 'epidemiologic transition' from a health scene dominated by infectious diseases to one in which the major causes of death and disability are cancer and other chronic diseases. Under these circumstances, applying science to the management and control of cancer has become as relevant to Kenya as it is in the United States. Similarly, what is learned about the prevention and treatment of cancer in the developing world literally has direct relevance to care in the United States. Cancer care and attendant research in Kenya, whose population is the most genetically diverse in the world, will catalyze the discovery of new genes of importance to our fight against cancer, new genomic predictors of cancer, and new genetic variants that predict response to therapy. Recognizing both emerging threats to population health and potential for advancing care and science, the IU Simon Cancer Center (IUSCC) and the IU-Kenya AMPATH Program have been actively pursuing resources to respond. The focus of the partnership is to develop a sustainable and comprehensive academic clinical care program that will serve the citizens of western Kenya, and in the process, create a unique program of international collaboration for patients with, or at risk for, malignancies. The mission of the AMPATH Oncology Institute (AOI) is to be the premier cancer program in Sub-Saharan Africa, noted for excellence in cancer prevention, treatment and palliative care. AOI activities will directly contribute to advances in cancer care, accelerate discoveries in the biology and treatment of cancer, and provide support for the IU Simon Cancer Center's quest to become a federally designated Comprehensive Care Center. Naftali Busakhala will characterize the awareness, beliefs, attitudes and behaviors of women coming to AMPATH's clinician breast exam screening as volunteers, comparing these beliefs to those of a community-based sample of women. He will also characterize the yield of the AMPATH screening program, the kinds of cancers detected, and the quality of care achievable in Western Kenya at present, with comparison against an international standard of care. Chite Asirwa will similarly characterize the awareness, beliefs, attitudes and behaviors of a |

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| | community-based sample of women, comparing their beliefs to those of their husbands, often a key influence on behavior in traditional societies. Taken together these two studies should reveal a great deal about how to influence women's behaviors and encourage participation in the only breast cancer screening program available presently - clinician examination. Both of these studies will use the BCAM (Breast Cancer Awareness Measure), a survey tool developed in Great Britain. We have worked carefully through the standard BCAM to sort questions into theoretically sound domains, using the Health Belief Model as a framework. Violet Naanyu will be conducting field testing and focus groups to do a culturally appropriate Kiswahili version. |
| **Site(s)** | Mosoriot Rural Health Training Centre, Turbo Health Centre, Kapsakworny |
| **Project Period** | 10/1/2011 – 7/1/2014 |
| **Funding Status** | Funded – Walther Cancer Foundation |
| **Direct Award (USD)** | $1,200,000 |
| **Update** | In the past six months all elements of data-gathering were closed for all sub-studies proceeding under the auspices of the Walther project. Two manuscripts written from study findings were accepted for publication, three are currently under review by journals, and one is in preparation. |
| **Future Plans** | The principal activities of the next six months will be to 1) design and implement an integrated cancer screening program for breast and cervical cancer secondary prevention at a site in the AMPATH delivery system and 2) continue to pursue publication of our research results in peer-reviewed journals. |
| **Publication(s)** | 1. Wachira J, Chite AF, Naanyu, V, Busakhala N, Kisuya J, Keter A, Mwangi A, Inui T and The Walther Project Team. Barriers to uptake of breast cancer screening in Kenya. East African Medical Journal 2014; 91(11): 391-397. 2. Naanyu V, Asirwa CF, Wachir |
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| **Study Title** | **The Role Faith Leaders Towards Promotion HIV-Testing Alongside Voluntary Male Circumcision in Nyanza, Kenya** |
| **Principal Investigator(s)** | Eunice Kamaara, Moi University<br>Amy Nunn, Brown University |
| **Co-Investigator(s)** | |
| **Working Group(s)** | Behavioral and Social Sciences |
| **Description** | The Nyanza region of Kenya has high rates of HIV infection, even among individuals. The faith community plays an important role in shaping social norms about HIV testing, prevention treatment and retention in care. Local home based HIV testing efforts have been effective in reducing AIDS related morbidity and mortality. This proposed study will explore the role of faith leaders in promoting HIV testing, treatment and linkage to care. In spite of increased national success in HIV testing and treatment, HIV prevalence in Nyanza has increased from 14.9 in 2007 to 15.1 % in 2011. Unfaithfulness combines with |

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| | ignorance of HIV status to register new infections. The proposed exploratory study will use qualitative interviews and focus group discussions (FGDs) with purposively selected participants to explore the role of faith leaders in promoting home based HIV testing and linkage to care. The aim of the proposed study is to better understand the role that faith leaders could play in promoting and normalizing home based HIV testing, treatment and linkage to care in Nyanza. This will inform and help expand home-based HIV testing program of AMPATH in Nyanza for improved prevention, control and management of HIV and AIDS. The specific objectives include: 1. To explore the beliefs of faith leaders about home-based HIV testing and treatment 2. To investigate barriers to home based HIV testing and treatment 3. To identify opportunities for promotion of home-based HIV testing, treatment and linkage to care. 4. To conduct a pilot study about the role of faith leaders in promoting HIV testing, treatment and linkage to care in home-based HIV testing program of AMPATH in Nyanza. |
| **Site(s)** | Mosoriot Rural Health Training Centre, Port Victoria Sub-District Hospital |
| **Project Period** | 11/1/2014 – 10/30/2015 |
| **Funding Status** | Funded – Brown University - Center For AIDS Research |
| **Direct Award (USD)** | $25,000 |
| **Update** | All 12 FGDs with faith leaders carried out and all qualitative oral interviews carried out with HIV care providers/researchers. Transcription of oral interviews is ongoing. I have presented work in progress at AMPATH. |
| **Future Plans** | over teh next 6 months I hope to complete data management and analysis and to compiete the final report as I prepare at least one paper for possible publication. |
| **Publication(s)** | |

| | |
|---|---|
| **Study Title** | **Vincristine Optimization in Kenyan Children with Cancer** |
| **Principal Investigator(s)** | Jodi Skiles, Indiana University - Purdue University in Indianapolis (IUPUI)<br>Festus Njuguna, Moi University |
| **Co-Investigator(s)** | G Olbara, MBBS S Langat J Musimbi T Vik, MD S Mostert, MD,PhD GJL Kaspers,MD,PhD N Busakhala F Asirwa P Loehrer J Renbarger, MD1 |
| **Working Group(s)** | Oncology, Pediatrics |
| **Description** | In resource-limited settings, access to chemotherapeutic agents is confined to a few therapies. Vincristine (VCR) is a mainstay in such settings due to its low cost and lack of myelosuppression, however, little is known regarding its disposition and true optimal dosing, especially in the pediatric population. Negative clinical outcomes, such as serious side effects due to drug overdosing or lack of efficacy due to sub-therapeutic dosing, may result. VCR is associated with highly variable cumulative dose-dependent peripheral neuropathy (VIPN). While pediatric oncology patients in the U.S. who receive VCR experience significant VIPN and excellent disease outcomes, Kenyan children with cancer |

who receive VCR experience little to no VIPN, highlighting the opportunity for optimization of VCR in this population. While there are clearly multiple factors that contribute to poor disease outcomes in Kenya, suboptimal dosing of VCR is the piece we aim to address in this study. The biological basis for the minimal VIPN we have observed in Kenyan children is uncertain but includes such things as genetic differences in VCR pharmacologic pathways as well as genetic variability in susceptibility to neuropathy. This gap in knowledge provides a clear opportunity to optimize use of this medication in Kenyan children with cancer and evaluate genetic associations with VIPN in order to personalize this medication for individual children once VCR dosing is augmented. Preliminary data has shown that Kenyan children with cancer (n=100) experience minimal VIPN. Despite the negligible neuropathy observed, subclinical VIPN can be detected using a very detailed, non-invasive assessment tool that we developed for detecting even very minor toxicity. Utilization of this tool in Kenyan children allowed us to identify an association between VIPN severity, CYP3A5 genetic polymorphisms, and an individual's ability to metabolize VCR, such that children with an allelic variant of CYP3A5 that results in a high VCR metabolizer phenotype experience less VIPN. Variability in VCR response and toxicity may be particularly significant within Africa, where human genetic variability is greatest, and where ~90% of Kenyans patients were fast VCR metabolizers. In one recent study, pharmacokinetic (PK) variability was linked to overall survival in children with acute lymphoblastic leukemia (ALL), such that children with faster VCR clearance had a greater chance of relapse. If VCR disposition, response, and neurotoxicity are linked, it may be possible to optimize dosing based on easily obtained knowledge of genetic polymorphisms responsible for disposition and subsequent neurotoxicity variability. This research is of particular importance in Africa, where VCR is one of few available anticancer drugs and is used in the treatment of over half of all cancer patients. Furthermore, given that most Kenyan children are CYP3A5 high expressers and thus VCR fast metabolizers, they may tolerate and benefit from higher doses of vincristine than are conventionally used in the U.S. and Africa. This proposed prospective study will be conducted in two parts, which will both enroll pediatric patients age 1-18 years with newly diagnosed acute lymphoblastic leukemia or nephroblastoma. Part I will be a VCR dose escalation phase (in combination with routine multi-agent chemotherapy) to determine the maximum tolerated dose of VCR in a population of Kenyan children with cancer. Part II will be utilize the maximum tolerated dose of vincristine determined from Part I in place of the standard dose of VCR in combination with routine multi-agent chemotherapeutic protocols. DNA and pharmacokinetic samples will be collected on all subjects to allow determination of biomarkers of development of VIPN. Subjects will be monitored closely for development of toxicity with laboratory assessments as well as detailed neuropathy assessments. The specific aims (SA) for this proposal are as follows: SA1: To determine the maximum tolerated dose (MTD) of VCR administered in conjunction with conventional chemotherapy in cohorts of Kenyan children with ALL or Wilms tumor receiving VCR as part of their anti-cancer treatment. SA2: To validate our pilot study findings and to further evaluate the association between common or functional variants in genes in the vinca alkaloid pharmacologic pathway and across the human genome with VCR PK, VIPN, and disease response in the same populations as SA1. SA3: To further develop our pharmacologic prediction model of VIPN describing associations between pharmacogenetic, pharmacokinetic, and

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| | clinical biomarkers and carefully characterized VIPN in the same population of patients as SA1. SA4: To evaluate the validity and reliability of several chemotherapy-induced peripheral neuropathy (CIPN) measurement approaches when used to quantify neuropathy and associated neuropathic pain in Kenyan children receiving vincristine. |
| **Site(s)** | |
| **Project Period** | 2/3/2014 – 1/31/2018 |
| **Funding Status** | Funded – NIH - National Cancer Institute (NCI) |
| **Direct Award (USD)** | $103,254 |
| **Update** | This study commenced in February 2014 and 24 subjects have been enrolled to date and we are currently recruiting subjects for Phase I, Dose level 3. To date, no toxicity has been observed and dose escalation is still ongoing. Recruitment has been slower than anticipated due to issues with access to chemotherapeutic agents, however that issue is now resolved and recruitment is starting to pick back up. Additionally, it took longer than anticipated to get the NCI/Leidos Biomedical contract with IU (and subcontract with Moi) in place, which delayed the hiring of a dedicated study nurse. All contract issues have now been resolved and the study nurse has been hired. Ideally, we would like to complete recruitment for Phase I of this study within the next 3 months. |
| **Future Plans** | Completion of enrollment to Phase I of this study in the next 3 months with hopeful submission of a manuscript in 6-12 months. It is unlikely that Phase II of this study will be completed due to ongoing issues with abandonment of care in this population making it difficult to draw any meaningful conclusions about whether the dose escalation schema has any impact on outcomes/survival. |
| **Publication(s)** | |

# FIGURES & TABLES

**Figure 1: Cumulative Total of AMPATH Research & Training Awards (1998 – 2015)**

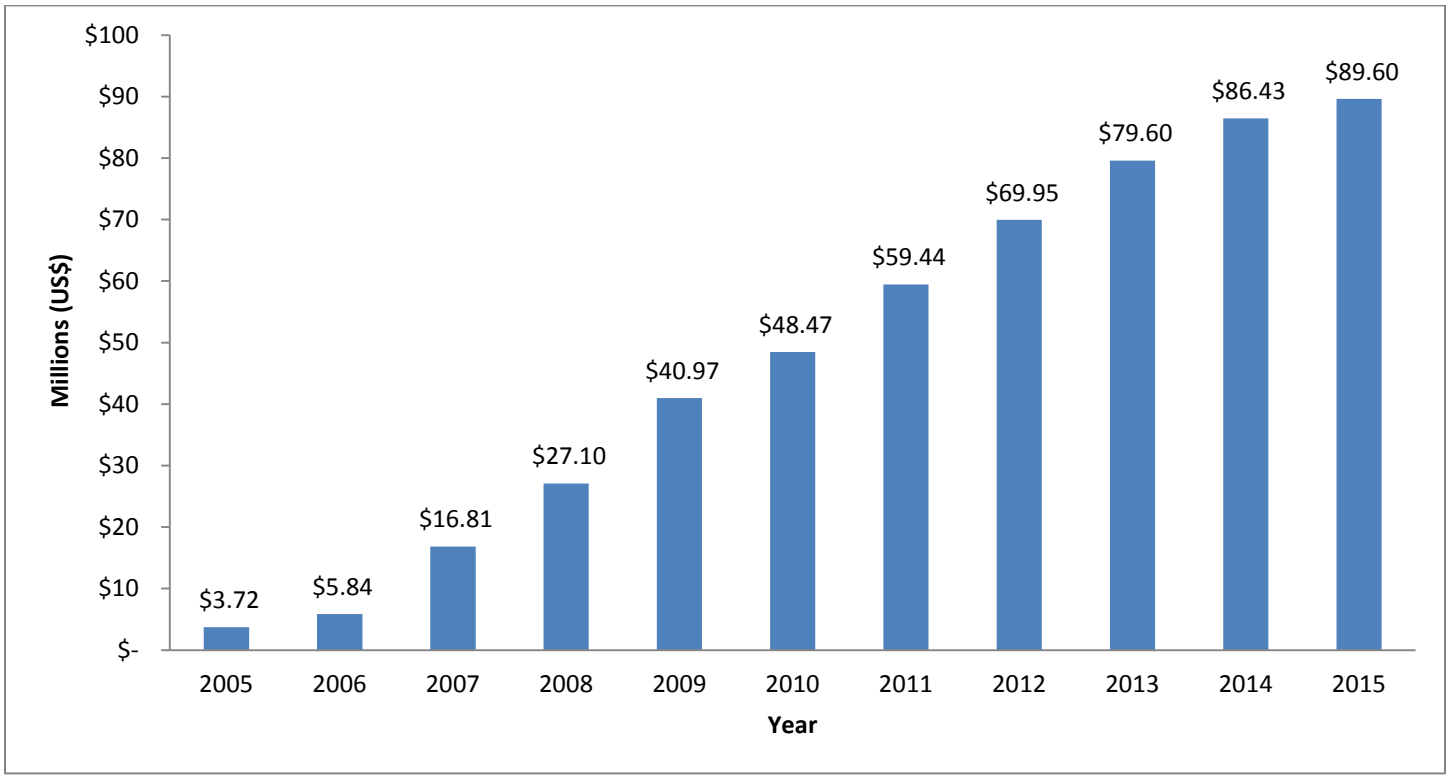



**Figure 2: Sponsors of AMPATH Research (January – June 2015)**

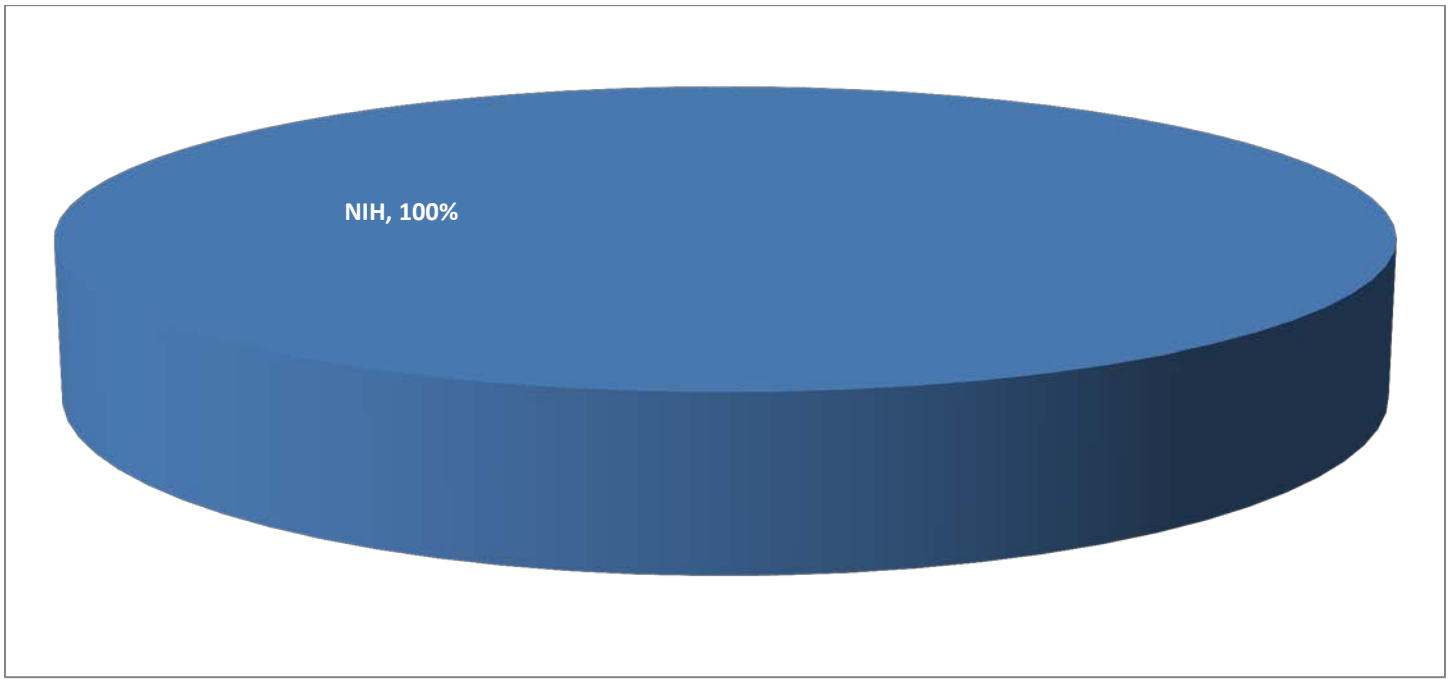


**Figure 3: AMPATH Research Sponsors (1998-2015) (Total Directs = US$89.6 million)**

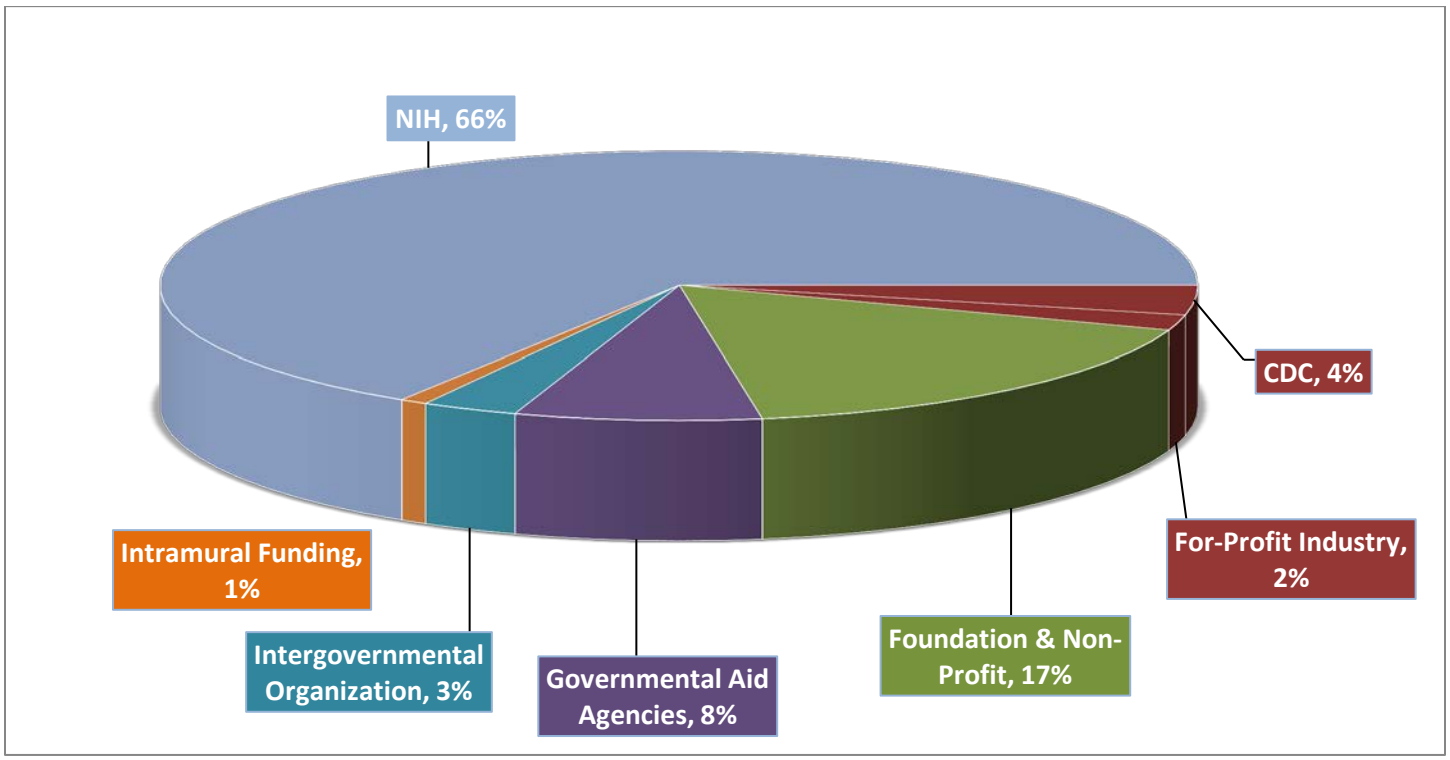
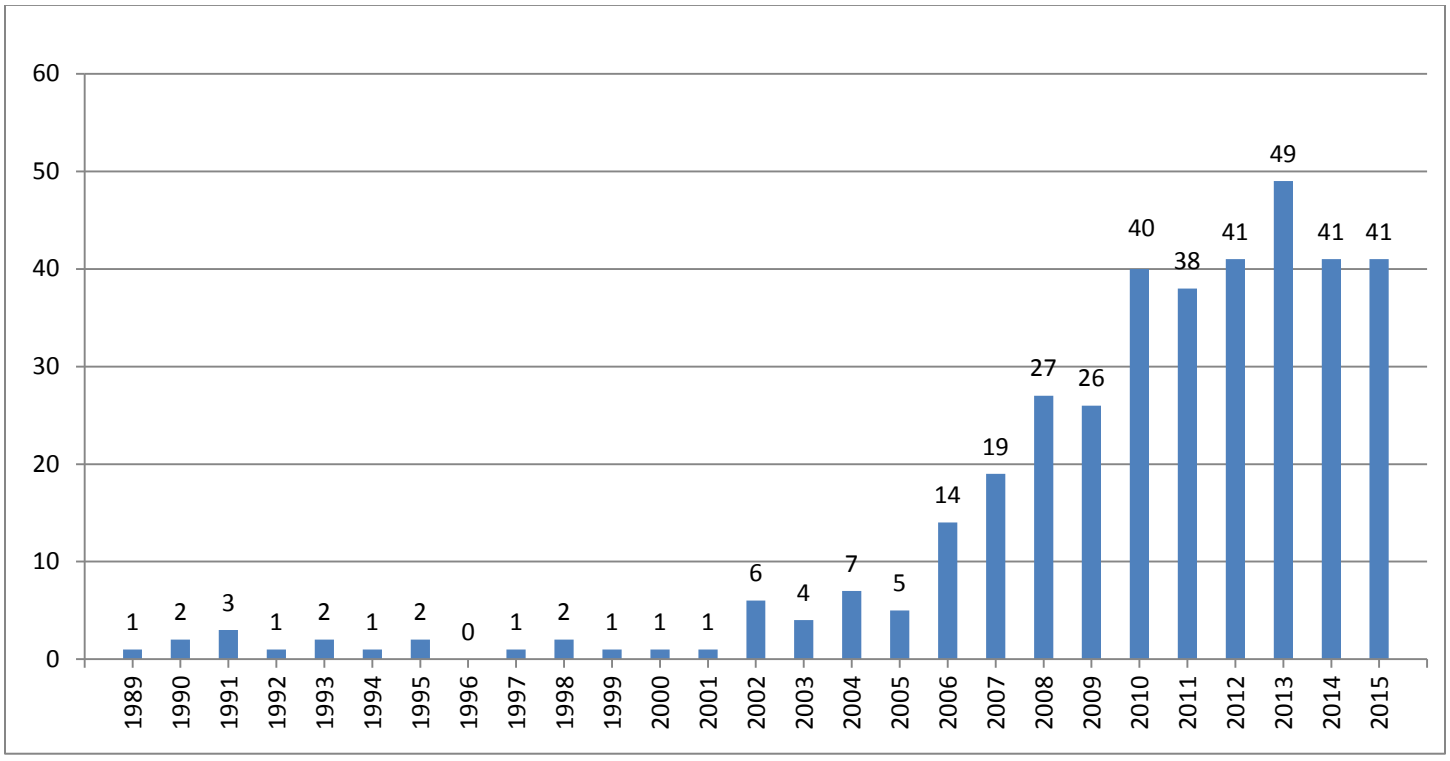



**Figure 4: AMPATH Publications by year published (1989-2015) (Total Publications = 376)**



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# INDEX

# APPENDIX A: IEDEA ANNUAL REPORT

# East Africa International Epidemiologic Database to Evaluate AIDS (IeDEA)

# Year 9 Science Report

# August 1, 2014- July 31, 2015

Kara Wools-Kaloustian M.D. M.S.
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Indiana University
Co-PI East African IeDEA

Grant Number: U01AI069911
May 11, 2015

## A. Specific Aims:

No change in specific aims from the last report.

## B. Studies and Results

### B1. Infrastructure:

*Composition and structure of the consortium*
The consortium consists of ten active HIV-treatment programs (Kenya-2, Tanzania-4, Uganda-4) and five U.S. universities (UC Berkeley is the fifth and only has access to de-identified data). The composition of the consortium is outlined in Table 1.

An investigator from each institution sits on the Executive Committee, which continues to meet every two months in order to address administrative issues within the consortium. The activities of the consortium continue to be divided between three cores (Scientific Development, Data, and Statistics/Methodology). Each core has a U.S.-based and an East-African-based co-chair. The Core Chairs meet at regular intervals to discuss interactions between the cores and to prioritize projects. Achieving investigator engagement in the Scientific Core Calls was a challenge. We found that we achieved much higher rates of engagement in smaller working group calls (e.g. KS, Cervical Cancer, TB, Hepatitis etc.) As such we have discontinued the Scientific Core Calls and now rely on the small working groups to move forward the scientific agenda in East African IeDEA. The Data Core is composed of the regional data managers and meets every four weeks in order to discuss issues related to the development of site-level master data sets as well as analysis data sets for individual concept proposals. The Statistics and Methodology Core is composed of Professors Yiannoutsos (IU) and Glidden (UCSF) along with Drs. Maya Petersen (Berkeley), Ann Mwangi (Moi) and Agnes Kiragga (Makerer). Members of this committee continue to meet (via phone, e-mail or in person) on an ad hoc basis to address specific analyses.

*Regulatory*:
The dates of original approvals and continuing reviews outlined in Table 1. Projects with prospective data collection are submitted and receive approvals separate from those for the primary consortium.

*Development and support of an EMRS infrastructure:*
All clinical sites contributing data to the consortium have stable electronic medical records systems (EMRS). An OpenMRS platform is utilized at all sites except Rakai, Kisesa and IDI. All sites have functional EMRS and have not had significant issues over the last year.

*Regional Data Center:*
During the past year the Regional Data Center has received complete data from all sites except for Rakai and the FACES sites. Rakai has recently transitioned to a new electronic medical records system and has only been able to submit partial data. The IT staff is currently working with the RDC to prepare the remaining data. Final submission is expected by the end of May. FACES has nearly completed preparation of the adult data and should be submitting by the end of April. Pediatric data are expected by July. The current composition of the Regional Database is outlined in Table 2.

| Table 1: Status of Regulatory Approvals 04.20.2015 | | | | | |
|---|---|---|---|---|---|
| Country | Site | Formal Name of IRB/IREC | Original Approval | Latest Continuing Review | Expiration |
| Kenya | AMPATH | Moi University College of Health Sciences (MU/CHS) & Moi Teaching and Referral Hospital (MT&RH) IREC | 20 Jun 2006 | 28 Oct 2014 | 27 Oct 2015 |
| | Nyanza Provincial Hospital (discontinued) | | 20 Jun 2006 | 28 Oct 2011 | 27 Oct 2012 |
| | FACES | Kenya Medical Research Institute/National ERC | 11 Nov 2008 | 27 November 2014 | 9 Dec 2015 |
| Tanzania | ORCI | The United Republic of Tanzania National Institute for Medical Research Coordinating Committee | 25 May 2007 | 26 September 2014 Report of 18 Sep 2014 | 10 Sep 2015 |
| | Tumbi Regional Hospital | | 25 May 2007 | | |
| | Morogoro Regional Hospital | | 25 May 2007 | | |
| | Kisesa | | 11 Sept 2012 | | |
| Uganda | MU-JHU MTCTplus (discontinued) | St. Raphael of St. Francis Hospital Institutional Review Ethics Committee | Local IRB: 23 Oct 2006 UNCST: 12 Feb 2008 | 25 Nov 2011 29 Jul 2011 | 24 Nov 2012 02 Jul 2012 |
| | St. Francis Nsambya (discontinued) | | Local IRB: 23 Oct 2006 UNCST: 12 Feb 2008 | 25 Nov 2011 29 Jul 2011 | 24 Nov 2012 29 Jul 2012 |
| | Mbarara University ISS Clinic | Mbarara University of Science & Technology Institutional Review Committee (MUST-IRC) | Local IRB: 20 Jun 2006 UNCST: 20 Jul2006 | 24 Jun 2104 2 Jul 2012 | 28 Jun 2015 16 Jul 2016 |
| | Masaka Regional Hospital | | Local IRB: 20 Jun 2006 UNCST: 20 Jul 2006 | 07 Jun 2103 2 Jul 2012 | 28 Jun 2015 16 Jul 2016 |
| | IDI | Makerere University School Medicine Research & Ethics Committee (MUSOMREC) | Local IREC: 3 Sep 2008 UNCST: 3 Feb 2009 | 28 Aug 2014 2 Jul 2013 | 2 Sep 2015 16 Jul 2016 |
| | Rakai | Uganda Virus Research Institute Science & Ethics Committee (UVRI-SEC) | Local IREC: 9 Nov 2010 UNCST: 8 Apr 2011 | 11 Nov 2014 2 Jul 2013 | 9 Nov 2015 16 Jul 2016 |
| US | Indiana University Consortium (11/25/15)) & Database (11/30/15) | Indiana University Institutional Review Board | 24 May 2006 | 26 Nov 2014 1 Dec 2014 | 25 Nov 2015 30 Nov 2015 |
| | University of California at San Francisco (UCSF) | University of California at San Francisco Committee on Human Research | 20 June 2006 | 10 Mar 2015 | 7 Apr 2016 |
| | Columbia University | Columbia University Medical Center Institutional Review Board | 8 July 2006 | Exempt | N/A |
| | New York University | New York University Committee on Activities Involving Human Subjects | Moved from Yale | Exempt | NA |
| | UC Berkeley | Berkley IRB | | Exempt | NA |

The Regional Data Center continues to receive and process data requests from the consortium investigators and has generated analysis data sets for nine concept proposals and has updated existing analysis data sets for six other proposals in the past year. The list of data requests, their concept numbers, and status can be found in Appendix 1-Project Tracking Table (links to the original concept sheets can be found in the tracking document on the EA-IeDEA website www.iedea-ea.org).

Table 2: Patient Enrollment as of 28 March 2015

| Country | Program /Site | Adults Enrolled | | Adults Receiving ART | | Children Enrolled | | Children HIV Infected | | Children Receiving ART | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | No. | (%) | No. | (%) | No. | (%) | No. | (%) | No. | (%) |
| Kenya | AMPATH | 142,670 | 55.5 | 102,407 | 71.8 | 44,173 | 85.0 | 26,492 | 60.0 | 19,649 | 74.2 |
| | FACES | 9,591 | 3.7 | 5,708 | 59.5 | 2,782 | 5.4 | 1,352 | 48.6 | 984 | 72.8 |
| Uganda | Masaka | 21,547 | 8.4 | 15,446 | 71.7 | 2,246 | 4.3 | 2,163 | 96.3 | 1,578 | 73.0 |
| | Mbarara (UCSF) | 24,975 | 9.7 | 14,137 | 56.6 | 80 | 0.2 | 80 | 100.0 | 33 | 41.3 |
| | IDI | 29,380 | 11.4 | 15,525 | 52.8 | 8 | 0.0 | 8 | 100.0 | 0 | 0.0 |
| | Rakai | 6,538 | 2.5 | 3,087 | 47.2 | 516 | 1.0 | 516 | 100.0 | 216 | 41.9 |
| Tanzania | Morogoro | 9,271 | 3.6 | 6,159 | 66.4 | 1,033 | 2.0 | 991 | 95.9 | 677 | 68.3 |
| | ORCI | 1,589 | 0.6 | 1,425 | 89.7 | 49 | 0.1 | 49 | 100.0 | 37 | 75.5 |
| | Tumbi | 9,115 | 3.5 | 4,802 | 52.7 | 913 | 1.8 | 889 | 97.4 | 520 | 58.5 |
| | Kisesa | 2,356 | 0.9 | 1,503 | 63.8 | 146 | 0.3 | 143 | 97.9 | 107 | 74.8 |
| TOTAL | | 257,032 | 83.0 | 170,199 | 66.2 | 51,946 | 17.0 | 32,683 | 62.9 | 23,801 | 72.8 |

*Education and Training:*

In the past year, **Agnes Kiragga**, a doctoral candidate at Makerere University in Kampala, Uganda, co-mentored by Dr. Yiannoutsos, successfully defended her doctoral dissertation and received her doctoral degree in Epidemiology. She continues to be employed as a statistical analyst at the Infectious Diseases Institute (IDI) in Kampala Uganda and is partially supported by EA-IeDEA. She has produced two papers (see next section) from her thesis in collaboration with Professor Yiannoutsos and Dr. Judith Lok, Associate Professor at the Department of Biostatistics at Harvard University School of Public Health. A Biostatistics intern, **Mr. Philani Mpofu**, originally from Zimbabwe, holder of a baccalaureate degree in statistics from Vassar University, was partially supported by IeDEA funds over the past year. Mr. Mpofu has completed one analysis, concerning the evolution of TB incidence over the first decade of ART scale-up in EA-IeDEA and is working on a new project, related to the causal effect of ART on TB incidence in East Africa (also see below). Mr. Mpofu has applied and was successfully admitted to the doctoral program in Biostatistics at the Indiana University Fairbanks School of Public Health in Indianapolis. He will be mentored by Dr. Yiannoutsos during his PhD training. **Mr. Joseph Nondi**, an EA-IeDEA scholarship recipient, completed his MSc degree in statistics at Kilimanjaro Christian Medical Center (KCMC) in Tanzania, with funding support from EA-IeDEA. He received support from EA-IeDEA to attend a course in STATA statistical programming in Mwanza, Tanzania. Mr. Nondi is employed at the National AIDS Control Programme in Dar es Salaam. In his role as the coordinator of the CTC Tanzanian AIDS database, he serves as a critical link between IeDEA and this enormous national resource. A supplement proposal, assessing the impact of point-of-care CD4 testing in the country, based on data gleaned from the national database, was submitted in April and serves, in addition to its epidemiological value, as a proof of concept for using a virtually untapped resource to address important research questions in that country.

Dr. Kara Wools-Kaloustian and Professor Yiannoutsos are part of **Ms. Samiha Sarwat,** a doctoral candidate in biostatistics within the Department of Biostatistics at the Indiana University Fairbanks School of Public Health, dissertation panel. Ms. Sarwat's research is sponsored by the Clinical and Translational Sciences Institute (Indiana CTSI). As part of her research, Ms. Sarwat is developing methodology to address patterns in weight evolution among patients starting ART (see below; Concept15). Ms. Sarwat will be defending her thesis early in the summer of 2015. A multi-regional manuscript is in preparation that involves over two million longitudinal weight measurements on almost 200,000 adult patients from five IeDEA regions. Preliminary results from this work were presented at the 19th International Workshop on HIV Observational Cohorts (IWHOD) held in Catania, Italy at the end of March 2015[1]. Dr. Nash and Dr. Yiannoutsos mentored **Mr. Eduardo**, a doctoral student at Columbia University Mailman School of Public Health, who used EA-IeDEA data to complete his thesis (Concept 14). Dr. Eduardo successfully defended his dissertation in the fall of 2015. One manuscripts from this work is in preparation[2]. Dr. Wools-Kaloustian and Dr. Yiannoutsos were co-mentors with Dr. Braithwaite for **Dr. Jason Kessler's** K-08 application entitled "Optimizing retention in care among HIV infected alcohol misusers in East Africa". This application proposed the utilization of data from the East African IeDEA cohort to refine models that assess the impact of various retention strategies directed toward alcohol misusers. Dr. Yiannoutsos and Dr. Giota Touloumi, of the University of Athens and the CASCADE collaboration, co-mentored **Elizabeth Syriopoulou**, whose master's thesis extended the methods developed by Drs. Agnes Kiragga, Yiannoutsos and Judith Lok (longitudinal CD4 count measurements adjusted for non-random dropout) to dichotomous or ordinal measures, with emphasis on adjusting adherence levels. The work

was presented by Dr. Lok at the Spring Meeting of the International Biometric Society East North Atlantic Region (ENAR) held in March 2015 in Miami, FL[3]. A manuscript is in preparation. **Dr. Aggrey Semeere** is being mentored by Dr. Jeff Martin and works directly with Dr. Martin on all aspects of the research related to Kaposi's sarcoma (KS) that is being conducted in East Africa IeDEA. Trained originally as a clinician, Dr. Semeere underwent formal training in epidemiology and biostatistics in the Master's Degree Program in Clinical Research at UCSF and has recently returned to a post-doctoral fellowship position at the Infectious Diseases Institute in Kampala. During this fiscal year, he completed a University of California Global Health Institute (UCGHI) GloCal Health Fellowship (sponsored by the NIH Fogarty International Center (FIC); www.glocalfellows.org), transitioned to a short-term fellowship supported by Gilead at the IDI, and more recently began a 5 year post-doctoral fellowship supported by NIH U54 CA190153. All of Dr. Semeere's work is being conducted within the auspices of IeDEA including his leadership of projects concerning the incidence of KS in the ART era (Concept 37), the impact of ART on KS incidence, and survival following KS diagnosis in the ART. He is also assuming administrative leadership of several aspects of the KS work, including chairing consortium-wide conference calls. Dr. Semeere exemplifies what can be achieved through dedication to a long-term rigorous training and mentoring plan. **Dr. Suzanne Goodrich,** under Dr. Wools-Kaloustian's mentorship, is working with IeDEA biostatisticians to analyze and report the findings from the NIDA-sponsored supplement looking at the impact of alcohol use on retention in care. In addition, In addition, Dr. Goodrich will be assuming a collaborative leadership role within EA-IeDEA for the AMPATH site. Dr. Wools-Kaloustian continues to provide informal mentorship to a number of clinician-investigators as they develop their concept sheets and manuscripts.

*Development of epidemiologic and statistical methods:*

The East Africa IeDEA Consortium has continued to develop statistical methods to address frequently encountered biases in the estimation of various aspects or characteristics of the patients who contribute data to our analyses. The focus of the statistical research efforts of our region has consistently been in the adjustment of estimates based on loss to follow-up and the resulting unrepresentativeness of the dropout population by the patient population still in care, a core assumption of all routinely used statistical methods. East Africa IeDEA investigators have made critical contributions in this area, starting with important papers in the use of double sampling techniques that take advantage of the availability of patient outreach data in some of our sites[4-7]. We have also been the first to carefully delineate the subtle differences between loss to follow-up, disengagement from care and retention and connection to care [8]. In this past year we continued these efforts by publishing several manuscripts that were directly informed by our double-sampling methodology.

*Adjustment by double sampling on mortality and longitudinal measures:*
Dr. Agnes Kiragga, published one manuscript related to mortality estimation adjustment after taking into consideration data from double sampling of patients who were lost to follow-up [7] and adjustment of longitudinal measurements (specifically CD4 total lymphocyte counts) collected over time, by the fact that sicker patients (and thus those with lower CD4 count, are more likely to die, drop out and to be disengaged from care. This non-random removal of these patients from the populations entering in the usual estimation of average CD4 counts at the program level, results in a dramatic overestimation of CD4 counts over time and, by extension, misleads stakeholders and decision makers in their effort to monitor and evaluate HIV care and treatment programs. Dr. Kiragga published a second manuscript on this issue [5]. We have expanded these efforts for the case of longitudinally collected dichotomous (yes/no) and ordinal (e.g., low, medium, high)

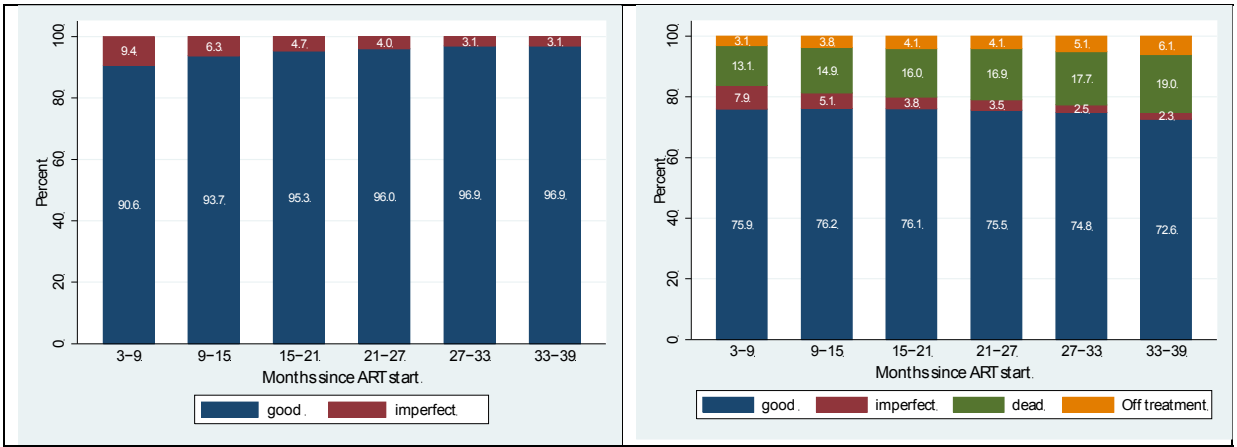


**Figure 1.** Naïve (left) and adjusted estiamates of adherence levels over time

outcomes. These methods were applied in the estimation of adherence levels among patients initiating ART in East Africa. Usually adherence is measured solely on patients who continue to participate in care and treatment and do not take into consideration the possibly non-random nature of patient dropout and death which is likely related to the level of adherence while the patient was still receiving care. Figure 1 below shows the difference between this routine (naïve) estimation of self-reported adherence rates (left panel) and the adjusted ones after death and dropout, and the resulting lower rates of treatment access, have been taken into consideration (right panel). Developing these methods formed the core of a master's thesis in biostatistics by Elizabeth Syriopoulou. A presentation of these methods, which included adjustments for both longitudinal measures (i.e., CD4 counts and adherence levels) was made at the most recent conference of the International Biometric Society, East North Atlantic Region, by Dr. Judith Lok [3]. As was the case with respect to CD4 counts, levels of adherence, even under the best case scenario of self-report, are likely to be significantly overestimated even under conservative assumptions of treatment access among patients who have dropped out of care.

*Non-random selection of patients to be double sampled*

In a recent paper, Drs. Frangakis and An, two of our external collaborators and Dr. Yiannoutsos published a follow-up paper to their 2009 Biometrics paper on double sampling[4] which extended the methodology so that the sampled subset of patients who have been lost to follow-up will focus on particularly informative subgroups (e.g., those who have been in care less time) thus reducing the variability in the data and increasing the

| | | Risk for dropout | | | | | Risk for dropout | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Low | Med | High | | | Low | Med | High |
| (a) Discretized double sampling ($\sum_k n_k$ fixed) | | | | | (b) Number of people double sampled in original design (variance=$7.1\times10^{-5}$) | | | | |
| Dropout time | Short | $n_1$ | $n_2$ | $n_3$ | Dropout time | Short | 32 | 79 | 88 |
| | Med | $n_4$ | $n_5$ | $n_6$ | | Med | 37 | 102 | 78 |
| | Long | $n_7$ | $n_8$ | $n_9$ | | Long | 36 | 88 | 81 |
| (c) Number of people to double sample for more efficient design when using ART (variance = $4.5 \times 10^{-5}$) | | | | | (d) Number of people to double sample for more efficient design when not using ART (variance = $4.3 \times 10^{-5}$) | | | | |
| Dropout time | Short | 121 | 124 | 15 | Dropout time | Short | 127 | 86 | 26 |
| | Med | 0 | 168 | 193 | | Med | 0 | 183 | 199 |
| | Long | 0 | 0 | 0 | | Long | 0 | 0 | 0 |

ART, antiretroviral therapy.

**Table 3.** Designs for double sampling and resulting variance of the 1-year mortality estimate form PEPFAR data in the paper by An et al.[9]

precision of the estimates. From a practical perspective, this paper allows the reduction of the number of patients who are sought for tracing, thus making the incorporation of patient outreach as a routine component of program monitoring and evaluation (M&E) an easier to implement intervention.

Table 3 shows the improved efficiency of sampling attained with careful consideration of suitable subsets of the population to be selected for tracing. It is also an indirect confirmation of the AMPATH policy to more aggressively pursue for tracing patients who have been on ART for the shortest period. Although the AMPATH policy is motivated by clinical considerations, this work shows that the data generated by the AMPATH outreach efforts provide the maximum information for double sampling adjustments to various M&E indicators such as mortality estimation among AMPATH HIV-infected patients.

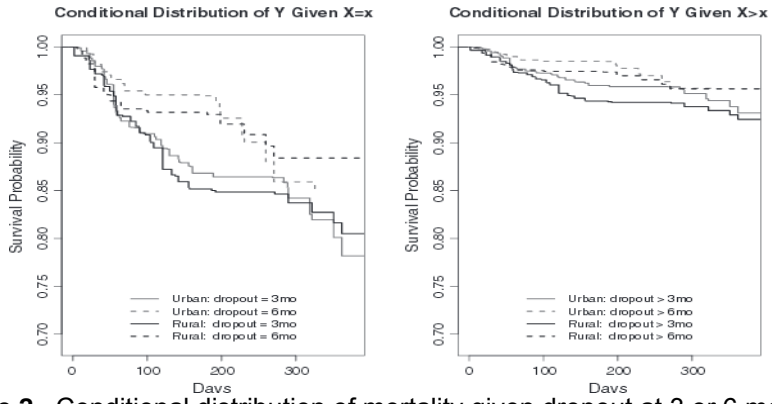


**Figure 2.** Conditional distribution of mortality given dropout at 3 or 6 months (left) and given *retention* at the original clinic (i.e., non-dropout) for at least 3 or 6 months. The lower levels of mortality seen in the right panel and the differences in the mortality estimates within each panel, underline the benefits of retaining patients in care. The differences in mortality in all cases among patients treated in rural settings, underline the variability in patient outcomes due to contextual factors surrounding care provision.

*Double sampling and competing risks*

A new research emphasis in the region is the development of methods which exploit data available from double sampling of dropouts to make adjustments for competing risk data. Such data arise frequently when one event (e.g., death) precludes observation of another (e.g., loss to follow-up, treatment modification, pregnancy, etc.). If, as is usually the case, mortality is underestimated, then estimates of the cumulative incidence of the competing event will be biased, frequently in an unexpected manner. In a recent paper published in the Scandinavia Journal of Statistics, Drs. Yiannoutsos and Yu, a colleague from the University of Wisconsin, developed revised estimates of death to LTFU in a competing risk analysis using double-sampling data (Figure

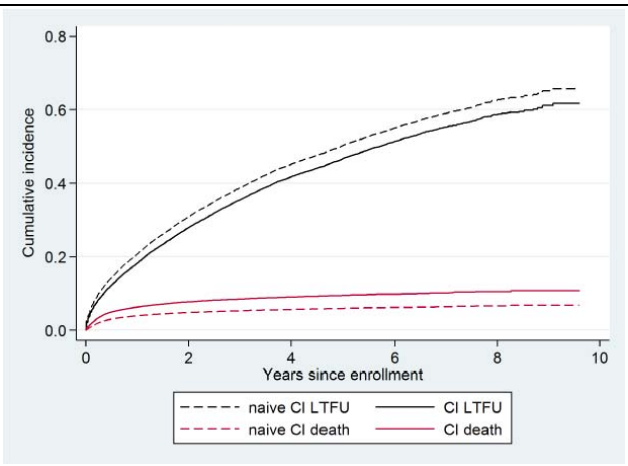


**Figure 3**. Cumulative incidence estimation of the competing events of death and loss to follow-up (LTFU). Solid lines are the adjusted estimates, while dashed lines show the usual estimates based on available information only.

2)[10].

In a more recent effort, Dr. Giorgios Bakoyannis, along with Drs. Yu, Frangakis and Yiannoutsos, presented a paper at the most recent IBS conference, East North Atlantic Region (ENAR) region, which attempts to quantify the impact of death under-reporting (and resulting "misclassification" of the death endpoint as loss to follow-up) when trying to estimate the cumulative incidence of these two semi-competing events[11]. By "semi-competing" we mean that LTFU does not preclude death, however without patient outreach the outcome of death after LTFU cannot be observed. Death, however, always prevents the observation of loss to follow-up. A highlight from this presentation is given in Figure 3.

These results show that, while the rate of LTFU is slightly overestimated in the naïve analyses (because of unreported deaths), patient mortality is drastically underestimated (because of misclassification of a large majority of deaths as LTFU). While these results are largely in line with previous reports [4,6,7,12,13], none of those methods took into account the competing risk of loss to follow-up in the estimation.

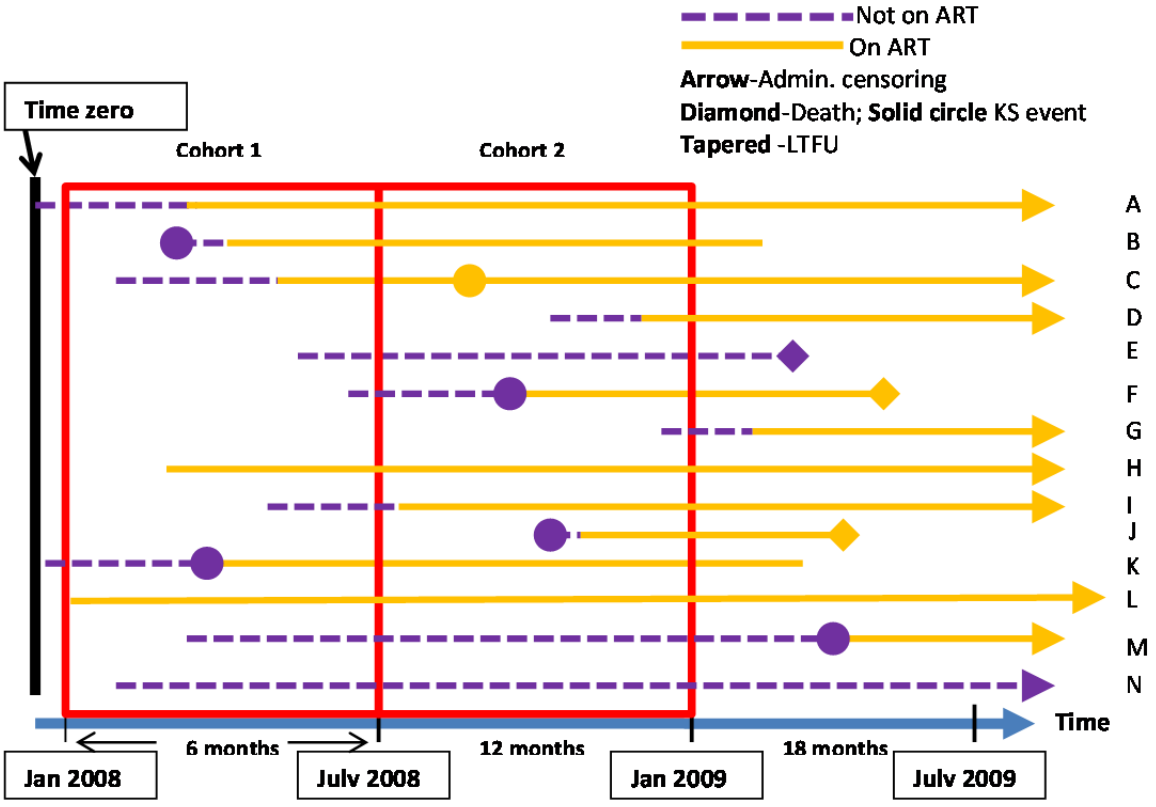


**Figure 4.** Implementation of the "new user" approach in the KS study.

*"New user" methods*

The East Africa IeDEA regional consortium has done seminal work in painstakingly assessing the impact of Kaposi Sarcoma (KS) on patient mortality and the salutary effect of antiretroviral therapy on the incidence and mortality of KS.

However, as the available data are observational, the effect of ART can be masked by the risk profile of KS patients who initiate ART or of ART users developing this disease. Cases

of such biases occurring in the setting of observational data analysis are nowhere as well known as in the case of the possible benefit of estrogen therapy and the risk of heart disease. In that situation, which closely mirrors the problem of ART and KS mortality, early observational studies showed great promise for the use of estrogen therapy on heart disease, only to be subsequently debunked by the findings of randomized clinical trials, which showed no effect and, in some cases, an increased risk for heart disease among women using estrogen therapy. The reason for the discrepancy was the so-called "healthy user bias", in that, women who took hormone-replacement therapy (HRT) were fundamentally different in terms of the risk of heart disease (lower risk) than women who did not. Thus, using HRT was a *marker* of behaviors associated with lower risk of heart disease and not the cause of the lower risk of heart disease (i.e., it was the *effect* and not the cause). Similarly, in our case, patients who use ART (existing users) have different risk for developing KS compared to patients who do not but also have different likelihood to initiate ART (i.e., sicker patients who may be at higher risk to initiate ART are also at higher risk to develop KS). At the same time longer ART use is over-represented among patients who did not start ART because of an early KS event when CD4 counts were low (survivor-bias) but also, there may be KS events among long-term (prevalent) ART users who adhere to their therapy and thus are maintained on follow-up for longer periods.

We use an approach called "New User" methodology[14], which subdivides the time of follow-up in a number of intervals and considers each such interval as the time of initiation of a new randomized clinical trial ("randomized" to receive ART or not) and then selectively removes existing ART users at each interval. In this setting, patients can participate in multiple such hypothetical trials. The impact of considering multiple "copies" of each patient is addressed in the estimation by the use of robust standard errors (which inflate the variability of the estimators and thus accounts for the under-estimation of the variability resulting by the artificially inflated sample size. A clear description of this method is discussed in the article by Hernan and colleagues[15] and is applied in re-analysis of the Women's Health Study data[16]. Figure 4 shows how the method is implemented in the KS study: Three "cohorts" are identified based on the time interval. The first spans the first half of 2008, the second the second part and the third the first part of 2009. The data have been updated since then, but these data correspond to a completed analysis presented earlier. As part of the method, subjects B, D, G, J and L are removed from cohort 1 (B because he/she had a KS event at enrollment, D, G and J because they did not start follow-up in the cohort and L (most importantly) because he/she were a prevalent user of ART. For cohort 2, subjects A, B, C, H, J, K, and L are removed, A, B, C, H, K and L because they are prevalent ART users and J because they have a KS event at entry. Note that subjects M and N participate in both clinical trials (cohorts 1 and 2). Using this methodology, we showed that use of ART is strongly associated with the observed reductions in KS incidence over the last decade in Kenya and Uganda. A presentation describing these results was given at the most recent 19th International Workshop on HIV Observational Cohorts (IWHOD)[17].

*Contributions to the Global IeDEA Consortium:*

**Dr. Rachel Vreeman** continues to serve as chairperson of the Pediatric Working Group and Dr. Jeff Martin continues to serve as the co-Chair of the Cancer Working Group. **Ms. Beverly Musick** was elected chairperson for the Data Harmonization Working Group.

***New Administrative Supplement to Enhance Data Infrastructure:***

*Automation of data extraction from OpenMRS*

For the supplement titled "Automation of data extraction from OpenMRS", Aims 1 and 2 have been completed and work for Aim 3 is ongoing. We have designed a system to house and display the current data state. This system identifies the relationship between the AMPATH Medical Records System (AMRS) concepts and the data collection form elements (both questions and answers) and allows users to code and group specific responses in order to create new variables. We have populated this system with the existing information (variables and response codes) from the current SAS extraction program (Aim 1). We have developed Macros for generating SAS conditional statements to derive the variables for specific data elements. SAS Macros have also been designed to generate SAS formats for these data elements. In addition, we have implemented a prototype for real-time decision making regarding the derivation of and formatting for new variables (Aim 2). We have conducted some preliminary tests of this software with the OpenMRS installation from Masaka Regional Hospital. Results appear to be promising but further modifications are needed in order to generalize the code for use with other OpenMRS installations. Once these adjustments are complete, we plan to share the software with data managers for FACES and Mbarara (Aim 3). Objectives and progress were presented at the East Africa Principal Investigators meeting in October and plans for a manuscript are underway.

**B2. Scientific Productivity:**

**Aim 1: Determine the short and long-term outcomes of adults and children along the entire spectrum of HIV care and examine patient and site-level factors associated with these outcomes.**

***Project 1.1*** *Describe the multi-level determinants of late ART-initiation in adults and children.*

This project is being addressed by Concept 39 "Characteristics of patients at enrollment into HIV care and outcomes prior to therapeutic ART eligibility or initiation in the IeDEA East Africa cohort" initiated by Dr. Elul. The statistical analysis for this project was completed by Dr. George Bakoyannis, a Post-Doctoral Fellow supervised by Professor Yiannoutsos. A manuscript is in preparation, and it is anticipated that it will be submitted for publication during the summer of 2015.

***Project 1.2*** *Investigate the incidence and determinants of treatment-limiting adverse events (AE) among ART-treated populations in East Africa.*

As previously noted, due to funding constraints this project could not be initiated as outlined in the original grant application. A modification of this project was submitted and funded as a supplement. In addition, a WHO-funded project which relies on in-kind support from East African IeDEA also addresses these specific aims. These projects are taking place at the AMPATH site in Eldoret, Kenya:

***Administrative Supplement:*** *"Building off the HIV Platform: Extension of Pharmacovigilance to Populations with Tuberculosis or Malignancies".*

*Tuberculosis Pharmacovigilance:* Clinicians utilized the new TB encounter forms with the supplemental pharmacovigilance section from January 2013 to June 2013. In the six

months of data collection, approximately 800 encounter forms were completed. A data request has been developed for this project, reviewed, and approved by the data management and analysis teams. The analysis to assess the incidence of adverse drug reactions (ADR) per person-months of TB drug exposure will be completed within the next few months with the goal of assessing results and completing a manuscript in late 2015.

**Preliminary results:** There were 315 HIV-TB co-infected patients with TB Supplemental Forms completed between January and September 2013. Among these patients 47 (14.9%) experienced at least one adverse drug reaction (ADR) associated with an anti-TB medication. Twenty (42.6%) patients experienced the first ADR during the initial phase of TB treatment. The most common ADR was jaundice with 9 (19.1%) patients initially reporting this side effect. Seven (14.9%) reported neuropathy, 5 (10.6%) reported rash, 5 reported joint pain, 4 (8.5%) experienced hepatitis, 3 (6.4%) experienced lactic acidosis and 4 experience other ADRs. Two (4.3%) patients experienced hearing loss and 1 (2.1%) patient had loss of appetite. Note that patients may have reported more than one ADR. Due to the complexities in calculating exposure times, incidence rates could not be calculated without further discussion with investigators. Since the data collection form did not specify when the ADR occurred and patients have a varying number of encounters, as well as, variation in the timing of these encounters with respect to treatment initiation, we are not certain that exposure time can be accurately calculated. Dr. Yiannoutsos suggested that simple proportions may be sufficient in describing this cohort.

***Oncology Pharmacovigilance***

The Oncology pharmacovigilance forms were used at the AMPATH Eldoret and Chulaimbo Clinics. The forms were completed by pharmacology technologists, pharmacists, and other staff during the clinical care of the patient. ADRs/symptoms reported from January 2012 – December 2012 were compared to the number of ADRs/symptoms reported from January 2013 to July 2013. The team's hypothesis is that the use of a symptom screening tool will capture more ADRs/symptoms than what is captured by clinicians during a routine clinical encounter.

**Preliminary results:** Through the AMPATH Eldoret and Chulaimbo Oncology Clinic sites, 133 patients with Kaposi's Sarcoma were evaluated. Of the 133 patients, 77 patients received chemotherapy in 2012, serving as the comparison group. In the 2012 group, 150 (0.38/per patient visit) ADRs/symptoms were reported in the patient files. In the 2013 group (n=39), preliminary results suggest that 269 (1.38/per patient visit) ADRs/symptoms were reported by the symptom screening form. These data suggest that patients are more likely to report ADRs/symptoms if specific questions are asked that probe for potential ADRs. Cleaning was completed on these in June 2014 and will be secondarily processed by the PI in June 2015 for final analysis. We anticipate that a manuscript will be ready for submission by December 2015.

***WHO/Gates funded grant****:*

*"Pharmacovigilance & Toxicity Documentation in the Context of Antiretroviral treatment-threatening: Comparative Evaluation of 4 Strategies in a Resource- constrained setting".*

The objective of this project evolved to evaluate the feasibility and effectiveness of five approaches to targeted spontaneous reporting (TSR) for documenting treatment-threatening serious adverse drug reactions (SADR) to antiretroviral medications in a

large clinical program within a resource-constrained clinical setting (AMPTH-Eldoret). All five arms have been closed to enrollment and all data collection has been completed. Associated clinical data have been requested for analysis. Below is a description of the different arms and their preliminary data analysis:

*TSR1. Completion of the "Kenya National Suspected Adverse Drug Reaction" form for patients with a change or discontinuation in their ART.*
From October 1st, 2012 to December 31st, 2013 there have been 262 cases of treatment-limiting SADRs documented on the Poison's and Pharmacy Board (PPB) SADR forms and reported to the national pharmacovigilance center (Table 4). For further details of comparisons between source documents and reporting to PPB see TSR5. This service has been continued to ensure that Kenya is able to evaluate ART associated SADRs. Moi Teaching and Referral Hospital (MTRH-AMPATH) remains the largest contributor of SADR data on ART to the PPB in Kenya.

*TSR2. Clinical encounter forms that have been enhanced to collect a limited amount of Suspected Adverse Drug Reaction data.*

In February 2014 a data request was submitted to the AMPATH Data Analysis Team (ADAT) to extract the data collected in the AMPATH Medical Record System (AMRS) related to this approach. A data quality assessment of 28 randomly sampled patient charts carried out in January 2014 showed significant differences in the number of symptoms reported during patient interviews (see below) and the data obtained from the AMRS (data collected using the enhanced encounter form). The chart review identified 81 medication-related symptoms captured during the patient interviews as compared to none captured by the clinicians using the enhanced encounter forms.

**Table 4**: SADR and drug association

| Suspected Drug | SADR cases No. (%) |
|---|---|
| Stavudine | 207 (79.0) |
| Zidovudine | 29 (11.1) |
| Nevirapine | 12 ( 4.6) |
| Tenofovir | 6 ( 2.3) |
| Efavirenz | 7 ( 2.7) |
| Abacavir | 1 ( 0.4) |
| Total | 262 |

*TSR3. Patient in-depth interviews conducted by HIV-infected peers and (TSR4) Patient in-depth interviews conducted by pharmacy personnel.*

**Table 5**: Reason for ART change

| Cause of ART regimen change | No. (%) |
|---|---|
| SADR | 458 (61.3) |
| Treatment failure | 96 (12.9) |
| Drug-drug interactions (mostly Rifampicin) | 52 ( 7.0) |
| Pregnancy | 7 ( 0.9) |
| Undocumented | 50 ( 6.7) |
| Phasing out | 84 (11.2) |
| Total | 747 |

A total of 844 participants out of the planned 1000 were enrolled into the study. The following interview categories were filled: Adult 1st line initiation (250), Adult 2nd line initiation (50), Adults stable (200), PMTCT (38) and Child stable (200). The child 1st line initiation (38/150) and the 2nd line initiation (6/50) groups did not reach full enrollment. Non- disclosure of HIV status to children and adolescents coming to clinic unaccompanied made recruitment of children challenging.

*TSR5. Routinely captured pharmacy data*.

From the pharmacy data we documented 747 changes in ART regimen over the study period. Table 5 provides a summary of the reasons given for the regimen changes. Of the 458

SADR cases identified through pharmacy data, 262 were reported to the national pharmacovigilance center while the remaining 196 (42.8%) were not reported due to inadequate documentation on the pharmacy prescription form and/or clinical encounter forms. Analysis is on-going for this project and should be completed by 2015.

***Project 1.3*** *Clinic and Patient-level determinants of durability of first-line ART regimen and time from first-line failure to second-line ART initiation in children in the international IeDEA cohort.*

This project is **Concept 40** "Clinic and Patient-level determinants of durability of first-line regimen and time from first-line failure to second-line ART initiation in children in the International IeDEA Cohort" a multi-regional project led by Dr. Wools-Kaloustian. The preliminary results of this analysis were presented at the 6th International Workshop on HIV Pediatrics, Melbourne, Australia. July 18-19, 2014 under the title "Time to First-Line ART Failure and Switch to Second-Line ART in the IeDEA Pediatric Cohort"[18](abstract in last year's report. Since this presentation we have made numerous modifications to the analysis datasets. Changes include the addition of key variables at the time of ART initiation, corrections of viral load status (from routine to confirmatory), addition of nutritional status variables, correction of laboratory results from South Africa, and revisions to the definition of switch to second-line ART. Analyses have been re-run on the updated datasets and we are in the process of including contextual variables in the analysis. The current plan is to have the analysis completed by the end of July and a draft paper ready for circulation by August 2015.

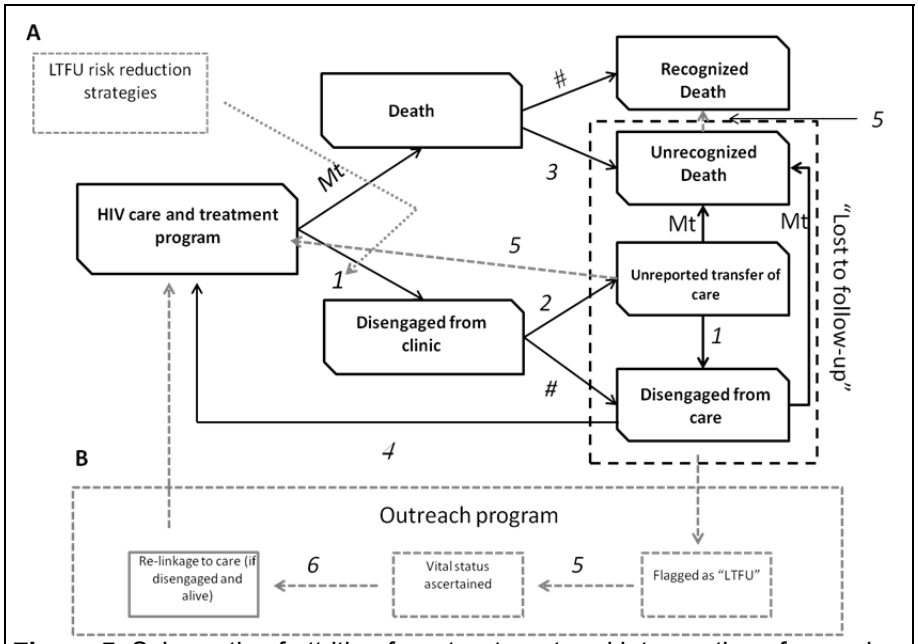


**Figure 5**. Schematic of attrition from treatment and interventions focused on mitigating attrition or its effects in computer simulation

***Project 1.4*** *Preventing 200,000 HIV infections in East Africa through better use of existing resources: a simulation modeling approach.*

The modeling team has completed planned substantive enhancements our computer simulations that include a) explicitly accounting for attrition and retention in HIV treatment programs amongst patients presenting for care and b) accounting for emerging high-risk groups in this setting, most notably men who have sex with men and substance abusers (including injection drug users and alcohol misusers).

Following the development, validation and debugging of our simulation model(s) of the HIV epidemic in East Africa we have conducted a wide array of analyses. These analyses have involved instantiating a group of evidence-based HIV prevention interventions within the simulation model, evaluating the effects in terms of infections averted and costs of implementation of each of these interventions independently, and evaluating the impact and cost of all relevant multi-component combinations of these HIV prevention approaches. These analyses have focused on the outcomes of HIV infections averted and costs per infection averted as well as quality adjusted life years gained and cost-per-QALY gained. The team currently has one paper under revision entitled "Value in Health. Impact and cost effectiveness of hypothetical strategies to enhance retention-in-care within HIV treatment programs in East Africa" with Dr. Kessler as first and Dr. Braithwaite as the senior author[19]. Figure 5 outlines the schematic of attrition from treatment and interventions focused on mitigating attrition within the computer simulation model reported in the Kessler paper.

***Other projects that fall within Specific Aim 1:***

There are a number of other projects that fall under the umbrella of Specific Aim 1 (see Appendix 1- Concept Tracking Document).

***Concept 9****: "A comparison of the immunologic efficacy of antiretroviral therapy in resource-replete versus resource-limited settings"*

This multi-regional analysis was led by Dr. Geng and Dr. Martin and resulted in a paper entitled, "CD4+ T cell recovery during suppression of HIV replication: a global comparison of the immunologic efficacy of antiretroviral therapy" that was published in the International Journal of Epidemiology [20].

***Concept 11:*** *Facility and program characteristics of HIV care and treatment programs in the IeDEA collaboration, "Characteristics and Comprehensiveness of Adult HIV Care and Treatment Programs in Asia-Pacific, sub-Saharan Africa, and the Americas: Results of a Site Assessment conducted by the International epidemiologic Databases to Evaluate AIDS (IeDEA) Consortium"*

This project was led by Dr. Denis Nash resulted in a JIAS paper.[21]

***Concept 13:*** *"Models of patient outreach and their associated rates of loss to follow-up in the East African IeDEA consortium"*

This project is led by Dr. Braitstein and has been renamed "**Facility factors affecting retention among East African IeDEA sites"**

Although much is known about patient-level determinants of retention and losses to follow-up, less is known and very little quantified about the impact of facility-level factors including program structure, human resources, laboratory testing, among others. The IeDEA consortium is uniquely positioned with its facility-level data to evaluate these effects. We began in 2011 with examining the effect of different structures of outreach programs and other interventions to ascertain mortality and reduce losses to follow-up (presented at CROI 2011). Since then expanded the analysis to incorporate numerous other site-level factors and a mature draft is circulating to the co-authors prior to submission to *Lancet HIV*[22]. Below is the abstract from the draft manuscript.

**Background**: Retention in HIV care is critical for continued access to ART, leading to improved patient outcomes, viral suppression and decreased HIV transmission. Unfortunately, loss to follow-up (LTFU) remain an important programmatic challenge. While numerous patient-level factors have been associated with LTFU less is known about facility-level factors.

**Methods:** Using data from the East African International epidemiologic Databases to Evaluate AIDS (EA-IeDEA) Consortium, we sought to identify facility-level factors associated with LTFU from care before and after antiretroviral therapy (ART) initiation. All facilities associated with IeDEA in Kenya, Tanzania and Uganda were included. Patients were defined as LTFU if they had no visit within 12 months of the study endpoint for pre-ART patients or 6 months for patients on ART with no documentation of patient death or transfer. LTFU rates were stratified by country and programs. Adjusting for patient-level factors, shared frailty proportional hazard models, which account for the association between patients from the same EA-IeDEA program, were used to identify the facility-level factors associated with LTFU for the pre- and post-ART periods.

**Results:** Data from 88,152 patients and 29 clinics (Kenya 23, Tanzania 3, Uganda 3) were analyzed. Median age at enrolment was 36.0 years (IQR: 30.1, 43.1), 63.9% were women and 58.3% initiated ART. The overall rates (95% CI) of LTFU were 25.1 (24.7-25.6) and 16.7 (16.3- 17.2) per 100 person-years in the pre-ART and post-ART periods, respectively (HR=X, 95% CI Y-Z). Facility-level factors associated with increased LTFU before and after ART initiation included no onsite-availability of secondary-level care, HIV RNA PCR turnaround time >14 days, and no onsite availability of CD4 testing. Increased LTFU was also observed for the pre-ART period when no nutritional treatment was provided by the facility, and when symptomatic TB patients were treated within the ART program. After ART initiation, increased LTFU was associated with the facility being open ≤4 mornings per week.

**Discussion:** LTFU rates were higher in pre- versus post-ART periods. Facility-level factors associated with LTFU both pre- and post-ART initiation included the facility level of care and availability and timeliness of labs. Our findings have implications for the development of facility-based strategies to improve retention in pre-ART and ART care. This can help to improve the proportion of patients initiating ART who achieve viral suppression.

***Concept 14:*** *"Factors associated with CD4 count and ART initiation and their relationship to survival"*

This project is led by Dr. Eduard Eduardo under the direction of Drs. Nash and Yiannoutsos, two of Dr. Eduardo's former doctoral thesis advisors. The goal of the project is to assess whether, and to what extent, implementation of approaches to active screening (e.g. Provider Initiated Counseling and Testing) at the programmatic level translate into higher patient CD4 cell counts at ART initiation and improved patient survival. Furthermore, the project aims to assess whether a detected association between active screening and patient survival was mediated by patient CD4 cell count. Sites were classified as active or non-active screening based on whether 1) they conducted active screening at the site and 2) their primary source of patients were referred from entry points known to historically conduct active screening.

Three analyses have been finalized as part of Mr. Eduardo's PhD dissertation: 1) Association between site active screening and patient CD4 cell count at ART initiation, 2) Association between site active screening entry points and patient CD4 cell count at ART

initiation, and 3) Association between site active screening entry point and patient survival. Two manuscripts summarizing these analyses are currently in circulation and will be completed prior to the end of the next funding year. The key finding for Analysis 1 is that mean patient CD4 cell count at ART initiation does not differ materially between sites with and without active screening; The main finding from Analysis 2 is that sites with active screening entry points have higher patient CD4 cell counts at ART initiation than sites without active screening entry points and the main finding from Analysis 3 is that patients in sites with active screening entry points have a rate of death that is 18% *lower* than patients in sites without active screening entry points (results narrowly miss statistical significance – 95% CI 0.64-1.06). The relationship between active screening entry point and survival is mediated by patient CD4 cell count at ART initiation as hypothesized. In other words, active screening results in an over-representation of patients with higher CD4 counts (and thus better survival) compared with non-active screening entry points into care..

***Concept 15: "****Weight evolution in patients on effective ART: a comparison among different regions and different regimens"*

This is a multi-regional analysis led by Dr. Colebunders and the previous leadership of the Central African IeDEA region. Since the beginning of the current funding cycle the leadership of this project has been transferred formally to the West African region. The analyses for this project were recently completed under the leadership of West Africa IeDEA region and a manuscript, titled "Determinants of weight evolution among HIV-positive patients initiating antiretroviral treatment in low resource settings, the IeDEA collaboration" is under revision at the Journal of AIDS (JAIDS)[23].

***Concept 19:*** *"Estimates and correlates of pediatric ART adherence"*

This concept is led by Dr. Vreeman. There have been multiple revisions of these analyses and the manuscript over the course of the last year, ultimately describing adherence over time, by program and by a number of related factors using a hierarchical, three-level, logistic-regression model to examine adherence, with observations nested within patient and patients within the 8 programs providing pediatric HIV care in East Africa IeDEA. In the final hierarchical model, variance in reported adherence associated with the site was substantial along with the variance associated with individual patients. Longer time on ART was associated with slightly higher adherence, and older age (i.e. as patients approach the teenage years) with lower levels of adherence, while no associations were detected with respect to the size of the program or the duration that a program was in existence. In a sub-analysis involving AMPATH data only, orphan status was, predictably, associated with much lower adherence levels. There was a delay in the manuscript submission planned for this funding year as the team chose to conduct additional analyses prior to completing the manuscript. It is expected that the completed manuscript will be submitted in mid-summer 2015.

***Concept 20: "****Adolescent Care in East Africa"*

This project is led by Dr. Gisore, a Pediatrician at AMPATH. The first set of analyses were completed for this study by Dr. Ann Mwangi of Moi University, and were shared with the regional membership during the meetings in Athens Greece in October 2014. During this review, there were some issues highlighted based on the findings that needed revision before the analysis could be finalized. Revisions to these analyses have been made and will

be reviewed by Dr. Yiannoutsos during his visit at AMPATH in May 2015. We anticipate that a manuscript will be in preparation within the summer 2015.

***Concept 25:*** *"Sub-optimal CD4 reconstitution among patients on antiretroviral therapy in the developed and developing countries; Frequency and patterns, determinants and clinical significance"*

This project is led by Drs. Easterbrook at the WHO and Damalie Nakanjako, Agnes Kiragga at the Infectious Diseases Institute. The data analysis for this project is complete and a manuscript entitled "AIDS-related illnesses among sub-optimal immune responders to first-line HAART within the IeDEA-East Africa cohorts" is under preliminary acceptance for publication at BMC Infectious Diseases.

The main results from these analyses is that sub-optimal immune response was associated with a high incidence of AIDS-related illnesses, while only half of cART-treated adults 'normalized' their CD4 counts after 5 years after starting cART. Further knowledge of mechanisms of sub-optimal immune recovery, including genetic predictors, is required to inform targeted therapeutic interventions to optimize short and long-term immune recovery**.**

***Concept 27:*** *"Predicators and factors associated with treatment failure among HIV-infected children on ARVs"*

This project is led by Dr. Irene Marete, a pediatrician at AMPATH. The results were presented in the East African IeDEA meeting in Greece in October of 2014. A number of revisions have been completed since then and the final analysis has been completed by Dr. Ann Mwangi and forwarded to Dr. Marete.

The main results from this analysis is that CDC class at ART start is, predictably, the main predictor associated with higher hazard of clinical failure while family caregiver is also a significant factor predisposing children to fail clinically. CD4 count and percent at ART initiation are the main factors associated with increased hazard of immunological failure. Dr. Marete is working on the first draft of the manuscript.

***Concept 30****: "Immunodeficiency at the start of ART: a global view*"

This is a multi-regional project led by Southern Africa. The project has resulted in a publication this year titled, "Immunodeficiency in children starting antiretroviral therapy in low-, middle- and high-income countries by Koller and colleagues (and a letter to the editor)[24,25].

***Concept 31:*** *"Modification of the effect of deferred regimen modification following loss of viral suppression on first-line therapy by CD cell count and HIV RNA level"*

This project is led by Dr. Petersen resulted in a publication at the journal *AIDS*, entitled "Delayed switch of antiretroviral therapy following confirmed virologic failure is associated with elevated mortality among HIV-infected adults in Africa"[26].

***Concept 32:*** *"Revising mortality estimates and predictors of mortality among HIV-infected children in western Kenya"*

This project is led by Drs. Paula Braitstein and Ann Mwangi. As has previously been shown, the true mortality rate among adult HIV-infected patients in care depends heavily on knowing the mortality rate of patients who have fallen out of care. This is equally true of pediatric patients and in 2010 we published our findings from having traced a random sample of 98 HIV-infected and exposed children. We are now aiming to use these data to revise pediatric mortality estimates. The dataset is in the final leg of preparation and the regional data manager reports it will be finalized by the summer 2015. The process of creating this dataset has been more complex than previously realized. Our intended timeline is to have an abstract ready for submission to CROI and/or IWHOD later this year.

***Concept 33:*** *"What is the capacity for the Conduct of adverse event/toxicity monitoring in resource-constrained settings?"*

This is a multi-regional analysis being led by Dr. Braitstein. Dr. Braitstein's post-doctoral fellow, Dr. Beth Rachlis, has made tremendous progress on this project over the last year. There is a mature draft of the manuscript being circulated to the co-authors. We greatly appreciate the patience of our IeDEA collaborators and the NIH as we recognize how long this project has taken!

***Concept 34: "****Development of low-tech and context-appropriate tools for monitoring ART in children in resource poor-settings: weight and CD4 velocity reference standards"*

This is a multi-regional concept led by Dr. Yotebieng from the Central Africa IeDEA Region. This effort has resulted in a publication in AIDS entitled "Age- and sex-specific weight gain norms to monitor antiretroviral treatment in children in low- and middle-income countries"[27].

***Concept 42:*** *"The incidence of first-line ART failure and incidence and determinants of initiation of second-line ART in adults meeting local criteria for first-line failure"*

This project is led by Dr. Suzanne Goodrich. Early data on rates of failure by failure type (clinical, immunological or virological) resulted in a poster at IAS, in Melbourne Australia, in July 2014[28]. A manuscript entitled "The incidence of first-line ART failure and the incidence and determinants of initiation of second-line ART in adults in the East African IeDEA cohort" is under author review and expected to be submitted for publication in summer 2015.

***Concept 45: "****Clinical characteristics and outcomes of adolescents attending HIV clinics in IeDEA East Africa"*.

This project is led by Dr. Nuwagaba-Biribonwoha, Columbia University and ICAP, and is supported by Dr. Kiragga at IDI. The analysis has recently been completed. The results are under review and will be finalized during Dr. Yiannoutsos' visit to Kampala in late May 2015.

The preliminary findings show that the CD4 counts at enrollment into care and at ART initiation are higher for adolescents than adults. In addition, a lower proportion of adolescents have WHO stage III and IV than adults at enrollment and ART initiation. It is anticipated that the statistical analysis will be completed during the summer 2015 and a manuscript will be forthcoming by October of 2015.

***Concept 53****: "Switching of ART to second- and third-line regimens: a global view"*

This is a multi-regional concept led by Dr. Egger of the Southern African Region. A poster entitled "Monitoring and Switching of First-line ART in sub-Saharan Africa" was presented at the 2015 CROI[29] and a manuscript entitled "Monitoring and Switching of Antiretroviral Therapy in sub-Saharan Africa: Collaborative Analysis of HIV Cohort Studies" has been revised and submitted for re-review to Lancet-HIV[30]. The abstract of this paper is outlined below:

***Background:*** HIV-1 viral load (VL) testing is recommended to monitor antiretroviral therapy (ART) but not universally available. We examined monitoring of first-line and switching to second-line ART in sub-Saharan Africa, 2004-2013.

***Methods:*** Adult HIV-1 infected patients starting combination ART in 16 countries were included. Switching was defined as a change from a non-nucleoside reverse-transcriptase inhibitor (NNRTI)-based regimen to a protease inhibitor (PI)-based regimen, with a change of ≥1 NRTI. Virological and immunological failures were defined per World Health Organization criteria. We calculated cumulative probabilities of switching and hazard ratios with 95% confidence intervals (CI) comparing routine VL monitoring, targeted VL monitoring, CD4 cell monitoring and clinical monitoring, adjusted for programme and individual characteristics.

***Findings:*** Of 297,825 eligible patients, 10,352 patients (3·5%) switched. Compared to CD4 monitoring hazard ratios for switching were 3·15 (95% CI 2·92-3·40) for routine VL, 1·21 (1·13-1·30) for targeted VL and 0·49 (0·43-0·56) for clinical monitoring. Overall 58.0% of patients with confirmed virological and 19·3% of patients with confirmed immunological failure switched within 2 years. Among patients who switched the percentage with evidence of treatment failure based on a single CD4 or VL measurement ranged from 32·1% with clinical to 84.3% with targeted VL monitoring. Median CD4 counts at switching were 215 cells/μl under routine VL monitoring but lower with other monitoring (114-133 cells/μl).

***Interpretation:*** Overall few patients switched to second-line ART and switching occurred late in the absence of routine viral load monitoring. Switching was more common and occurred earlier with targeted or routine viral load testing.

***Concept 54:*** *"Treatment outcomes on first-line, second-line and third-line ART: a global view"*

This is a multi-regional concept led by Dr. Egger of the Southern African Region. The East African data was transferred in May, 2013

***Concept 55:*** *"CD4 trajectory adjusting for dropout among HIV-positive patients receiving combination antiretroviral therapy in an East African HIV care center"*

This project was led by Drs. Agnes Kiragga, formerly at Makerere University and the IDI and Yiannoutsos and was part of Dr. Kiragga's doctoral dissertation. This concept resulted in a manuscript of the same title, published in JIAS.[31]

***Concept 56: "****HIV among adults aged 50 years and older over the continuum of care (testing and diagnosis, clinic registration and ART initiation) in East Africa: characteristics treatment outcomes, co-morbidities, and ART toxicities"*

This project is led by Dr. Easterbrook. Analysis datasets for this project were finalized in October 2013 and the statistical analyses were completed in early 2014. A manuscript will be circulated by summer 2015.

***Concept 58:*** *"Adherence to antiretroviral therapy (ART) for HIV-infected children and adolescents followed in Global IeDEA sites"*

This is a multi-regional analysis led by Dr. Vreeman. The primary objectives of the proposed analyses are to describe pediatric ART adherence and associated factors among children and adolescents followed in IeDEA. With these analyses, we will achieve the following specific aims: (1) Describe pediatric ART adherence and measurement methods among HIV-infected children in the global IeDEA cohort; (2) Determine site-level and individual-level factors associated with ART adherence; and (3) Assess evidence of the impact of non-adherence on clinical outcomes such as treatment failure and mortality, and programmatic factors such as loss-to-follow up. This project uses an adherence-focused pediatric site survey and analysis of existing pediatric patient-level data.

Most global sites have now completed the survey on adherence and disclosure, and data cleaning is underway. Survey data should be ready for analysis by May 2015. The patient-level datasets are also being gathered from each region. Patient-level data have been submitted for cleaning and analysis from Central Africa and subsequent queries have been sent to the regional data manager. CCASAnet has also submitted data and queries are expected to go out by mid-April. Asia-Pacific, East Africa and Southern Africa are on track to submit patient-level data by the end of April. West Africa has completed the site surveys and is considering participation in the patient-level portion as adherence measure inclusion criteria have recently been expanded. We anticipate that all patient-level data will be ready for analysis by July 2015, analyses will be completed by the end of 2015, and manuscript submitted for review in early 2016.

***Concept 60:*** *"Effect of nucleos(t)ide reverse transcriptase inhibitor sequencing on second-line antiretroviral therapy outcomes in sub-Saharan Africa"*

This was a multiregional concept led by Southern Africa. Data for this analysis were submitted in May 2013 and after the preliminary analyses was reviewed it was determined that there was insufficient power to perform this analysis in a meaningful way.

***Concept 62:*** *"2014 Update of concept-Immunodeficiency at the start of ART: a global view"*

This is a multi-regional analysis led by Southern Africa. This concept resulted in two 2015 CROI Abstracts "Immunodeficiency at the start of ART in children: A global view"[32] and "Immunodeficiency at the start of ART: A global view"[33] .

***Concept 63:*** *"Disparities in the overall and cause-specific mortality between HIV-positive women from Europe, North America and sub-Saharan Africa"*

This is a multi-regional analysis led by Dr. Julia del Amo. East African IeDEA has not received a data request for this project.

**Supplement for HIV/AIDS implementation science in PEPFAR:** *"Engagement in care among HIV-infected patients in resource limited settings: A Protocol for Assessing the*

*Magnitude of and Reasons for Failure to Engage in Care among HIV-infected Patients in the East Africa International Epidemiologic Databases to Evaluate AIDS (IeDEA) Consortium"*

This is Concept 52 and is led by Drs. Geng and Martin at UCSF.

All data collection is complete and data analysis and manuscript preparation are underway. One manuscript has been published: Estimation of mortality among HIV-infected people on antiretroviral treatment in east Africa: a sampling based approach in an observational, multisite, cohort study[34]. A second manuscript titled "Implementation of a Sampling-Based Strategy to Ascertain Outcomes of HIV-infected Patients Lost to Follow-up in a Network of HIV Care and Treatment Programs in East Africa" is under review[35]. A third manuscript titled "Application of a Sampling-Based Approach to Estimate Retention on Treatment among HIV-infected Patients in Five Settings in Eastern Africa" is being sent out for peer review. A fourth manuscript titled "Evaluating Interactions in Barriers to HIV Care in East Africa" is being drafted. Several additional analyses are underway to evaluate (1) the effect of tracing, (2) apply competing risks over time to capture not only multiple patient retention states but also allow patients to go in and out of states of retention and thereby more accurately reflect reality, (3) a causal effect of retention on mortality – which has currently not been carried out.

**Supplement from NIDA:** *"Prevalence and Impact of Alcohol Use in Patients Enrolling in HIV Care: An East African International Epidemiologic Databases to Evaluate AIDS (IeDEA-EA) Project"*

This project is led by Drs. Wools-Kaloustian and Goodrich. The aims of this project are to determine: 1) the prevalence of hazardous alcohol consumption in patients newly enrolling in care and compare their baseline characteristics to non-drinkers; 2) compare clinician and research assistant collected AUDIT screening data at AMPATH; and 3) assess the impact of hazardous drinking on patient outcomes including time to ART initiation, medication adherence, retention in care and death.

Study enrollment and follow-up was completed December 31, 2014 at all sites (AMPATH, Mbarara and FACES). A total of 786 patients have been enrolled. Data entry is complete at two sites and all data entry is expected to be completed in the spring of 2015. Data analysis for AIM 2 is underway and a manuscript is expected to be complete by June 2015. Data analysis for AIMs 1 and 3 will be complete by mid-2015 with an anticipated manuscript in 2016.

**Supplement from NIAID:** *"Linkages from Testing to Care in the USAID-AMPATH Partnership"*

This project is led by Dr. Braitstein. It is designed to address questions related to the uptake and engagement in care both by persons previously known to be HIV-positive but who haven't engaged in care, as well as for persons newly testing HIV-positive in a large home-based HIV counseling and testing (HBCT) program in western Kenya. Specifically, this supplement supports the electronic merging of data from the baseline HBCT and the repeated testing uptake and outcomes with clinical HIV data of persons who have enrolled into HIV care through AMPATH programs. The aims of this supplement are to: 1) Determine the time from testing to initial linkage to care; 2) Estimate the rate and determinants of initial

linkage to care following HIV testing in HBCT through ART initiation; 3) Examine the determinants of failure to link to care.

We successfully published the data earlier this year.[36] The findings were important and generated much discussion including an editorial[37]. It was a good news-bad news story. The good news included a) the fact that we identified nearly 1400 people living with HIV who were not previously aware of their status; b) nearly 90% of people who already knew they had HIV were in care; c) from a population perspective, 58% of the population of people living with HIV in the catchment were in care, mostly on ART. On the other hand, the major bad news was that only 15% of the newly diagnosed had enrolled in care over a median of 3·4 years since diagnosis representing our next big challenge.

Using these data we have partnered with the HIV Modeling Consortium to undertake modeling of the HIV care continuum and what some of the 'best buys' of interventions along it could be in aiming for 90-90-90. It has been a successful partnership with one manuscript well developed. The manuscript is under review by the authors.

Dr. Braitstein and her team are in the process of merging in the HIV re-testing data for the catchment. There were major delays in the project for two reasons. First was a lack of IT support from within the AMPATH care program upon which we were depending for IT support. Second was that we discovered that the team on the ground issued new identifiers to most people in the catchment so, although we issued universal identifiers specifically to prevent having to do a major merge, unfortunately it has been a much longer undertaking than planned because of this. Currently we have a team of data assistants reviewing the possible matches and hope to have the process completed within a few months. The program has recognized the value of having the data together as one virtual cohort as a result of these initial investments (and the paper in Lancet HIV) and they are aiming to have all the baseline and repeat HBCT merged together and migrated into the AMPATH Medical Records System (AMRS) and are investing more in the on-the-ground data management and support into the program.

***Collaborations with international organizations within specific aim 1:***

**UNAIDS:**

The East Africa IeDEA region continued to actively participate in collaborations with international organizations. The most recent example of this collaboration was work that the East Africa IeDEA Regional Consortium has led for the United Nations Joint Program in HIV/AIDS (UNAIDS). UNAIDS periodically issues a new version of their software Spectrum, (http://www.unaids.org/en/dataanalysis/datatools/spectrumepp2013), which generates estimates of various characteristics of the epidemic (there are several examples of country-level reports in the above web site). Dr. Yiannoutsos and Ms. Musick have previously worked closely with the UNAIDS to provide inputs for the Spectrum software, with respect to mortality of HIV-infected adults. That work, which involved all seven IeDEA regions in Africa, North and South America and Asia Pacific, plus the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) and EuroSIDA in Europe, culminated in a major article in the Journal of Sexually Transmitted Infections[38].

UNAIDS approached IeDEA for a similar effort with respect to HIV-related mortality in pediatric and adolescent populations around the world. The request was made in early fall of 2014 for the release of the new version of the Spectrum software in early 2015. The East

Africa Regional Data Center was able to leverage the experience and analytical software that was created for the 2012 adult Spectrum analyses, plus an existing multi-regional concept proposal, submitted by Dr. Annette Sohn, of the IeDEA Asia Pacific region, which endeavors to assess, among other issues, pediatric and adolescent mortality. The East Africa Regional Data Center collected data from five of the six participating regions (West, Central and East Africa, plus South America and the Caribbean and Asia Pacific) and provided the analysis files to Dr. Mary-Ann Davies at the Southern Africa IeDEA region so that she could perform the same analyses with Southern Africa IeDEA Data. Mortality estimates resulting from these analyses were submitted to the Futures Institute which compiles these data for the new Spectrum implementation. A white paper summarizing the results from the five regional data analyzed by Dr. Yiannoutsos was created and is attached to this progress report. Some of the results of the analyses provided by Drs. Yiannoutsos and Davies were summarized by Dr. Mary Mahy of the UNAIDS Evidence, Strategy and Results Department, in a meeting organized by the Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) at the conclusion of the 18th International Workshop for HIV Observational Cohorts (IWHOD) in Catania Sicily.

The analyses have resulted in two papers, under preparation, led by Dr. Sohn with analytical support by Drs. Yiannoutsos and Davies, one deals with mortality in infants and pre-teen children (ages 0-9 years) and the second paper addresses mortality in adolescents and young adults (ages 10-19 years).

**World Health Organization:**

The East Africa IeDEA Consortium has also actively participated in discussions with the World Health Organization (WHO) for support of the WHO Strategic Information (SI) initiative. Discussions with the WHO were initiated by Dr. Matthias Egger from the IeDEA Southern Africa region and five projects of mutual interest between the IeDEA Collaboration and the WHO have been identified. The East Africa region is supporting the Southern Africa region in East Africa's area of expertise, Retention in Care, by providing the WHO with corrected estimates of retention in care, based on work completed as part of an administrative supplement assessing the rates of retention in care by five sites within the East Africa IeDEA Collaboration. It should be noted, that East Africa is the only region with available data on retention in care after patients are lost to a program (through data collected as part of the aforementioned supplement plus data available from patient outreach performed as part of routine care in 2 sites within the region). Experience with retention in care and results from the administrative supplement have resulted in a major paper describing the estimated mortality in the region (see Figure 3 from this paper)[7]. As shown in Figure 7, mortality is substantially under-reported in the region resulting in a number of frequently unanticipated biases well beyond those related to underestimation of mortality. These results suggest that extreme caution has to be exercised when attempting to estimate mortality data under high rates of loss to follow-up.

Having these data available is the only way to inform WHO's "90-90-90" initiative (90% of all people living with HIV will know their HIV status, 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy and 90% of all people receiving antiretroviral therapy will have viral suppression by 2020). The definition of the above initiative, requires that 90% of people with HIV will be receiving antiretroviral therapy *somewhere*, which implies that individuals who have left one program but are receiving treatment elsewhere (and, unless they have formally transferred, they are lost to follow-up with respect to this program), are still retained in care and are part of the 90% on sustained antiretroviral therapy envisioned by the WHO. Thus, if, as it has been suggested, retention in care is defined as loss to program (or, conversely, as retention in care *at the original treatment program*), the rate of retention will be underestimated, possibly significantly. The East Africa IeDEA region has led the way in undertaking ground-breaking research in delineating the frequently inadequately understood difference between loss to follow-up (or loss to program), retention in care and engagement in care (the latter two terms being similar but focusing on the program and on the patient respectively).

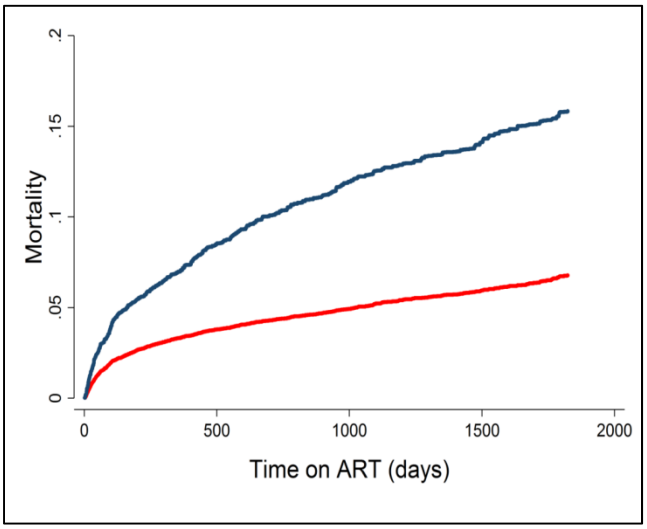


**Figure6.** Corrected (blue) and uncorrected (red) cumulative incidence of mortality in East Africa.

A related issue, identified as an area of mutual interest by the WHO and IeDEA, is long-term survival of HIV-infected patients. Again, this is an area where the East Africa IeDEA Regional Consortium will contribute significantly, as correct estimation of survival ("long-term" or otherwise) is a function (complement) of mortality, and thus requires complete ascertainment of death among HIV patients. Short of that, mathematical corrections must be applied based either on speculation (sensitivity analysis) or data external to the study. The East Africa IeDEA Consortium has developed a number of methods to correct for the incomplete ascertainment of death, due to the high rate of loss to program observed in our region, most recently resulting in a statistical publication[9] (see Figure 6).

**CIPHER:**

Dr. Wools-Kaloustian continues to work with the Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) to complete two projects: "Duration of first-line antiretroviral regimens in children: a global perspective" (Concept 59) on which she service as the scientific Co-Chair and "Global epidemiology of adolescents with perinatal HIV-infection" (Concept 61). The data for these projects have been received from the participating cohorts and the data center at the University of Cape Town is currently working toward the creation of analysis datasets.

Drs. Vreeman and Yiannoutsos participated in a conference organized by CIPHER in the periphery of the recent 19th IWHOD Conference in Catania Italy where Dr. Mary Mahy, Senior Adviser, Epidemiology, for the UNAIDS, presented some of the findings of the work on adolescents, which was performed by Dr. Yiannoutsos as part of the work with the UNAIDS and the Spectrum software (see references to the work with UNAIDS above). They also participated in the second CIPHER Conference in Venice, Italy, in May 3-4, 2015.

**New Administrative Supplements**

***"**Prospective validation of an adherence monitoring tool among HIV-infected children and adolescents at IeDEA sites-ICAMP"*

This is a multi-regional project led by Dr. Vreeman from the East Africa Region. Sustaining high levels of adherence to antiretroviral therapy (ART) are critical to achieving good clinical outcomes, decreasing HIV-related morbidity and mortality, and reducing the risk of transmission and viral resistance. Adherence to ART and factors associated with adherence among HIV-infected children in resource-limited settings are still poorly described. Furthermore, there is no gold standard to measure pediatric adherence. HIV care sites use various methods to evaluate adherence, such as pill counts, pharmacy refills, and heterogeneous questionnaire items, which makes comparing adherence rates across sites difficult. Moreover, the validity of many of these adherence assessments remains unknown.

The primary objective of the "Prospective validation of an adherence monitoring tool among HIV-infected children and adolescents at IeDEA sites" is to validate adherence questionnaire items for routine ART adherence monitoring, using electronic dose monitoring as external criterion for adherence and patients from 3 large and diverse pediatric IeDEA sites globally. Our secondary objectives include collecting prospective data on pediatric and adolescent adherence to ART and identifying factors associated with adherence. With these data we will achieve the following specific aims: (1) Validate a 10-item adherence questionnaire for routine use as a pediatric adherence measurement tool in resource-limited settings; (2) Describe ART adherence prospectively among samples of HIV-infected children at 3 large IeDEA sites using a standard pediatric ART adherence measure; (3) Evaluate factors associated with pediatric medication adherence; (4) Assess evidence of the impact of non-adherence on clinical outcomes such as treatment failure and mortality, and programmatic factors such as loss-to-follow-up.

This study involves three pediatric sites across three global IeDEA regions. The project is led by a team at the Academic Model Providing Access to Healthcare (AMPATH) – a large HIV treatment program in western Kenya, a program within the EA-IeDEA consortium. The following sites are participating in this study:

- Busia Health Clinic, AMPATH (Busia, Kenya) – East Africa IeDEA
- HIV-NAT Clinic, TREAT Asia Network (Bangkok, Thailand) – Asia-Pacific IeDEA
- Empilweni Services Research Unit, Rahima Moosa Mother and Child Hospital (Johannesburg, South Africa) – Southern Africa IeDEA

The project is being called the IeDEA Comprehensive Adherence Measure for Pediatrics (ICAMP). A study database has been constructed using the REDCap database software and is being finalized for implementation at each site. In early 2015, Principal Investigator Rachel Vreeman and Project Manager Michael Scanlon made a site visit to each of the ICAMP sites to help with rollout and implementation of the study protocol and project trainings.

By the end of 2014, all sites had submitted the project protocols and relevant materials to their local institutional review and ethics boards. The Thailand site and Kenya site have ethics approval and the Johannesburg site is waiting for revisions to be approved. The Thailand site is actively recruiting. The Kenyan site is hiring and training personnel in preparation for recruitment.

Goals: The study aims to complete the recruitment of 100 children at each site by June 2015. By the end of 2015, they aim to complete data collection and 6-month follow-up for all study participants.

*"Point of Care CD4 testing for people who fail to engage in care after testing HIV positive"*

This supplement is led by Dr. Paula Braitstein. This study's primary aim is to characterize the immunologic (CD4) and vital status of individuals lost on the HIV care continuum. We will use trained field-based HIV counselors and peer outreach workers to trace a random sample of eligible adults and conduct vital status ascertainment, point-of-care CD4 testing, and a brief patient survey. We seek to contact patients lost at three points on the HIV care continuum: 1) those who tested positive during HCT and did not engage in HIV care (did not have an initial encounter with an HIV clinician) identified as a result of data merging so knowing who has linked and who has not, 2) those who registered within AMPATH following HCT, but did not have an initial clinical visit, and 3) patients who had linked to care following HCT (had an initial visit) but have become lost-to-follow-up (defined as no contact with the clinic for >90 days since the scheduled return to clinic date. Primary hypothesis: A high proportion of individuals not engaged in care will be eligible for ART at thresholds for initiation of both 350 and 500 CD4 cells/μL. Secondary aims will be to: a) describe the association between CD4 count and failing to engage in HIV care; b) estimate the mortality rate among persons who have not engaged compared to those who have; and c) conduct in-depth interviews with a randomly selected sub-set of individuals traced and found alive to better understand linkage and engagement in care as described in detail in previously approved protocol IREC Number 2013/81.

The second aim will be to estimate the impact of delayed initiation of care and ART on disability-adjusted life-years (DALY). This aim will be addressed using a combination of the immunologic and mortality data from the sample of patients traced for Aim1 and mortality information from the electronic medical records of those HIV-infected individuals from the catchment who have engaged in care. We will estimate DALY's averted using mathematical modeling in partnership with the HIV Modeling Consortium with whom we have an existing collaboration. Primary hypothesis: The number of DALY's that could have been averted by increasing engagement in care will be substantial.

Local ethics approval was obtained on March 31, 2015. The protocol will be submitted to the North American IRB's prior to the end of May. The point-of-care CD4 testing machines have been ordered. We have used separate funds to buy two of them as this supplement will be paying for one. This will allow us to trace and test participants using two counselors at a time. We are hoping to start field work in May.

*"Implementation of Causal Modeling Technology to Assess and Improve the Effects of Antiviral Therapy in Children"*

This project is led by Joseph W. Hogan, ScD at Brown University and head of biostatistical research at AMPATH. This project will use new methods of causal inference to estimate the causal effect of different dynamic treatment rules on disease outcomes of HIV-infected children. Specifically, we will compare rules such as 'start treatment when CD4<750' and 'start treatment when CD4<500' on outcomes such as growth parameters, CD4 cell count or percent, and (if enough information) mortality. The analysis will use the combined data from the EA-IeDEA cohort.

Data Management: The team has been using a large subset of the AMPATH data to develop the methods. They have developed and submitted an EA-IeDEA data request that will allow them to update the AMPATH data and augment the full dataset with outcomes from other sites.

Data Analysis: Analysis of AMPATH 'test' dataset has been largely completed. The team has finished development of methods that compare treatment strategies, as described above, defined in terms of CD4 percent on 1104 cART-naive children aged 5 to 14, and completed an analysis that compares effectiveness of CD4-percent-based treatment initiation rules for this cohort. The results show that treatment policies that call for initiation

***Concept 66**: "Developing global surveillance estimates for perinatally infected adolescents on antiretroviral therapy transitioning to adulthood" SPECTRUM* (See ***Collaborations with international organizations within specific aim 1)***

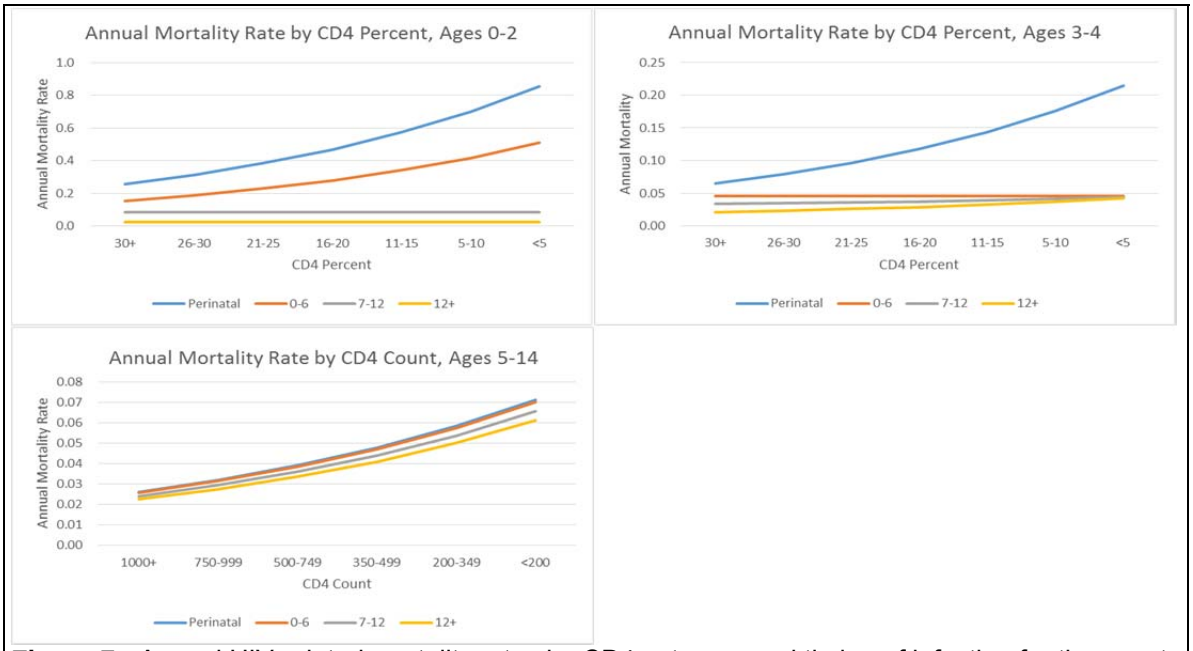


**Figure 7:** Annual HIV-related mortality rates by CD4 category and timing of infection for those not on ART

at a CD4% levels less than 20 are demonstrably worse than rules that call for initiation at 20 or higher, or the rule that calls for immediate treatment initiation. In addition, rules calling for immediate initiation are not demonstrably better than rules calling for initiation at CD4 percent less than 20 or 25. This latter finding could be a result of insufficient power, which is why the lager dataset will help clarify this issue.

The above results were submitted to IWHOD 2015 and selected for oral presentation, which was delivered by co-author Liangyuan Hu[39]. The team received very helpful feedback following the presentation, which will be valuable as they write-up these preliminary results. The Goals for 2015 are the completion of the full cohort analysis using methods already developed, submission of the manuscript describing key findings (for separate age groups) and submission of a methodological manuscript.

***New Concepts 2014-2015***

Preliminary work on this concept was completed in January 2015. Figure 7 above is from a presentation by Dr. Mary Mahy, Epidemiology Consultant at the UNAIDS, presented at the meeting of Collaborative Initiative for Pediatric HIV Education and Research (CIPHER) at the periphery of the most recent IWHOD conference.

As noted previously, two manuscripts summarizing the mortality among infants and small children (ages 0-9 years of age) and pre-teen and adolescents (ages 10-19 years of age) are in preparation under the coordination of Dr. Annette Sohn of the Asia Pacific region. We expect that the first of these will be submitted by mid summer 2015.

***Concept 67****: "SiZER maps to investigate significant features of weight changes in HIV-infected patients"*

A "spin-off" paper from Concept 15 involves the more narrow question about whether d4T-based regimens at ART initiation are associated with shorter-term weight change compared to non-d4T-based regimens. To answer this question, one must estimate the first time that the weight increase, which follows starting ART, ceases. The East Africa IeDEA Region has led a sub-analysis of these data as part Ms Sarwat's doctoral dissertation. The results of these analyses were presented recently at the 19th International Workshop on HIV Observational Cohorts (IWHOD) in Catania, Italy[1]. A manuscript is forthcoming.

The analysis is based on extensions of a method called Significant Zero Crossings of the Derivative (SiZer)[40], which focuses on the time point where the first derivative of the weight changes over time crosses from above the horizontal (zero) axis. When this happens, weight gain has effectively stopped (as positive derivative signifies weight gain, while a negative derivative denotes weight loss; a zero derivative signifies no weight change). Coupled with smoothing techniques, and accounting for the within-subject correlation of repeated weight measurements, the preliminary results suggest that d4T-based regimens are associated with slightly faster earlier weight gain which however has a much shorter duration compared to non-d4T-based regimens among patients starting ART. In East Africa (Figure 8) the estimated duration of weight gain was 54.8 weeks versus 80.1 weeks for d4T-based and non-d4T-based regimens respectively.

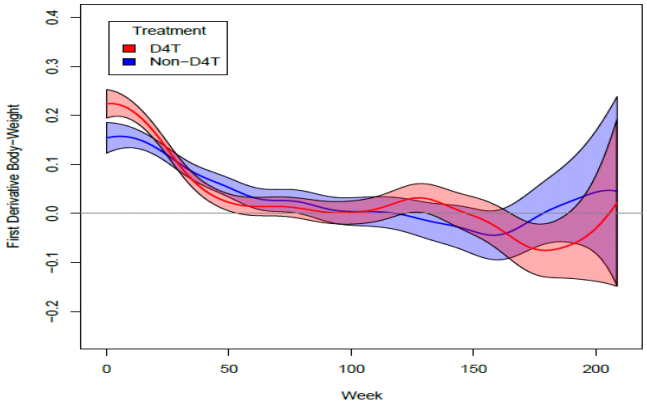


**Figure 8.** Plot of the first derivative of weight among patients starting ART on d4T-based and non-d4T-based regimens in East Africa (with 95% confidence interval).

These results were consistent across all five regions participating in this project. A number of limitations of this approach, including change of ART regimen (either substitutions of first-line regimens or changes to second-line regimens) as well as the fact that these data are based on patients who engage in care (similar to the traditional approach at CD4 count estimation which we have shown to be biased) need to be addressed in the near future. In addition, issues such as administration of a specific type of therapy, timing of ART initiation among sicker patients (confounding by indication), who may experience different rates of weight gain (time-varying confounding) have not been widely addressed in the context of non-linear longitudinal measurements such as weight gain. Neverheless, the results suggest that d4T-based regimens, in addition to the well-documented problems with respect to neuropathic pain, may also be associated with shorter durability of weight gain among ART-naïve patients.).

***Concept 68****: "Changes in the comprehensiveness of care provided at HIV care and treatment programs in the IeDEA collaboration from 2009 to 2014."*

This is a multi-regional proposal which aims to evaluate the array of WHO-recommended HIV prevention, care, and treatment comprehensive services offered at sites in all 7 IeDEA regions in 2014 including a comparison of trends in the availability of such services over time; namely between SA 1.0 (2009) and SA 2.0 (2014). It will also look specifically at the capacity of laboratories to perform WHO recommended viral load monitoring, and capacity for diagnosis of select opportunistic infections, as well as monitoring for certain ARV medication-related toxicities.

There are three aims to this study:

- To evaluate the implementation of WHO recommended comprehensive HIV prevention, care and treatment services across 7 regions of IeDEA in 2014. NOTE: Comprehensiveness refers to the provision of HIV counseling and testing, HIV prevention services, prevention of illness, management of opportunistic infections and co-morbidities, ART adherence support, patient monitoring on ART, and palliative care.
- Among the subset of sites with data from both SA 1.0 and 2.0, to evaluate trends in capacity to deliver WHO recommended comprehensive HIV prevention, care, and treatment services.
- To further explore the laboratory component of "*comprehensiveness*" by determining the existing laboratory capacity at all adult sites in IeDEA in 2014 a) to perform routine viral load monitoring, in accordance with new WHO recommendations, as part of expanded comprehensive services, b) to perform ARV-medication related toxicity monitoring (including renal, hepatic and hematologic assessments), and c) to diagnosis select priority opportunistic infections using recently available new opportunistic infection diagnostic/screening approaches (i.e. TB screening using GeneXpert, lateral flow and/or conventional Cryptococcal meningitis screening, other new/novel modalities).

**Aim 2: Assess the penetrance and outcomes of PMTCT strategies.**

***Project 2.1****: Automating the linkages between mother and infant records.*
This project is led by Dr. Wools-Kaloustian. The team is finalizing the 2014 data set for submission to the ART in Pregnancy Registry. Currently AMPATH data goes up to August

2014 and once the replication issues are fixed on the research database the team will finish that work. The FACES data currently goes through November 2014, but I have received the rest of their data, and will be catching that up shortly. There are some issues that require our attention going forward that we need to focus on the rest of the year:

- There are problems with correctly tracking stillbirths at AMPATH (very large numbers of stillbirths currently in the database) and we believe that this excessive number may be caused by the layout of the forms. These need to be reviewed with the FORMS team and in clinic.
- At AMPATH, there are issues with staff, either at the clinical level, or in the data entry level, correctly entering the data that will allow linkage of children with their mothers.
- Some data points could use training review to increase the accuracy of reporting. For example, a number of entries from FACES don't have LMP, etc.
- The team is slowly working towards automating the process, but there are still a large number of anomalies and occasional discrepancies and miscellaneous other data issues that require manual review.

Dr. Edith Apondi, a Pediatrician at AMPATH, has an approved concept sheet that utilizes the maternal-infant data linkages that were developed for submission of data to the ART in Pregnancy registry from AMPATH and FACES. The overall objective of this concept is to investigate the association between in-utero exposure to ART and congenital anomalies and will address the following aims:

- Describe the common ART regimens provided to HIV infected pregnant women in this region
- Determine the median duration of prenatal ART exposure in our region
- Determine the rates of congenital malformations infants exposed to ART in-utero
- Describe the congenital abnormalities identified in infants exposed to ART in-utero
- Describe the association between in-utero ART exposure, maternal factors and congenital anomalies

***Project 2.2:*** *PMTCT program evaluation following the introduction of the 2010 WHO guidelines.*

This project has been tabled due to insufficient data.

***Project 2.3:*** *Long-term outcomes of women exposed to intermittent antiretroviral regimens for PMTCT.*

This project is being addressed under **Concept 35:** The impact of intermittent 3-drug pMTCT on long term outcomes of women initiated on ART for treatment" and is led by Dr. Wools-Kaloustian.

An extensive review of the eligible cohort within East Africa revealed insufficient numbers in the group exposed to single or dual-drug pMTCT. As such, the concept proposal has been modified accordingly and preliminary analyses are underway. Additional EA IeDEA sites have been added to the cohort and updated analysis data sets will be ready by May. Complete analyses and manuscript draft are expected by the end of 2015.

***Other projects that fall within Specific Aim 2:***

***Concept 8:*** *"Incidence and determinants of pregnancy in women enrolled in care and treatment programs in East Africa"*

This project is led by Dr. Elul. The analyses for this concept have been completed and a mature manuscript is under final review by co-authors (see abstract below)[41].

Background: HIV service scale-up in Africa has transformed the context of childbearing for HIV-positive women, and may impact pregnancy incidence in HIV care and antiretroviral therapy (ART) programs.

*Methods:* Using observational data from 47,313 HIV-positive women at 26 HIV clinics in Kenya and Uganda, crude rates of first incident pregnancy were calculated for the pre-ART and on-ART periods, and compared as rate ratios (RR). The effect of ART status on incident pregnancy was assessed via: (1) multivariable Cox models with an interaction term between ART use and enrollment pregnancy status; and (2) stabilized inverse probability weighted marginal structural models.

*Results:* Pregnancy incidence was 8.6 per 100 women years (WY) and 6.7 per 100 WY during the pre-ART and on-ART periods, respectively, for a RR of 0.79 (95% CI 0.75-0.83). In Cox models, ART use was not significantly associated with incident pregnancy (aHR: 0.98; 95% CI: 0.91-1.05), but effect modification was observed with women pregnant at enrollment and on ART having an increased risk of incident pregnancy compared to those not pregnant at enrollment and not on ART (aHR: 1.11; 95% CI: 1.01-1.23). In marginal structural models, ART use was associated with a slightly higher likelihood of incident pregnancy with borderline statistical significance (aOR=1.06; 95% CI: 0.99-1.12).

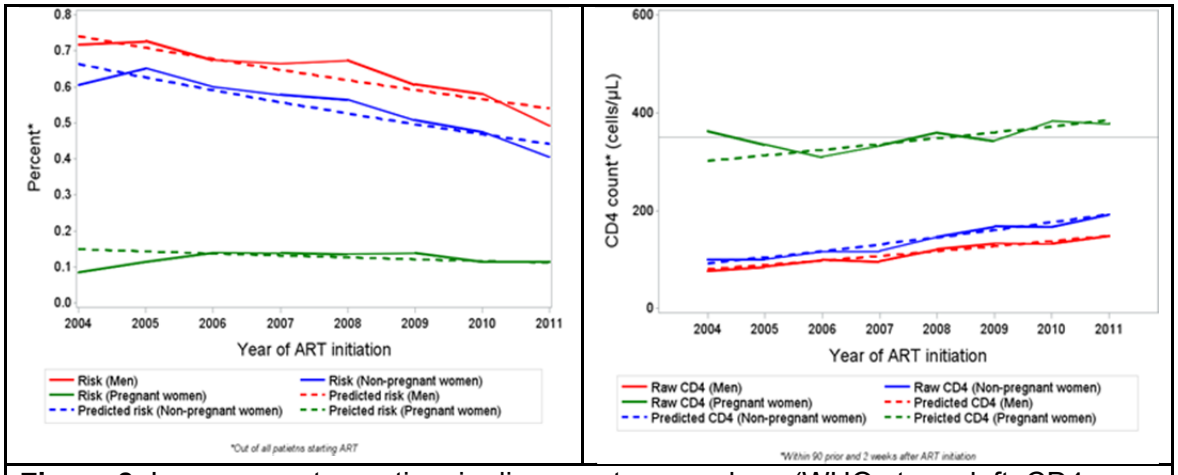


**Figure 9.** Improvement over time in disease stage markers (WHO stage, left, CD4 counts, right) at enrollment into care.

*Conclusions:* We found little evidence that ART initiation is associated with incident pregnancy. The high pregnancy incidence observed before and after ART initiation underscores the importance of enhancing access to reproductive health services for all women engaged in HIV care, regardless of ART status.

***Concept 46:*** *"PEPFAR: Programmatic and Clinical HIV Treatment Outcomes in Pregnancy"*

A multi-year collaboration between East Africa IeDEA and the President's Emergency Plan for AIDS Relief (PEPFAR) was completed this year. The collaboration involved a multi-factorial investigation of the temporal trends of pregnancy and enrollment in ART programs. Data used for this project spanned the entire period of option A and B (i.e., up to the start of the current standard, option B+). As such, these data are an authoritative summary of the first ten years of ART scale-up in the region.

The analyses clearly show the increase proportion of pregnant women among all patients (including men) who enrolled in care during this period. The analysis also documents the trend towards healthier patients enrolling into care over time (i.e., increases in CD4 counts and lower WHO stage at enrollment). Figure 9 summarizes these findings.

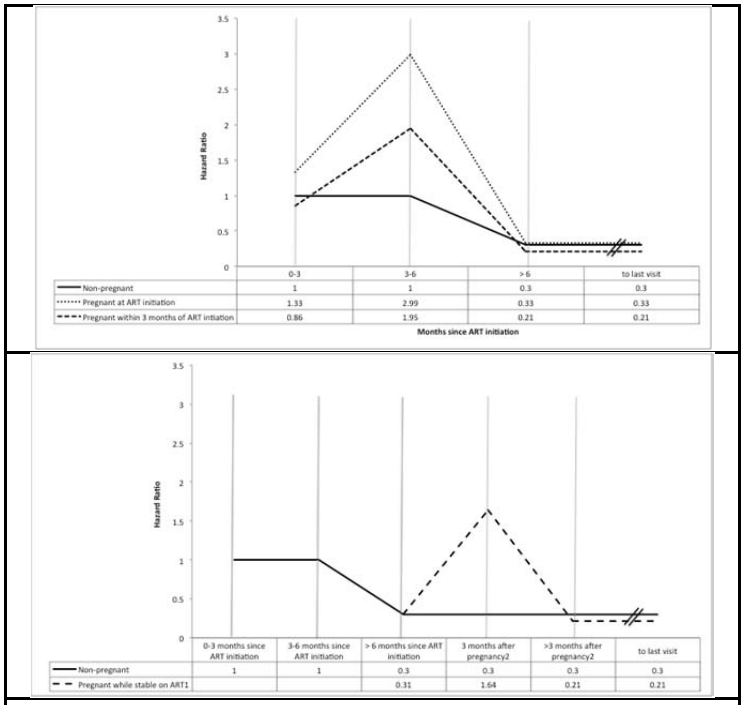


**Figure 10.** Hazard of attrition among women who were pregnant at ART initiation or became pregnant within 3 months of ART start (upper panel) and women who became pregnant after at least 6 months of ART (lower panel).

Perhaps a more important finding from these analyses is how critical pregnancy is as a risk factor for patient attrition (i.e., death or non-retention in care), particularly at the time of ART initiation (i.e., among women who are pregnant when they start antiretroviral therapy). However, a transient elevation of the risk of non-retention, was observed even among women who were stable on ART(i.e., having received > 6 months of ART) when they became pregnant, albeit not at the levels seen among women who were pregnant at ART initiation or who became pregnant within 6 months from starting ART.

A schematic of the changes in the risk of non-retention is shown in Figure 10. The paper resulting from this work, under the leadership of Dr. Charles Holmes, is being submitted for consideration to the special JAMA 2015 edition on HIV[42].

***Year 6 Administrative Supplement:*** *"Understanding low uptake of PMTCT services by HIV-infected women in rural Tanzania"*

This project is led by Dr. Gourlay under the direction of Dr. Zaba and Dr. Urassa.

The quantitative portion of this study links ANC and HIV clinic records with sero-surveillance records from a rural community (Kisesa) in north-western Tanzania, in order to assess the PMTCT cascade. The qualitative portion of this project is designed to identify motives and barriers to uptake of PMTCT services.

The qualitative investigation has resulted in two publications: one in *BMC Med Res Methodol.* and another in PLOSONE by Dr. Gourlay, as well as three conference poster presentations and one oral presentation [43-46].

With regard to the quantitative investigation (double) data entry and cleaning of routine clinic data was completed in December 2013. This was later than originally proposed due to limited data manager capacity at the National Institute of Medical Research, time taken to make repeated field trips to locate missing data, and complexity of the project including the need to develop many different data entry screens for each register series. Linkage of the clinic data to the community surveillance data and a draft statistical analysis was conducted in January-February 2014 (based on linkage methods that were being developed during 2013), and an abstract presented at the AIDS 2014 conference Melbourne Australia, July 2014[45]. The resulting manuscript, entitled "*Uptake of services for prevention of mother-to-child transmission of HIV in a community cohort in rural Tanzania from 2005 to 2012*" has been submitted to JAIDS[46] and a manuscript based on this work entitled and to "*Factors associated with uptake of services to prevent mother-to-child transmission of HIV in a community cohort in rural Tanzania"* has been submitted for publication to Sexually Transmitted Infections[44].

Analyses presented within these manuscripts indicate that coverage with HIV care at the ANC or ART clinic, among HIV-positive pregnant residents, was fairly low overall during the period 2005-2012 (estimated as 57% after adjustments to account for the sensitivity of the linkage algorithm), but improved considerably over time (to over 90% in 2012) as PMTCT services were implemented within the study area. Coverage with antiretrovirals was estimated as 29% in 2005-2012 overall, and 62% by 2012 (adjusted estimates). There were weaknesses identified throughout the PMTCT cascade. In multivariate logistic regression analyses, residence in more urbanized areas, prior voluntary counselling and HIV testing, increasing age, increasing year of pregnancy, and increasing duration of HIV-infection, were associated with greater access to HIV care, while separated or widowed women were less likely to access HIV care. The same factors were associated with access to antiretrovirals during pregnancy, with the exception of residence area. After adjusting for other factors in the multi-variate models, there was no statistical evidence for an association between partner HIV status and access to HIV care or antiretrovirals, although the small fraction of women linked to partners with test results limited the statistical power and conclusions we could draw.

**Aim 3: Monitor the translation of evidence into practice for managing co-infections with an emphasis on Tuberculosis (TB).**

Although the global response to human immunodeficiency virus (HIV) has made tremendous strides, tuberculosis (TB) remains a recalcitrant threat to persons living with HIV (PLHIV) in resource-limited settings. In 2012, the World Health Organization estimated that there were 1.1 million cases of TB disease among 35.3 million PLHIV. TB accounted for approximately 20% of all deaths in PLHIV, which equates to 320,000 deaths annually. The continued threat and high mortality from TB among PLHIV stems largely from the lack of timely identification and management of active tuberculosis cases as well as the increased risk of activation of latent tuberculosis in PLHIV in endemic countries. The gaps or barriers that are encountered in the real-world application of intensified TB case finding and isoniazid preventive therapy are multi-fold and poorly understood. We identified the key processes in the diagnosis of HIV-TB co-infection from symptom screen to smear microscopy result and evaluated the rate and completeness of this "TB diagnostic cascade"

in a large HIV clinic in a rural, resource-limited setting.

Mbarara (ISS Clinic) Progress:

As a part of this supplement 2,613 newly enrolled patients were evaluated at the ISS clinic during the study period. The median age of all new patients was 30 years (IQR: 25 – 38) and 1034 (40%) were male. The majority of patients (71%) entered the clinic after routine testing and counseling had identified their HIV diagnosis and 53% had WHO Stage I disease. Of this group, 2439 (93%) were screened for symptoms of tuberculosis at their initial clinic visit and 682 (28%) had at least one of the following four symptoms: cough, night sweats, fever, or weight loss. The most common symptom was cough (70%). Sixty-six percent had only one symptom positive and 34% had at least two symptoms positive. Of all patients who screened positive, 90 (13.2%) had a sputum sample collected within 14 days of their visit (all patients with a sputum order had a sputum sample collected). Of the sputum-collected group, 75 (83%) completed the TB diagnostic cascade and 12 (13%) were diagnosed with TB based on sputum smear microscopy. Of note, four additional patients in the sputum-collected group were diagnosed with TB from a sputum ordered > 14 days from the initial clinic visit (Day 21, 82, 147 from a sputum ordered at a subsequent clinic visit; Day 22 without a subsequent clinic visit). Of the 90 patients who had a sputum collected, 75 (83%) completed the cascade in a median of 3 days. Fifty percent of patients had completed the entire cascade within one day of the initial clinic visit. The majority of patients who completed the cascade did so within the first four days (67 of 75 (89%)).

Overall we observed that processes in TB diagnostics operate efficiently and effectively in a prototypical HIV/TB clinic in Uganda but that the gaps in TB care stem from clinical uncertainties about how to evaluate patients who screen positive for one or more TB symptoms. Further development of diagnostics or potentially additional screening questions (such as the presence of alternative reasons for symptoms) can be used to reduce the number of patients without TB who screen positive and therefore streamline HIV/TB care more generally in Africa.

AMPATH Progress:

The AMPATH system is complex and includes co-management of TB patients at some sites while other sites refer co-infected patients to the TB clinic for management. Though many of the previously-identified challenges to ascertainment of accurate TB data at AMPATH have been addressed, additional issues have continued to require intervention during this year in order to optimize TB data collection and validation. The team has focused on improving data at each of the following time points: 1) Time from symptom screen to sputum order 2) Sputum order to collection 3) Collection to receipt in laboratory 4) Receipt of sputum in laboratory to testing 5) Testing to result reporting and 6) Result reporting to clinical action. The AMPATH TB group continues to work on ensuring improved data quality and documentation is occurring at all steps in the collection process in a way that is readily accessible for analysis.

The AMPATH Team has been able to achieve the following in the past year: 1) Improved documentation of TB screening data at the initial patient visit and all subsequent follow-up visits; 2) Implemented spot sputum collection at patient's initial visit to the TB clinic; 3) Added patient's AMPATH number, module number, telephone contact number as well as the dates of sputum collection, lab delivery and return results to the Cough Monitor's log; 4)Included patient's AMPATH number and module number as needed for data entry into the

Laboratory Information Management System (LIMS) on all lab request forms; 5)Consistent recording of specimen receipt and processing dates in the laboratory log book; 6)Manual entry of patient identification information and lab results (2012-2104) into AMRS. 7). Fixing the LIS program in the lab to be able to accept patients I.Ds (Ampath I.Ds and/or MFL coded numbers). 8). LMIS now automatically connects to AMRS to allow direct data transfer.

The AMPATH TB team will continue to pursue the following goals:

1. Create a mechanism to assess the TB diagnostic cascade from sputum request by clinicians- sputum collection – sputum processing in lab – result receipt by clinician- clinical action – availability of results in LIS and AMRS
2. Utilize analyzed data (Dr. Pettit) from the TB data collection project in order to inform the team on QA/QC.

***Other projects that fall within Specific Aim 3:***

***Concept 4: "****Impact of HIV-TB integration on TB incidence among persons receiving HIV-care and treatment in East Africa"*

This project was initially led by Dr. Tsiouris at Columbia University and transitioned to Ms. Suzue Saito working under the direction of Dr. Batya Elul.

An analytic dataset for this project was generated in November 2013 and included data on patients enrolling in care and initiating ART between 2003 and 2012 at 35 health facilities in Kenya, Uganda, and Tanzania. Analysis was completed in the Fall of 2014 by a statistical intern, Mr. Philani Mpofu, under the coordination of Dr. Constantin Yiannoutsos, and showed a substantial decrease in facility-based annual TB incidence rates among patients engaged in HIV care that temporally coincides with HIV care and ART scale up in these countries. The decline was observed in both pre-ART and ART patients and across all ages. The trend persisted after accounting for the decreasing TB incidence rates estimated in the general population in these countries during the study period. A manuscript summarizing these results was submitted to the *Journal of Acquired Immune Deficiency Syndromes* in March 2015. A causal association between ART scale-up and TB incidence will be the objective of a follow-up paper.

***Concept 47: Multi-regional Project:*** *"Tuberculosis in HIV treatment treatment programmes in low-income countries within the global IeDEA network: A survey on integration of services, diagnostic, screening, preventive and treatment practices."*

This multi-regional project was led by Dr. Fenner from the Southern African Region. Eight East African sites participated in this project. A publication has resulted from this project this year, "Detection and Management of drug-resistant tuberculosis in HIV-infected patients from low- and middle-income countries"[47].

***(Sterling, Pettit) Multi-regional Project: "****Collection of key tuberculosis (TB) variables in ART programs within the IeDEA consortium: diagnostics, treatment and risk factors for incident TB"*

This multi-regional project is being led by Drs. Pettit and Sterling from CCASAnet. Four programs within East Africa are taking part in this project including: AMPATH, Kenya; Masaka Hospital, Uganda; Kisesa Clinic, Mwanza, Tanzania; and Tumbi Regional Hospital,

Kibaha, Tanzania.[48] As of mid-March, 920 patient records have been collected at AMPATH, 86 at Tumbi, 44 at Kisesa and 274 at Masaka.

A number of concept sheets utilizing these data have been developed including:

- "Collection of key Tuberculoisis (TB) variables in ART Programs within the IeDEA consortium: diagnostics, treatment and risk factors for the incident TB". This project is led by April Pettit.
- "Evaluation of Xpert MTB/RIF implementation among HIV programs in the IeDEA Consortium" This project is led by Kate Clouse
- "Diagnosis and Treatment of TB HIV co-infected children" led by Marie Ballif from the IeDEA-Southern Africa
- "Management of tuberculosis in HIV-infected pregnant women" led by Marie Ballif

***Multi-regional Project: "****Impact of HIV infection on the population genomics of drug-resistant Mycobacterium tuberculosis: insights from macro-evolutionary analyses"*

This project is led by the Southern African Region. One East African site (AMPATH) participated in the pilot phase and is currently participating in the project phase of this study.

Enrollment has commenced at Moi/AMPATH. We have approached the head of the national TB program to request the ability to enroll at the Kisumsu lab. Sixty eight samples have been sent to Geneva for sequencing and all of the data on these specimens have been entered into REDCap. A slowdown was observed during the winter due to a stock out of LJ slants.

An abstract by Clouse et al., was submitted to the 2015 Union meeting and is entitled *"Low implementation of Xpert MTB/RIF among HIV/TB co-infected adults: A 19 low/middle income country survey from the IeDEA Collaborative"*.

**Background:** The World Health Organization (WHO) recommends Xpert MTB/RIF (Xpert) as the initial TB diagnostic for HIV-infected individuals but there are limited data describing real-world implementation of Xpert. We present Xpert implementation data from a large, global network of HIV treatment sites.

**Methods:** We conducted an observational cohort study among HIV-infected adults enrolled in HIV care/antiretroviral (ART) program sites participating in the International Epidemiologic Databases to Evaluate AIDS (IeDEA) Consortium and clinically diagnosed with TB from 2012-2014. Data were collected on all HIV/TB co-infected adults (age ≥18) regardless of ART status using a standardized electronic form. TB case validation was performed at sites by file review. We provide proportions for categorical variables and medians and interquartile ranges (IQR) for continuous; we use log-binomial models to estimate adjusted risk ratios (aRR) and 95% confidence intervals (95%CI) for unfavorable TB treatment outcome (death, default, failure, or undocumented).

**Results:** Twenty-two participating sites in 19 low/middle income countries provided data on 2780 patients; we excluded 283 (10.2%) missing Xpert utilization data, leaving 2497 participants. A majority was male (60.3%). At TB diagnosis, median age was 35 years (IQR:29-42) and median CD4 count was 115 cells/μl (IQR:38-245). Of 2497 patients, 123 (4.9%) had a documented Xpert result; the remainder either did not have Xpert performed

(70.2%) or had no recorded Xpert results (24.9%). Among 123 with Xpert performed, 75 (61.0%) were positive, 48 (39.0%) were negative, and none were invalid. Rifampicin resistance (RIF-R) was identified in 15 (20.0%) of Xpert-positive TB cases. Overall, 1626 (65.1%) TB cases were not bacteriologically confirmed by Xpert, AFB smear, culture or other nucleic acid amplification test. Adjusted for age, sex and CD4 at TB diagnosis, cases that had no documentation of an Xpert test or result were more than twice as likely to have an unfavorable treatment outcome than cases with an Xpert test (aRR:2.12, 95%CI: 1.14-3.92).

**Conclusions:** Use of Xpert for TB diagnosis among HIV co-infected patients in care in this global network is low. A majority of TB cases in this analysis had no documentation of Xpert testing on file, which was associated with unfavorable treatment outcomes. Future operational research must address implementation challenges of Xpert in order to adhere to the WHO recommendations.

**New Administrative Supplement:**

*"Liver Disease in HIV program survey"*

This is a multiregional project led by Gilles Wandeler of the West and Southern Africa Regions.

Two East African sites are participating in the chart review (IDI, AMPATH) and seven sites are completing the site survey (IDI, AMPATH, Morogoro, ORCI, Kisesa, FACES, Mbarara). The objectives of this project are:

- To describe the preventive measures for liver disease (including HBV vaccination) performed in the different ART programs.
- To assess the liver disease-related screening practices and monitoring in ART programs in sub-Saharan Africa (SSA), and compare them with international and national guidelines.
- To describe diagnostic and staging practices of liver disease, including the evaluation of liver fibrosis and cancer and evaluate the current treatment strategies for viral hepatitis infections and other liver diseases.
- To compare demographic and clinical characteristic between patients who are tested for HBV and HCV co-infections and/or have any other liver-related diagnostic measurement performed and those who do.

Using an internet-based (REDCap) survey, the team is evaluating important practices regarding the diagnosis and management of liver disease across the IeDEA regions. Approximately 30 HIV programs in SSA are included and are expected to complete the survey by end of May 2015. In addition, 10 sites from the Asia-Pacific region and 10 from CCASAnet also chosen to participate.

The retrospective chart review is ongoing at two sites in each African region. By the end of March 2015, all sites in IeDEA-Southern Africa and West Africa had finished the chart review. In East Africa the chart review at IDI and AMPATH commenced in mid-December 2014. Since then, IDI has reviewed 170 charts and entered 87 of these into the database. As of March 20, AMPATH had reviewed 160 charts and entered 133 of these into the

database. Chart review at both sites will continue until they meet the target of 300 charts per site. Both sites report that they hope to complete this chart review by the end of May.

Some of the results including data from the chart review in the West African sites were presented by Dr. P. Coffie at the *7th Conférence francophone VIH/SIDA* (AFRAVIH, Montpellier, France, 27-30 April 2014). The first overall results are anticipated to be available during the second half of 2015 and will be presented at an international HIV conference. The first draft of a manuscript will shortly follow and a final version is expected to be submitted for publication in late 2015.

**Aim 4: Determine the prevalence, incidence, determinants and outcomes of malignancies in East Africa with a focus on Kaposi's sarcoma and cervical cancer.**

***Project 4.1:*** *Epidemiology of Kaposi's sarcoma (KS) in the ART era*

Systematic identification of biopsy-confirmed KS in the large population base of East Africa" continues to be led by Dr. Martin and the UCSF team. The foundation of this project is IeDEA's support of the provision of skin punch biopsies for the histological confirmation of KS by local clinicians during the course of routine clinical care at several participating East Africa IeDEA sites. In the past year, the Masaka clinical site has been added to the existing sites at Mbarara, AMPATH and IDI. The enhanced diagnostic capacity of KS afforded by biopsy confirmation, in combination with the large well-enumerated denominator of IeDEA, has resulted in creating a population laboratory for the study of KS in East Africa. In the past year, we have completed several studies evolving from this population laboratory and laid the groundwork for several others. In the realm of diagnosis, we have demonstrated the feasibility of task-shifting from physicians to lower-level personnel (e.g., nurses and technicians) in the performance of skin punch biopsies for KS[49]. Showing this should allow clinics throughout African to overcome the current obstacle of too few operators available to perform biopsies.

We have also shown the importance of biopsy by demonstrating that the positive predictive value of clinical diagnosis for KS is sub-optimal[50]. In addition, when comparing to a gold standard dermatopathologic read from the U.S., we found that local African pathologic interpretation is typically specific for KS but often lacks sensitivity[50]. By helping to confirm diagnoses of KS, we have been able to facilitate the conduct of translational research of the etiology of the cancer. Specifically, we have identified an association between two heretofore unstudied biomarkers with KS. We found that activity of the enzyme indoleamine 2,3-dioxygenase (IDO), as measured by plasma kynurenine/tryptophan ratio, as well as plasma levels of the high mobility group box 1 (HMGB1) protein are both associated with occurrence of KS. Having firm KS diagnoses has also made it possible for us to formally study incidence of KS[51] as well as survival after diagnosis in East Africa with the type of accuracy in estimation that has rarely been done before in the region. Finally, in future work, we were successful in our application in response to RFA-CA-13-010 (Sub-Saharan African Collaborative HIV and Cancer Consortia) in which U54 CA190153 will use a rapid case ascertainment approach in our IeDEA platform to study why patients continue to develop KS in the ART era.

An analyses looking at the incidence of KS in the East African IeDEA cohort has been completed by Dr. Martin and his team at UCSF. The cohort includes 159,036 patients (67% women), with a median age of 36 years (interquartile range (IQR): 30 to 43) and median CD4 count of 226 cells/$mm^3$ (IQR: 90 to 415) at clinic enrollment. Median follow-up was 5.4

years (IQR: 3.6 to 6.9) during which 1326 incident KS diagnoses were made (32% biopsy-proven), reflecting an overall incidence of 260 per 100,000 person-years (p-y). In the unadjusted analysis, patients not on ART had higher KS incidence than those on ART (347 vs 227/100,000 p-y). In the nested new user cohort analysis, which properly accommodates for time-dependent confounding/mediation, patients on ART had an 80% (95% CI: 70% to 90%; p<0.001) reduction in incident KS compared to those not on ART. CD4+ T cell count significantly modified the effect of ART; patients with the lowest CD4 counts (<100 cells/$mm^3$) had the greatest effect of ART (p<0.01) on KS incidence. The analysis to date used a complete case analysis and adjusted for most recently observed CD4 count (amongst other variables) as the main confounder. Two manuscripts related to this work are currently being drafted.

The UCSF team recently applied to a supplement opportunity to the P30 Cancer Centers to begin a prospective cohort of patients with KS that arises during their care at our IeDEA sites, to PAR-14-028 (Mobile Health: Technology and Outcomes in Low and Middle Income Countries) where we proposed to investigate confocal microscopy as a point-of-care diagnostic test for KS, and to RFA-CA-15-001 (Cancer Detection, Diagnosis, and Treatment Technologies for Global Health) where we have teamed with Cornell University to propose to study a PCR-based diagnofstic test for KS.

***NCI Supplement:*** [17,52] *"Survival among HIV-infected individuals with Kaposi's Sarcoma in Sub-Saharan Africa in the era of potent antiretroviral therapy".*

Prior to the availability of antiretroviral therapy (ART), survival after a diagnosis of HIV-associated Kaposi's sarcoma (KS) in sub-Saharan Africa was dismal (60-70% 1-year mortality). As ART has now become available in Africa, it is important to understand contemporary survival of KS, but previous research efforts have been effectively precluded by high losses to follow-up (LTFU). Indeed, in work we conducted across all four African IeDEA regions in Uganda, Kenya, Nigeria, Cameroon, and Malawi, we found that nearly half of patients diagnosed with KS in HIV primary care settings were lost to follow-up at two years following their diagnosis[52]. To overcome this substantial obstacle to estimating survival after KS diagnosis in the contemporary ART era, we developed a process whereby we systematically searched for lost patients in the community in order to update their vital status. We identified three groups of HIV-infected adults receiving care, at any time from January 2009 to July 2012, at two programs in the East Africa IeDEA consortium: ISS clinic, Mbarara, Uganda and AMPATH in Kenya. The first group included patients with newly diagnosed KS while not yet on ART, and this group was compared to: a) patients with newly diagnosed tuberculosis or cryptococcosis while not yet on ART ("Serious OI group"); and b) patients first meeting eligibility for ART by CD4 count criteria but with no prior WHO Stage III/IV diagnosis ("CD4 group"). Patients were followed until death or administrative database closure. Among those LTFU (defined as absent from clinic for at least 3 months since expected return date at the time of database closure), all those in the KS group were tracked in the community to update vital status as well as a random 15% sample of the Serious OI and CD4 groups.

Outcomes among the random sample of patients tracked were incorporated via probability weights into subsequent analyses. A total of 16,152 patients were included: 839 with KS, 3797 in the Serious OI group, and 11,516 in the CD4 group; median age was 36 years (IQR: 30-44) and 59% were women. Of those with KS, 38% became LTFU, compared to 32% of the Serious OI group and 22% of the CD4 group. Among those LTFU, we tracked 750 patients in the community and updated vital status in 93%. Prior to incorporating updated

vital status among those tracked, the "naïve" mortality estimate for those with KS was 20% (95% CI: 16-26) at 1 year and 27% (95% CI: 21-34) at 3 years. After incorporating the updated vital status of those LTFU, "corrected" mortality was 46% (95% CI: 40-52) at 1 year and 54% (95% CI: 49-59) at 3 years. After adjusting for age, sex, BMI, hemoglobin, CD4, and clinic site, being diagnosed with KS was associated with substantially higher mortality than being diagnosed with a serious OI (hazard ratio 2.7 [95% CI: 1.9-3.8]) or becoming ART eligible by CD4 count alone (hazard ratio 3.5 [95% CI: 2.5-5.0]). We concluded that despite growing ART availability, mortality after diagnosis of KS in East Africa is still high in absolute terms and substantially higher than in other HIV-infected patients. The findings dictate a call for action for faster and more complete access to ART and for more effective interventions above and beyond ART for persons with KS. This work was presented at the recent International Workshop on HIV Observational Diseases[17].

***Project 4.2:*** *"Assess the prevalence and determinants of high-grade cervical dysplasia and cervical cancer as well as compare treatment modalities".*

This project is currently being led by Dr. Wools-Kaloustian and Dr. Omenge.

The Team has spent a significant amount of time and effort trying to integrate cervical cancer screening data into the site level HIV-databases at AMPATH and FACES. Unfortunately due to a number of programmatic changes and technical difficulties full integration has not yet occurred. The team has come to the conclusion that the best way to approach the cervical cancer screening data is to have the sites send these data separately and then link the data at the level of the regional data center. For AMPATH is means pulling in data from the ECEL spreadsheets that were used to track patients before the program started direct data entry and for FACEs this means receiving data in a CSV format from their ODK server. These data have been requested as part of the current regional data merger. A concept sheet proposing to use these data "Rates of Cervical Cancer Screening Uptake and Predictors of VIA Positivity among Women in a Rural Western Kenya" is currently being circulated in the East African" is currently being circulated to the East African Cervical Cancer Working Group for comment.

***Other projects that fall within Specific Aim 4:***

**Collaboration with IARC:** *"Risk of Cancer in Persons Infected with HIV in Western Kenya"*

Due to the geographic overlap of the Moi Teaching and Referral Hospital Cancer Registry overlap with the AMPATH catchment linking the data from the AMPATH Medical Records System (AMRS) and the MTRH Cancer Registry appeared feasible. We facilitated the work of an Informatics Fellow Judy Wawira with IARC to link the AMPATH and MTRH CANREG databases. Unfortunately this project was more challenging than initially anticipated due to problems with backlogs in data entry into the CANREG and issues with matching identifiers between the two databases. This project was abandoned because of the backlogs could not be resolved prior to Judy Wawira completing her fellowship.

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***Concept 57: "****African Network for Cervical Cancer Screening and Treatment"*

This is a multi-regional concept initiated in collaboration with the CFARs led jointly by Dr. Wools-Kaloustian from East African IeDEA and Dr. Cu-Uvan from the Inter-CFAR collaboration on HIV-Research in Women.

A manuscript has been submitted to JAIDS, the abstract of which is outlined below.

**Objective:** Approximately 85% of cervical cancer cases and deaths occur in resource-constrained countries where best practices for prevention, particularly for HIV-infected women, still need to be developed. The objective of this study was to assess cervical cancer prevention capacity in select HIV clinics located in resource-constrained countries.

**Methods:** A cross-sectional survey of sub-Saharan African sites of four NIH-funded HIV/AIDS networks was conducted. Sites were surveyed on the availability of cervical cancer screening and treatment among HIV-infected and HIV-uninfected women. Descriptive statistics, and chi-square or Fisher's exact test were used as appropriate.

**Results:** Fifty-one out of 81 (63%) sites responded. Access to cervical cancer screening was reported by 49 (96%) sites. Of these sites, 39 (80%) performed screening on-site. Central African sites were less likely to have screening on-site (P= 0.02) versus other areas. Visual inspection with acetic acid (VIA) and Pap testing were the most commonly available on-site screening methods at 31 (79%) and 26 (67%) sites, respectively. HPV testing was available at 29% of sites with VIA and 50% of sites with Pap testing. Cryotherapy and radical hysterectomy were the most commonly available on-site treatment methods for premalignant and malignant lesions at 29 (74%) and 18 (46%) sites, respectively.

**Conclusion:** Despite limited resources, the majority of sites surveyed had the capacity to perform cervical cancer screening and treatment. The existing infrastructure of HIV clinical and research sites may provide the ideal framework for scale up of cervical cancer prevention in resource-constrained countries with a high burden of cervical dysplasia.

**C. Significance:**

The overall significance of this work remains the same as that outlined in the initial grant application. Significance is also outlined specifically for each new project in the narrative above.

**D. Plans**

The plans for each project are outlined within the project narrative.

# Progress Report Publication list (May 2014-May 2015)

**Papers (May 2014-2015):**


4. An MW, Frangakis CE, Musick BS, Yiannoutsos CT. The need for double-sampling designs in survival studies: an application to monitor PEPFAR. *Biometrics.* Mar 2009;65(1):301-306. http://www.ncbi.nlm.nih.gov/pubmed/18479488
5. Kiragga AN, Lok JJ, Musick BS, Bosch RJ, Mwangi A, Wools-Kaloustian KK, Yiannoutsos CT, East Africa Ie DEARC. CD4 trajectory adjusting for dropout among HIV-positive patients receiving combination antiretroviral therapy in an East African HIV care centre. *Journal of the International AIDS Society.* 2014;17:18957. http://www.ncbi.nlm.nih.gov/pubmed/25131801
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10. Yiannoutsos CT, Yu M. Marginal and conditional distribution estimation from double-sampled semi-competing risks data. *Scand J Stat.* 2015;42:87-103.
20. Geng EH, Neilands TB, Thiebaut R, Bwana MB, Nash D, Moore RD, Wood R, Zannou DM, Althoff KN, Lim PL, Nachega JB, Easterbrook PJ, Kambugu A, Little F, Nakigozi G, Nakanjako D, Kiggundu V, Ki Li PC, Bangsberg DR, Fox MP, Prozesky H, Hunt PW, Davies MA, Reynolds SJ, Egger M, Yiannoutsos CT, Vittinghoff EV, Deeks SG, Martin JN. CD41 T cell recovery during suppression of HIV replication: an international comparison of the immunological efficacy of antiretroviral therapy in North America, Asia and Africa. *Int J Epidemiol.* Feb 2015;44(1):251-263. http://www.ncbi.nlm.nih.gov/pubmed/25859596
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23. Huis in ‘t Veld D, Balestre E, Buyze J, Menten J, Jaquet A, Cooper D, Dabis F, Yiannoutsos C, Egger M, Hemingway J, Colebunders R. Determinants of weight evolution among HIV-positive patients initiating antiretroviral treatment in low resource settings. *For the International Epidemiologic Databases to Evaluate AIDS (IeDEA)*(*In press: manuscript accepted for publication by J AIDS*).
24. Koller M, Patel K, Chi BH, Wools-Kaloustian K, Dicko F, Chokephaibulkit K, Chimbetete C, Avila D, Hazra R, Ayaya S, Leroy V, Truong HK, Egger M, Davies MA. Immunodeficiency in children starting antiretroviral therapy in low-, middle-, and high-income countries. *Journal of acquired immune deficiency syndromes.* Jan 1 2015;68(1):62-72. http://www.ncbi.nlm.nih.gov/pubmed/25501345
25. Koller M, Althoff KN, Davies MA, Egger M. Authors' reply: immunodeficiency at the start of combination antiretroviral therapy: steady improvement or step changes? *Journal of acquired immune deficiency syndromes.* Jan 1 2015;68(1):e16-17. http://www.ncbi.nlm.nih.gov/pubmed/25321185
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**Abstracts (May 2014-2015)**

1. Sarwat S, Yiannoutsos Y, Wools-Kaloustian K, Musick B, Harezlak J. Shorter duration of weight increase in HIV-infected patients treated with d4T versus non-d4T-containing

regimens in IeDEA: an investigation through SiZer maps. Presented at: International Workshop on HIV Observational Databases, (IWHOD); Catania Sicily:*(poster)*

3. Lok J, Yiannoutsos C, Kiragga A, Bosch R. Inverse Probability of Censoring Weights under Missing Not At Random with Application to Long-term CD4 Outcomes in HIV-Positive Patients in Kenya. Presented at: The International Biometric Society Eastern North American Region (IBS-ENAR) Spring Meeting2015:*(oral presentation)*
11. Bakoyannis G, Yu M, Yiannoustos C, Frangakis C. Non-Parametric Cumulative Incidence Estimation Under Misclassification in the Cause of Failure. Presented at: The International Biometric Society Eastern North American Region (IBS-ENAR) Spring Meeting2015; Miami, FL:*(oral presentation)*
17. Semeere A, Freeman E, Wenger M, Busakhala N, Asirwa C, Bwana M, Kanyesigye M, Maurer T, Glidden D, Yiannoutsos C, Wools-Kaloustian K, Martin J. Mortality after diagnosis of Kaposi's sarcoma among HIV-infected adults in sub-Saharan Africa: overcoming high losses to follow-up to derive more accurate inferences. Presented at: International Workshop on HIV Observational Databases, (IWHOD) Catania Sicily:*(poster)*
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33. Panayidou K, Kirk O. Immunodeficiency at the Start of ART: A Global View. 2014 Conference on Retroviruses and Opportunistic Infections; February 23-26, 2015, 2014; Seattle, Washington, Abstract number 1094:*(poster)*
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42. Holmes C, Ssali J, Aluda J, Castelnuovo B. Increasing rates of pregnancy among individuals starting ART: Impact on programmatic characteristics and outcomes of PEPFAR-supported African HIV treatment programs (*manuscript*).
44. Gourlay A, Wringe A, Todd J, Cawley C, Michael D, Machemba R, Reniers G, Urassa M, Zaba B. Factors associated with uptake of services to prevent mother-to-child transmission of HIV in a community cohort in rural Tanzania. (*manuscript*).
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Estimated mortality of HIV-infected children 0-5 years of age treated with combination antiretroviral therapy, March 18, 2015 *(manuscript-see attached appendix)*

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# Targeted/Planned Enrollment Table

**This report format should NOT be used for data collection from study participants.**

**Study Title:** East African IeDEA

**Total Planned Enrollment:** N/A- Observational Cohort based on EMR

| TARGETED/PLANNED ENROLLMENT: Number of Subjects | | | |
|---|---|---|---|
| **Ethnic Category** | **Sex/Gender** | | |
| | **Females** | **Males** | **Total** |
| Hispanic or Latino | | | |
| Not Hispanic or Latino | 197,645 | 111,314 | 308,959 |
| **Ethnic Category: Total of All Subjects *** | 197,645 | 111,314 | 308,959 |
| **Racial Categories** | | | |
| American Indian/Alaska Native | | | |
| Asian | | | |
| Native Hawaiian or Other Pacific Islander | | | |
| Black or African American | 197,645 | 111,314 | 308,959 |
| White | | | |
| **Racial Categories: Total of All Subjects *** | 197,645 | 111,314 | 308,959 |

* The “Ethnic Category: Total of All Subjects” must be equal to the “Racial Categories: Total of All Subjects.”

# Appendix 1

# EA IeDEA Concept Tracker

# Tracking Document
## East African IeDEA Concept Proposals

# ACTIVE PROJECTS

| Proposal Number | Date | Requested By | Project Title | Project Status | Analysis Datasets | | |
|---|---|---|---|---|---|---|---|
| | | | | | Priority | Expected Delivery | Date Delivered |
| 4 | 28Aug07 | Tsiouris | Impact of HIV-TB integration on TB incidence among persons receiving HIV care and treatment in East Africa | DA/W | | 15Feb11 | 17Mar11<br>Revised 20Apr11<br>Revised 16Nov13<br>Revised 02Dec13<br>Revised 11Dec13 |
| 8 | 01Feb08 | Elul | Incidence and determinants of pregnancy among women enrolled in care and treatment programs in East Africa | DA/W | | 15Apr12 | 05Jun09<br>Updated 28Jan10<br>Updated 28Jan12<br>Updated 21May12 |
| 9 | 16Apr08 | *Multi-Regional* Geng | A comparison of the immunologic efficacy of antiretroviral therapy in resource-replete versus resource-limited settings | S | | 01Nov11 | 26Dec11<br>Revised 29Jan12 |
| 13 | Jul08 | Braitstein | Models of Patient Outreach and their Associated Rates of Loss to Follow-up in the East African IeDEA Consortium | DA | | 13Nov09 | 27Dec09<br>Revised 12Feb10<br>Revised 07Aug10<br>Revised 09Aug12<br>Revised 02Sep14 |
| 14 | Aug08 | Nash | Factors associated with CD4 count at ART initiation and their relationship to survival | DA/W | | 15May10 | Draft 30Jun09<br>Revised 23Aug10<br>Revised 01Nov10<br>Revised 30May12 |
| 15 | Aug08<br>Revised 30Jan10 | *Multi-Regional* Colbunders | Weight evolution in patients on effective ART: a comparison among different regions and different regimens | D | | 01Apr11 | 05Apr11 |
| 19 | 01Nov09 | Vreeman | Estimates and Correlates of Pediatric ART Adherence | D | | 01Oct10 | 11Jan11<br>Revised 23Feb11<br>Revised 08Sep13 |
| 20 | 09Feb09 | Gisore, Ayaya | Adolescent Care in East Africa IeDEA | DE | | 01Dec13 | 20Jun14 |
| 21 | 02Feb09 | Egger | Molecular and Clinical Epidemiology of Tuberculosis in Sub-Saharan Africa (Directed at AMPATH in EA) | DA,W | N/A | | |
| 25 | 31Jul09 | Easterbrook | Sub-optimal CD4 reconstitution among patients on Antiretroviral therapy in the developed and developing countries; Frequency and patterns, determinants and clinical significance. | D | | 15Apr12 | 14May12<br>Revised 24Jul12 |

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 27 | 09Nov09 | Ayaya, Marete | Predictors and factors associated with treatment failure among HIV infected children on ARVs. | DA | | 01Oct12 | 10Dec12<br>Revised30Jan13<br>Revised07Aug13<br>Revised21Aug14 |
| 32 | 18May10 | Braitstein | Revising mortality estimates and predictors of mortality among HIV-infected children in western Kenya | DE - AMPATH | 2 | 01May14 | |
| 33 | 18May10 | *Multi-Regional* Braitstein | What is the Capacity for the Conduct of Adverse Event/Toxicity Monitoring in Resource-Constrained Settings? | DA– Site assessment data only | N/A | | |
| 34 | 11Jun10 | *Multi-Regional* Yotebieng | Development of low-tech and context-appropriate tools for monitoring ART in children in resource poor-settings: weight and CD4 velocity reference standards | D | | 15Feb11 | 25Feb11 |
| 35 | 06Aug10 | Wools-Kaloustian | The impact of intermittent 3-drug pMTCT on long term outcomes of women initiated on ART for treatment | DE | 1 | 15Jun14 | |
| 36 | 10Jun10 | *Multi-Regional* Nash | Evaluation of documentation, screening, diagnostic and treatment capacity for AIDS-defining and non-AIDS-defining cancers | D | N/A | | |
| 37 | 20Oct10 | Martin | Epidemiology of Kaposi's Sarcoma in Africa in the Potent Antiretroviral Therapy (ART) Era | W – AMPATH, Mbarara, & IDI | | | 24Aug11<br>Revised 21Oct11<br>Revised 30Nov12<br>Revised 30Jul13<br>Revised 06Dec13 |
| 39 | Dec10 | Elul | Characteristics of patients at enrollment into HIV care and outcomes prior to therapeutic ART eligibility or initiation in the IeDEA East Africa cohort | DA | | 15Feb14 | 13Mar14<br>Revised 27May14<br>Revised 18Jul14<br>Revised 26Aug14 |
| 40 | Jan11 | *Multi-Regional* Wools-Kaloustian | Clinic and Patient-level determinants of durability of first-line regimen and time from first-line failure to second-line ART initiation in children in the International IeDEA Cohort. | DA | | 15Jun13 | 15Jul13<br>Revised 05Jan14<br>Revised 24Mar14<br>Revised 03Sep14<br>Revised 17Feb15 |
| 42 | Dec 2010 | Wools-Kaloustian / Goodrich | The incidence of first-line ART failure and incidence and determinants of initiation of second-line ART in adults meeting local criteria for first-line failure | DA | | 01Jul13 | 26Jul13<br>Revised 18Nov13<br>Revised 28Jan14 |
| 43 | Jan 2011 | Kessler / Braithwaite | Comparative effectiveness and opportunity costs of outreach strategies within anti-retroviral treatment programs in East Africa | DA | | 01Feb12 | 03Mar2012<br>Revised 13Aug12 |
| 44 | Feb 2011 | Nash | Trends in enrollment and ART initiation in the context of level funding from international donors | DA, W | | 01Jul14 | 02Oct2014 |
| 45 | Mar 2011 | Nuwagaba-Biribonwoha | Clinical characteristics and outcomes of adolescents attending HIV clinics in IeDEA Eastern Africa | DA | | 01Aug13 | 30Oct2013<br>20Dec2013 |
| 46 | June 2011 | Elul / Holmes | PEPFAR: Programmatic and Clinical HIV Treatment Outcomes in Pregnancy | D | | 15Sep2011 | 08Sep2011<br>Revised 03Jan13 |
| 50 | Nov 2011 | *Multi-Regional* Wools- | Pediatric cancer burden and treatment resources within the Pediatric IeDEA Consortium | W | | | 26Jul2012<br>Revised 10Apr13 |

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|---|---|---|---|---|---|---|---|
| | | Kaloustian | | | | | |
| 51 | May 2012 | *Multi-Regional* Giles, Law | Antiretroviral therapy initiation, durability and switching according to region and gender | DA | | | 21May2013 |
| 52 | Apr 2012 | Geng / Martin | A Sampling-Based Approach to Assess the Magnitude, Consequences, and Reasons for Losses to Follow-up among HIV-infected Patients in the East Africa IeDEA Consortium | DA | | 01Nov2012 | 13Nov2012 |
| 53 | Sep 2012 | *Multi-Regional* Egger | Switching of ART to second- and third-line regimens: global view | DA | | | 21May2013 |
| 54 | Sep 2012 | *Multi-Regional* Egger | Treatment outcomes on first-line, second-line and third-line ART: global view | DA | | | 21May2013 |
| 56 | Feb 2013 | Easterbrook | HIV among adults aged 50 years and older over the continuum of care (testing and diagnosis, clinic registration and ART initiation) in East Africa: characteristics, treatment outcomes, co-morbidities, and ART toxicities | DA | | 01Oct13 | 22Oct2013 Revised 24Mar14 |
| 57 | Nov 2013 | *Multi-Regional* Wools-Kaloustian, Cu-Uvan | African Network for Cervical Cancer Screening and Treatment | DA,W | | | 21Feb2014 |
| 58 | Nov 2013 | *Multi-Regional* Vreeman | Adherence to Antiretroviral Therapy (ART) for HIV-infected Children and Adolescents Followed in Global IeDEA Sites | DE | 3 | 01Sep14 | |
| 59 | Nov 2013 | *Multi-Regional* Wools-Kaloustian, CIPHER | Duration of First-line Antiretroviral Regimens in Children: A Global Perspective | DA | | 15Nov14 | 05Dec2014 Revised 17Feb15 |
| 60 | Nov 2013 | *Multi-Regional* Egger, Wandeler | Effect of nucleos(t)ide reverse transcriptase inhibitor sequencing on second-line antiretroviral therapy outcomes in sub-Saharan Africa | DA | | | 21May2013 |
| 61 | Sep 2013 | *Multi-Regional* Wools-Kaloustian, CIPHER | Global epidemiology of adolescents with perinatal HIV infection | DA | | 15Nov14 | 05Dec2014 Revised 17Feb15 |
| 62 | Dec 2013 | *Multi-Regional* Egger, Davies | 2014 update of concept "Immunodeficiency at the start of ART: a global view" (adults and children) | DA | | | 27Feb2014 Revised 05May14 |
| 63 | Jan 2014 | *Multi-Regional* del Amo COHERE | Disparities in the overall and cause-specific mortality between HIV-positive women from Europe, North-America and Sub-Saharan Africa | C | | | |
| 64 | Feb 2014 | Karwa | Building off the HIV platform: Extension of Pharmacovigilance to population with Tuberculosis or Malignancies (Data Description) | DE, AMPATH | 4 | | |
| 65 | Jan 2013 | Wools-Kaloustian | Evaluation of AMPATH Low Risk Express Care (LREC) Program | DA | | | 05Apr2013 Revised 22Jul2013 |
| 66 | Aug 2014 | *Multi-Regional* Sohn | Developing global surveillance estimates for perinatally infected adolescents on antiretroviral therapy transitioning to adulthood | DA | | | 06Nov2014 19Nov2014 |

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | SPECTRUM | | | | | 02Dec2014<br>22Dec2014<br>20Jan2015 |
| 67 | Sep 2014 | *Multi-Regional*<br>Yiannoutsos | SiZer maps to Investigate significant features of weight change in HIV-infected patients | C | | | |
| 68 | Sep 2014 | *Multi-Regional*<br>Quinn | Changes in the comprehensiveness of care provided at HIV care and treatment programs in the IeDEA collaboration from 2009 to 2014 | C | | | |
| 69 | Jan 2015 | Apondi | ART and congenital anomalies- an analysis of mother baby data on association of ART and congenital anomalies in Western Kenya | C | | | |
| 70 | Feb 2015 | *Multi-Regional*<br>Desmonde | Age-, CD4-, and viral load-stratified rates of opportunistic infections and mortality in youth ages 0-24: Descriptive analyses and derivation of inputs for simulation models | C | | | |

**PROPOSED PROJECTS – Concept Proposal Being Developed**

| Proposal Number | Date | Requested By | Project Title |
|---|---|---|---|
| C | Jan 2012 | Ssali | To understand the Effect patterns of switching or stopping the ARV regimen on; patients' CD4 levels, ART Adherence or completer treatment failures |
| D | Feb 2014 | Yiannoutsos, Ghys | HIV and aging: A descriptive study |

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## COMPLETED PROJECTS

| Proposal Number | Date | Requested By | Project Title | Project Status | Analysis Datasets | |
|---|---|---|---|---|---|---|
| | | | | | Expected Delivery | Date Delivered |
| 1 | 27Jun07 | Hunt | Changing Characteristics of HIV-infected Patients Initiating Antiretroviral Therapy in East Africa | P http://www.ncbi.nlm.nih.gov/pubmed/21955541 | | 17Jan09 Updated 30Jun09 Final 27Nov09 Revised 24Jan10 Revised 08Jul10 Revised 14Oct10 |
| 3 | Jul07 | Braithwaite | Comparing the effectiveness of alternative laboratory monitoring strategies for HIV patients in East Africa under various resource constraint scenarios | P http://www.ncbi.nlm.nih.gov/pubmed/21801434 | | 28May08 Completed |
| 7 | 11Dec07 | *Multi-Regional* Zhou | The use of zidovudine (AZT) containing antiretroviral regimens and its impact on the risk of anemia and survival in HIV-infected patients in developing countries | P http://www.ncbi.nlm.nih.gov/pubmed/22289654 | | 31Aug08 |
| 11 | 15Jun08 | *Multi-Regional* Nash | Facility and program characteristics of HIV care and treatment programs in the IeDEA collaboration | S – Data from IeDEA Site Assessment | | |
| 16 | - | *Multi-Regional* Dabis | Baseline characteristics, 24-month mortality and retention in antiretroviral programs in children in the IeDEA pediatric collaboration | P –JAIDS http://www.ncbi.nlm.nih.gov/pubmed/23187940 | 30Sep09 | 02Oct09 Revised 26Jan10 |
| 18 | | Braitstein | Pediatric losses to follow-up from a comprehensive HIV clinical care program in Western Kenya | S - AMPATH only http://www.ncbi.nlm.nih.gov/pubmed/23466646 | 15Sep09 | 18Sep09 |
| 22 | 05May09 | *Multi-Regional* Smith, Cooper | IeDEA Pediatric Program Cohort Profile | P - uses Peds Site Assessment | | |
| 23 | Jul09 | *Multi-Regional* Ciaranello Dabis | Pediatric Simulation Model | P in PLoS One | 15Jan10 | 25Feb10 Revised 01Oct10 Revised 01Jan11 Revised 29Sep11 Revised 25Jun12 |
| 26 | Revised Jul09 | *Multi-Regional* Egger | Information for article describing the African regions of IeDEA (Cohort Profile in Int J Epidemiol). | P http://www.ncbi.nlm.nih.gov/pubmed/21593078 | 01Sep09 | 9Dec09 Revised Dec10 |
| 28 | 09Nov09 | *Multi-Regional* Chi | Defining lost to follow-up (LTFU) in ART treatment programmes in sub-Saharan Africa | P | 01Jul10 | 30Jun10 |
| 30 | 12Nov09 | *Multi-Regional* Egger | Immunodeficiency at the start of ART: a global view | S | 30Apr11 | 06May11 |

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|---|---|---|---|---|---|---|
| 31 | 18May10 | Petersen | Modification of the effect of deferred regimen modification following loss of viral suppression on first line therapy by CD4+ T cell count and HIV RNA level | P -Mbarara (UARTO), Rakai | | 26Dec11<br>Revised 29Jan12 |
| 38 | 14Dec10 | Ciaranello | Natural history of HIV infection in children presenting before 1 year of age in East Africa: an IeDEA regional collaboration | P in PIDJ | | 01Jan11<br>Revised 29Sep11<br>Revised 25Jun12 |
| 47 | Sep 2011 | *Multi-Regional* Fenner | Tuberculosis in HIV treatment programmes in low-income countries within the global IeDEA network: A survey on integration of services, diagnostic, screening, preventive and treatment practices | P<br>http://www.ncbi.nlm.nih.gov/pubmed/24147059 | | |
| 55 | Sep 2012 | Kiragga, Yiannoutsos | CD4 trajectory among HIV positive patients receiving HAART in HIV care centres | P | | 02May2011 |

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## ABANDONED PROPOSALS

| Proposal Number | Date | Requested By | Project Title | Project Status | Analysis Datasets | | |
|---|---|---|---|---|---|---|---|
| | | | | | Priority | Expected Delivery | Date Delivered |
| 2 | Jul07 | Wools-Kaloustian | Models of Care: A description of HIV care and treatment sites participating in the East African IeDEA Collaboration | X | | | |
| 5 | 08Jan08 | Cohen | Pregnancy Related ARV Adverse Events and Treatment Failure | X 31Aug09 Data delivered to UCSF DM for processing | | TBD | |
| 6 | 10/01/08 | Geng | Virologic correlates of immunologic failure in African patients on antiretroviral therapy | ? EA data center not involved | | | 10Nov2008 Revised 21Mar09 |
| 10 | 16Apr08 | *Multi-Regional* Calmy | Prediction of CD4 Cell Count and percentage slopes in patients with virologic failure to first line of antiretroviral combinations in resource-limited settings. | X | | | |
| 12 | 28Jun08 | Sidle | Comparative outcomes between patients in resource-limited settings using efavirenz versus nevirapine-based regimens for first-line antiretroviral therapy. | X | | | |
| 17 | - | *Multi-Regional* Davies | Impact of PMTCT exposure and maternal health on outcomes of antiretroviral therapy in HIV-infected infants | X | | | |
| 24 | 31Jul09 | Kiragga, Nakanjako | Clinical consequences of missing data within large observational HIV/AIDS treatment cohorts in Africa | C | | | |
| 29 | 09Nov09 | *Multi-Regional* Egger | Switching of ART to second- and third-line regimens: Global view of patterns of switching and outcomes | X | | | |
| 41 | Jan11 | Ayaya | Progression of HIV/AIDS in children | DA – AMPATH only | | | Sep10 |
| 48 | Dec 2011 | *Multi-Regional* Bohliu | Incidence and prognosis of AIDS-defining cancers in the era of cART: Africa, Europe and North America compared | X | | | |
| 49 | Dec 2011 | *Multi-Regional* Lau | CD4 response to effective ART: Defining an appropriate immunologic response through a global perspective | C | | | |
| B | June 2011 | Lyamuya | Retention and predictors in pre-ART Population | | | | |
| | | | | | | | |

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# Appendix 2

## White Paper:
## Estimated mortality of HIV-infected children 0-5 years of age treated with combination antiretroviral therapy

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**Abstract**

Over the past decade we have witnessed a monumental scale-up of services providing antiretroviral therapy (ART) to millions of HIV-infected individuals in the developing world. By all accounts, this historic pharmacologic intervention has reduced rates of opportunistic infections, increased survival and enhanced the quality of life of the recipients of these services. Nevertheless, it is clear that the impact of therapy is not the same across all patient populations affected by the epidemic. Mortality is higher among patients with greater suppression of their immune system as indicated by lower CD4 lymphocyte levels or percents at the start of therapy, and response to therapy may not be as strong compared to patients with higher CD4 counts. Age plays a role as well, particularly among the youngest of children and among adolescents on one hand and older patients on the other (ref). For these reasons, it is necessary that overall estimates of patient survival be produced according to, at least, the starting CD4 count (or, in the case of young children under 5 years of age, the CD4 percent), gender and age at the start of ART. These estimates can then inform policy makers, modelers, epidemiologists and other stakeholders involved with antiretroviral programs in the resource-constrained setting. This paper addresses this need by assembling data from a number of cohorts of patients receiving therapy and routine medical care in HIV care and treatment programs located in sub-Saharan Africa, the Asia Pacific region, and South America and the Carribean.

# 1 Introduction

Thirty five years from the first description of the acquired immunodeficiency syndrome (AIDS), cases of the disease have been observed in every part of the world. More than 33 million individuals are living with the disease with the majority of them living in low and middle-income countries [14]. However there are also positive statistics. According to the same report, new infections have been reduced by 19% since 1999. In addition, up to 5.2 million people in low and middle-income countries were receiving care in 2009, 1.2 million of whom started therapy for the first time in that year; a significant 30% increase compared to only a year before. Still, this only represents just over one third of all persons, 15 million by some estimates, who need therapy now.

Table 1: Listing the date range for data provided from each cohort

| | **Enrollment date** | |
|---|---|---|
| **Cohort** | **Earliest date** | **Most recent date** |
| East Africa | 13 Aug 2002 | 15 Oct 2012 |
| Central Africa | 28 Jan 2004 | 05 Feb 2014 |
| West Africa | 26 Apr 2000 | 22 Aug 2014 |
| Southern Africa | | |
| Asia Pacific | 31 Jan 1992 | 3 Jan 2014 |
| CCASAnet | 26 Jul 1991 | 29 Jan 2014 |

Regardless of enormity of the challenge, it is clear that we are witnessing a historic undertaking with rapid scale-up of services providing antiretroviral therapy (ART) to millions of HIV-infected individuals in these countries. By all accounts, the largest pharmacologic intervention in human history has reduced rates of opportunistic infections, increased survival and enhanced the quality of life of the recipients of these services. It is clear however, that the impact of ART is not the same across all patient groups. Mortality is higher among patients with greater suppression of their immune system as indicated by lower CD4 lymphocyte levels at the start of therapy and response to therapy may not be as strong compared to patients starting treatment with higher CD4 counts. Gender and age plays a role as well. Men generally access treatment later than women, and may be less compliant to therapy once initiating it. Also, the disease may affect younger and older-age patients differently and drug adherence may vary significantly in young versus older patients (ref) For these reasons, it is necessary that overall estimates of patient survival be produced according to, at least, these three risk factors that is, starting CD4 count (or, for the youngest children, CD4 percent), gender and age. These estimates can then inform policy makers, modelers, epidemiologists and other stakeholders involved with antiretroviral programs in the

developing world.

Table 2: Listing of patients by cohort and gender.

| | Gender | | |
|---|---|---|---|
| | **Men** | **Women** | |
| **Cohort** | *N* | *N* | **Total** |
| East Africa | 2,237 | 2,190 | 4,427 |
| Central Africa | 417 | 375 | 792 |
| West Africa | 1,200 | 980 | 2,180 |
| Southern Africa | | | |
| Asia Pacific | 1,098 | 972 | 2,070 |
| CCASAnet | 328 | 386 | 714 |
| **Total** | | | |

This paper addresses this need by assembling data from a number of cohorts of patients receiving therapy and routine medical care in outpatient HIV care and treatment programs around the world and estimating mortality among infants, aged 0-5 years at the time of ART initiation. The size of the pediatric population assembled for this report, makes this the hitherto definitive study in pediatric HIV in the low and middle-income setting.

# 2 Patients and methods

## 2.1 Description of the cohorts involved in the study

In this paper we report on six cohorts, for estimating mortality of HIV-infected infants and young children aged 0-5 years at the time they initiated ART. These cohort come from six regions of the International Epidemiologic Databases to Evaluate AIDS (IeDEA) worldwide collaboration: The East, Central, West and Southern Africa regions, the Central America and the Caribbean and Asia Pacific regions (refs). Frequencies of descriptive statistics according to the three main predictors, age, gender and CD4 percent at ART start were generated.

A listing of the sites and the date range in their respective databases is given in Table 1. The overall number of patients by gender is given in Table 2. Children enrolling into these programs provided data in the analyses from the time they initiated ART (with the exception of CD4 data, which were taken up to 6 (?) months prior to ART initiation, see below) and were followed up their last clinic visit. Data from children who were lost to follow-up were treated identically to those who were censored by study closure, consistent with the assumption of non-informative missingness in the data (or, less technically, assuming that children remaining on observation were representative

of those who were lost to follow-up) (ref). Sensitivity assessment of this assumption were only possible in East Africa where a subset of children were followed after loss to follow-up and had their vital status ascertained. Successfully traced children provided adjustments to the mortality estimates using the Frangakis & Rubin technique (refs). CD4 percent at entry was defined as the observation temporally most closely to the time of initiation of therapy, no more than XX months prior to ART start and up to one week after therapy (the latter to ensure inclusion of CD4 counts which were obtained contemporaneously with the start of treatment but were recorded with a small delay). The CD4 percent categories used were <5, 5-9, 10-14, 15-19, 20-24, 25-29 and $\geq 30$. To explore the effects of age on patient mortality, we grouped ages to $0-1$, $1-2$ and $3-5$ years.

Table 3: Listing of patients by cohort and CD4 percent category. Patients who were lost to follow-up but were not outreached were excluded from all analyses.

| | CD4 percent category | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | <5 | 5-9 | 10-14 | 15-19 | 20-24 | 25-29 | $\geq 30$ | |
| Cohort | *N* | *N* | *N* | *N* | *N* | *N* | *N* | Total |
| East Africa | 163 | 494 | 763 | 524 | 238 | 157 | 195 | 2,514 |
| Central Africa | 31 | 96 | 133 | 95 | 39 | 38 | 31 | 463 |
| West Africa | 103 | 236 | 283 | 242 | 60 | 60 | 79 | 1,063 |
| Southern Africa | | | | | | | | |
| Asia Pacific | 311 | 257 | 249 | 267 | 160 | 116 | 139 | 1,499 |
| CCASAnet | 33 | 33 | 93 | 94 | 42 | 53 | 74 | 422 |
| **Total** | | | | | | | | |

## 2.2 Statistical methods

A Poisson model was fit, separately for the period up to six months from initiation of ART and a second model at 6-12, 12-24 and >24 months since the start of ART. This model assumes constant hazards within each period. (It is also called a piecewise exponential survival model [10, 11]). The first of these periods represents the critical first months after therapy is initiated where residual opportunistic infections, persistence of immunosuppression, drug toxicity and immune reconstitution syndrome (IRIS) render patients especially vulnerable. The second period represents a time of reduced but perhaps not yet stabilized mortality hazard, particularly among children with significant immunosuppression at ART start. The third period is the time of stable therapy while the fourth addresses the possibility of emergence of resistance and failure of first-line drug regimens. This is is a rather limited model in its ability to describe changes in mortality which occur after initiation of ART. However, it is useful because it is easy to implement and even easier to describe to stakeholders and decision

makers involved with antiretroviral programs around the world.

A sensitivity analysis was carried out using a subset of East Africa IeDEA data where vital status was ascertained in a subset of children who were lost to follow-up. In this situation, mortality estimates were adjusted by incorporating outreach data and using the Frangakis and Rubin method, which specifies that the hazard of mortality be weighted by the inverse probability of being outreached. The probability of outreach is estimated by the ration of all children who were outreached to those who were lost to follow-up by the end of the study (see Yiannoutsos et al. [17]).

Table 4: Listing of patients by cohort and age category.

| | Age category (years) | | | |
|---|---|---|---|---|
| | 0-1 | 1-2 | 3-5 | Total |
| Cohort | *N* | *N* | *N* | *N* |
| East Africa | 746 | 1,050 | 2,631 | 4,427 |
| Central Africa | 169 | 227 | 396 | 792 |
| West Africa | 359 | 595 | 1,226 | 2,180 |
| Southern Africa | | | | |
| Asia Pacific | 548 | 373 | 1.140 | 2,070 |
| CCASAnet | 221 | 171 | 322 | 714 |
| **Total** | | | | |

# 3 Results

A listing by IeDEA region and overall CD4 percent category is shown in Table 3. A listing of overall age categories by region is shown in Table 4). Baseline characteristics of each cohort are presented in Figures 1- 6. These underline both the relative frequency of patients with respect to age and CD4 percent at ART initiation.

Figure 1: Stacked bar of CD4 percent by age among females enrolled in East Africa: Counts (left) and proportions (right).

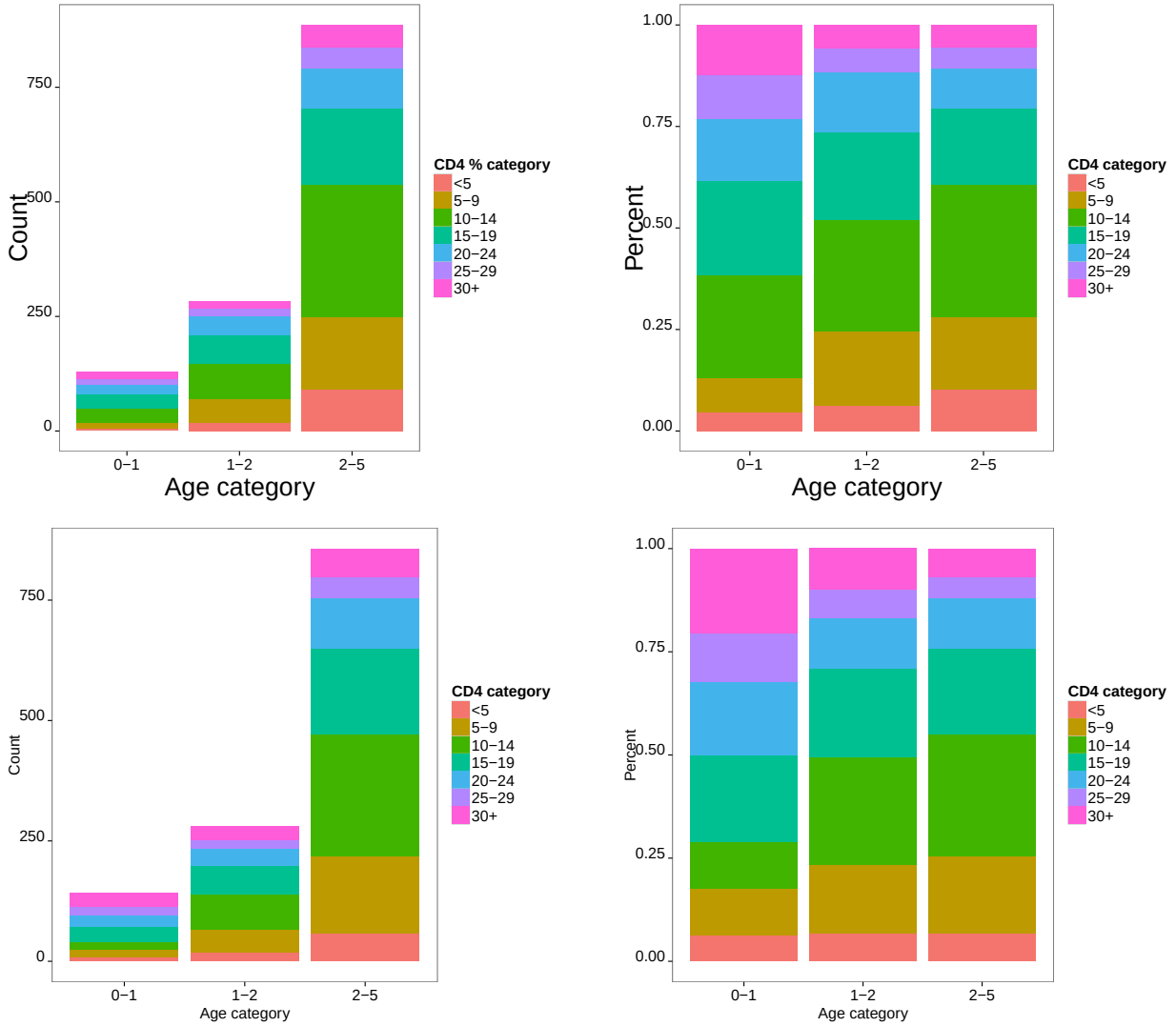


Figure 2: Stacked bar of CD4 count by age among men enrolled in Central Africa: Counts (left) and proportions (right).

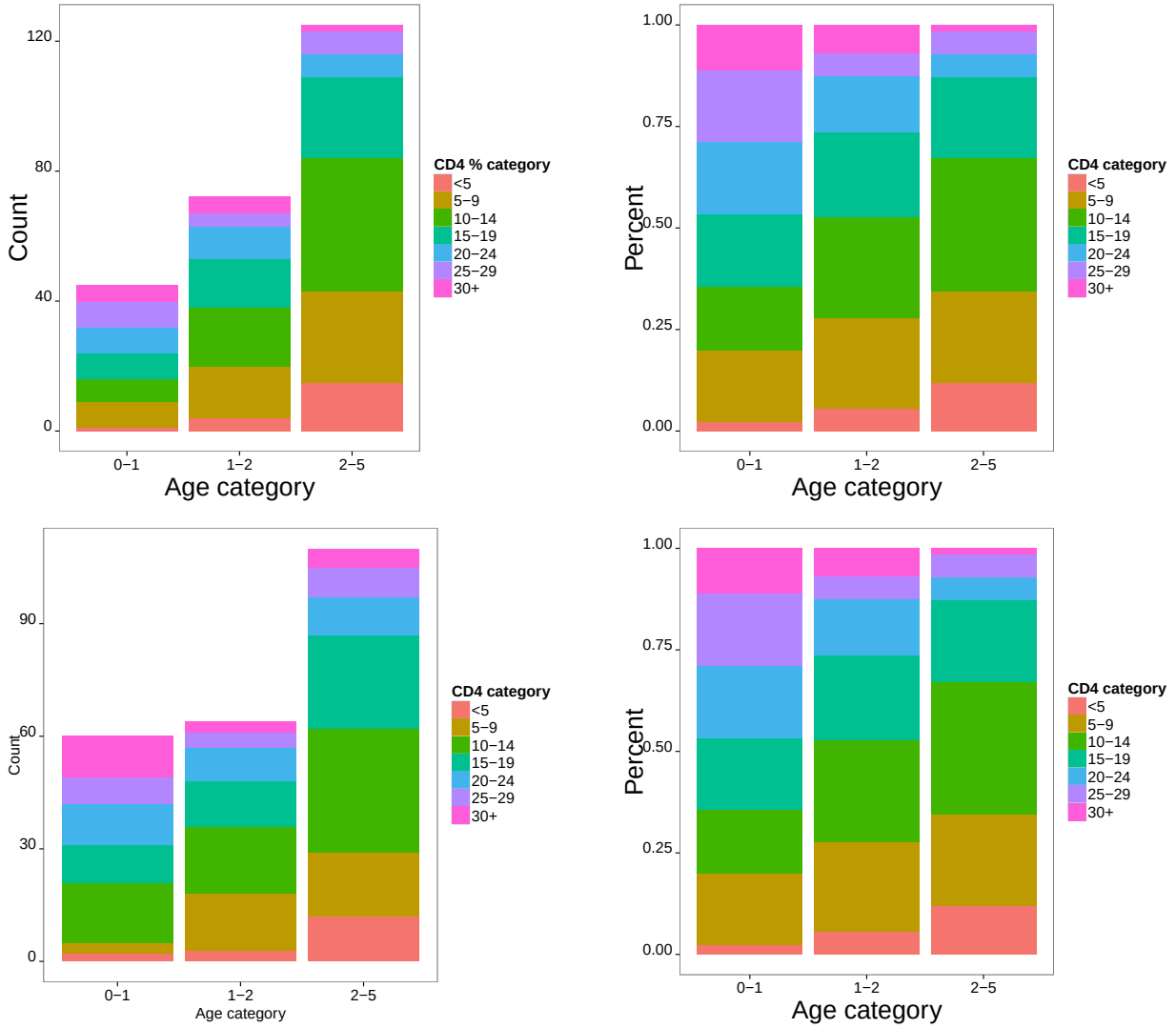


Figure 3: Stacked bar of CD4 count by age among men enrolled in West Africa: Counts (left) and proportions (right).

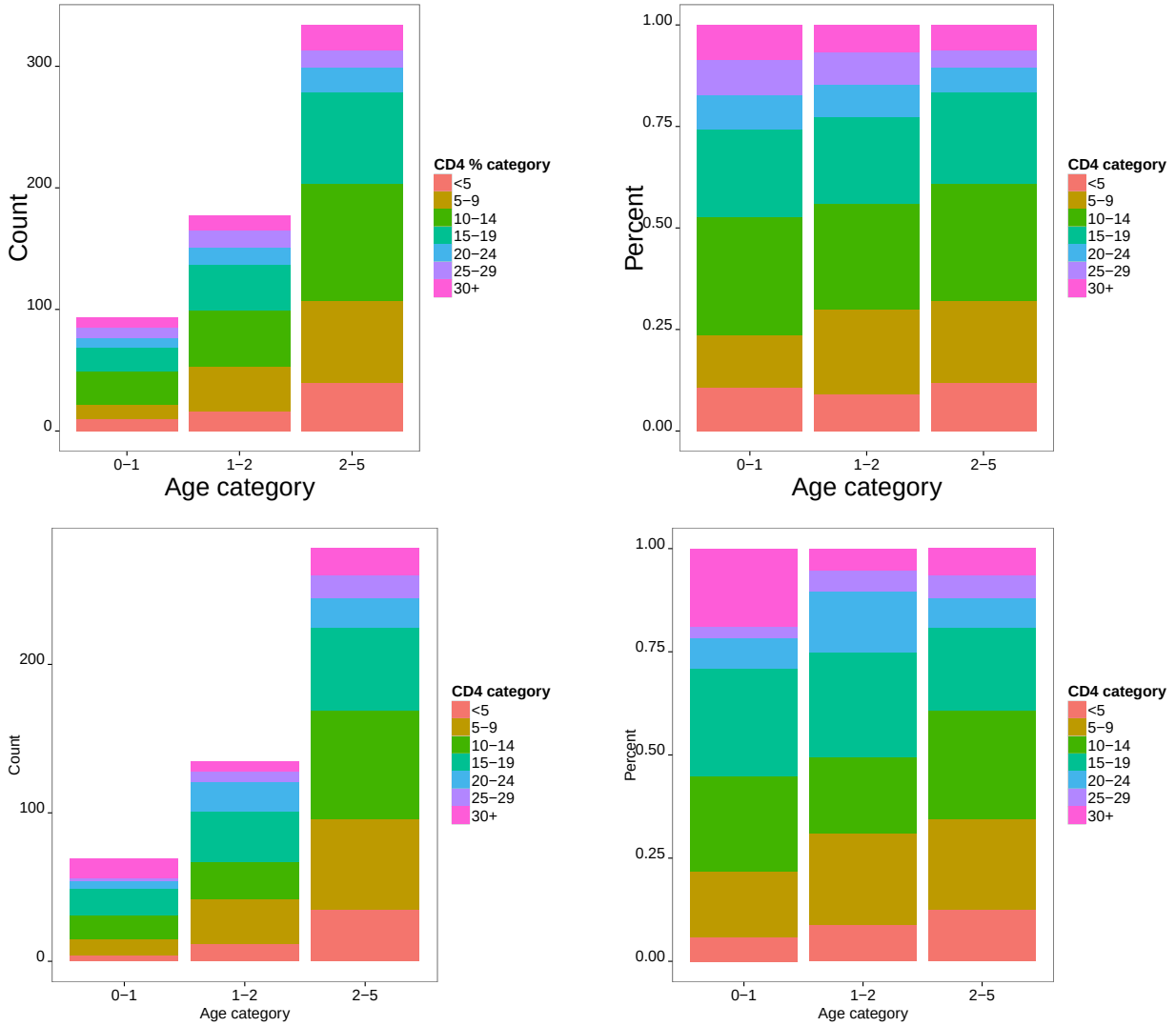


Figure 4: Stacked bar of CD4 count by age among men enrolled in the Southern Africa region: Counts (left) and proportions (right).

Figure 5: Stacked bar of CD4 count by age among men enrolled in the Asia Pacific IeDEA region: Counts (left) and proportions (right).

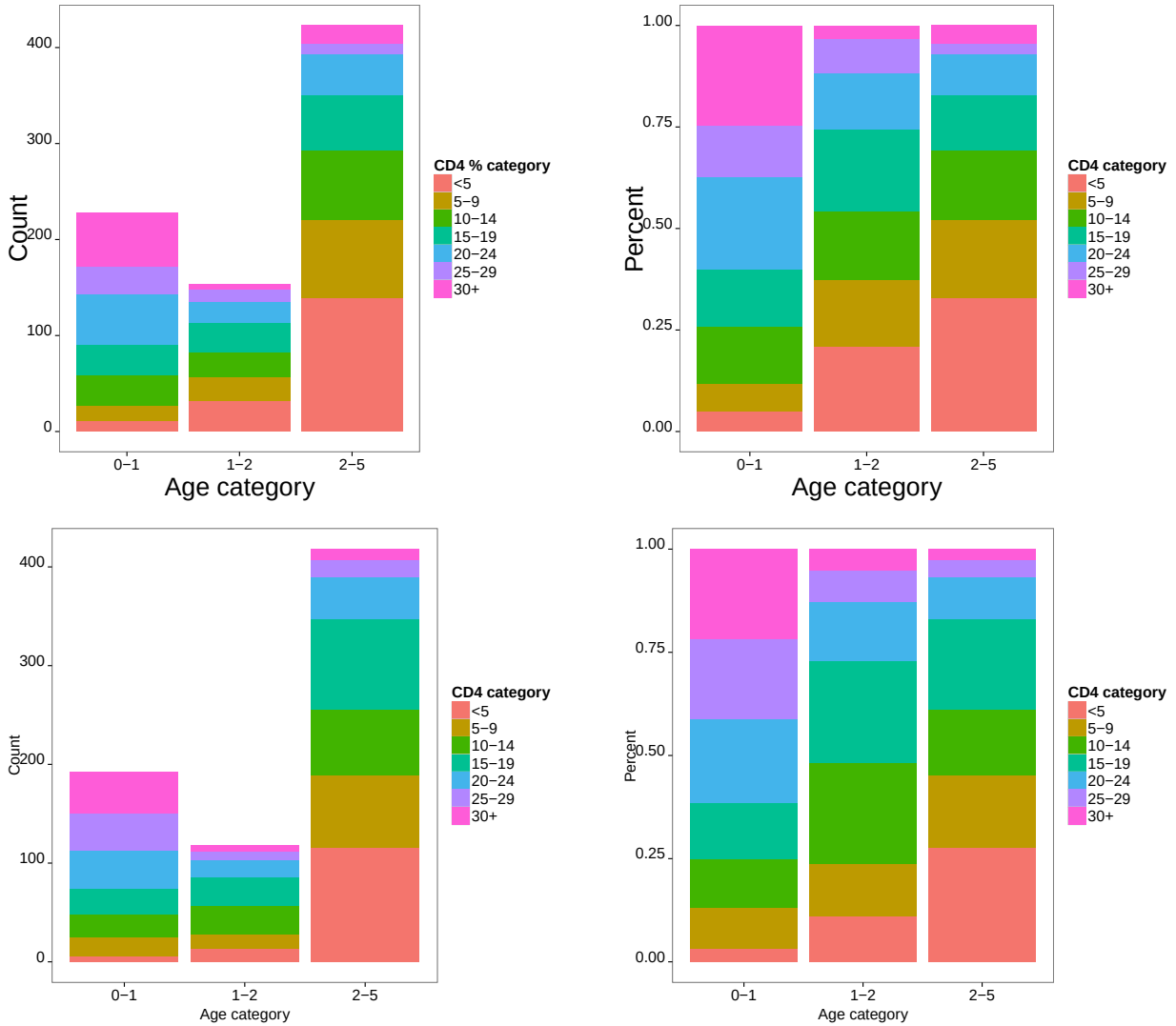
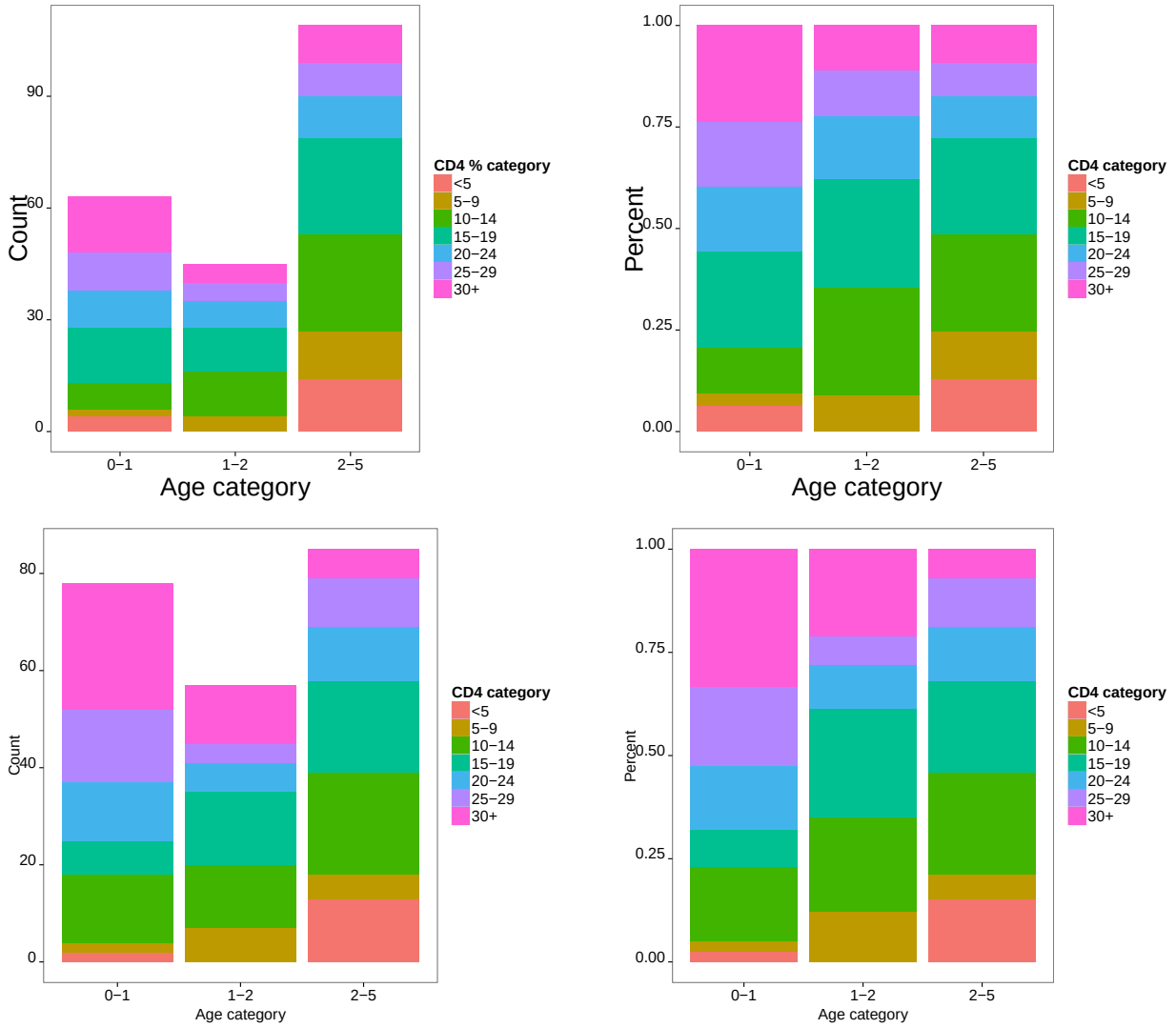


Figure 6: Stacked bar of CD4 count by age among men enrolled in Central South America and the Caribbean: Counts (left) and proportions (right).



Crude (i.e., unadjusted for loss to follow-up) estimates of mortality per 100 person-years of follow-up, for the six cohorts are given in Figures 7- 8 and Tables 5-XXX. Mortality is significantly higher during the first six months after treatment initiation

Figure 7: Estimated crude mortality by gender, age and CD4 count at ART initiation among children enrolled in East Africa: Boys left, girls right)

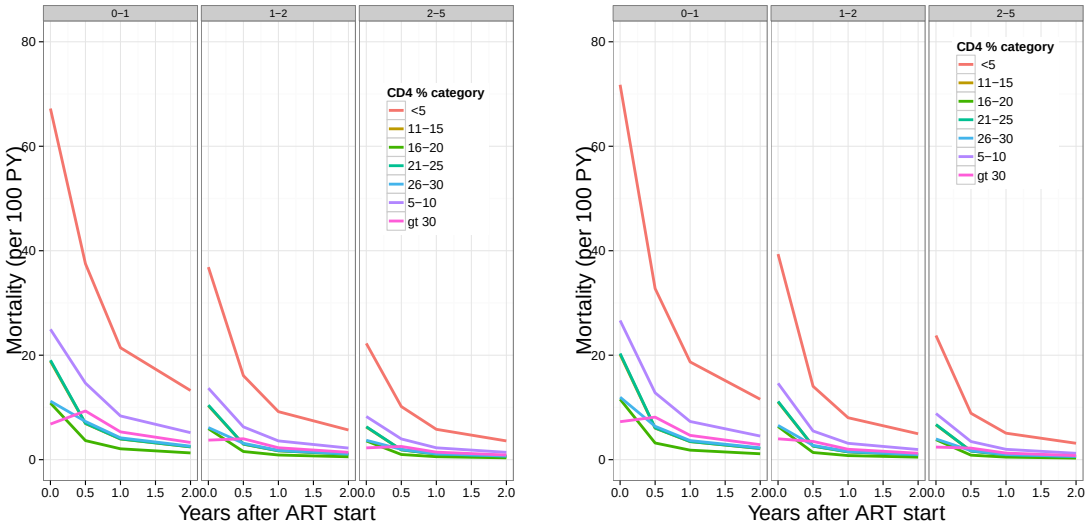
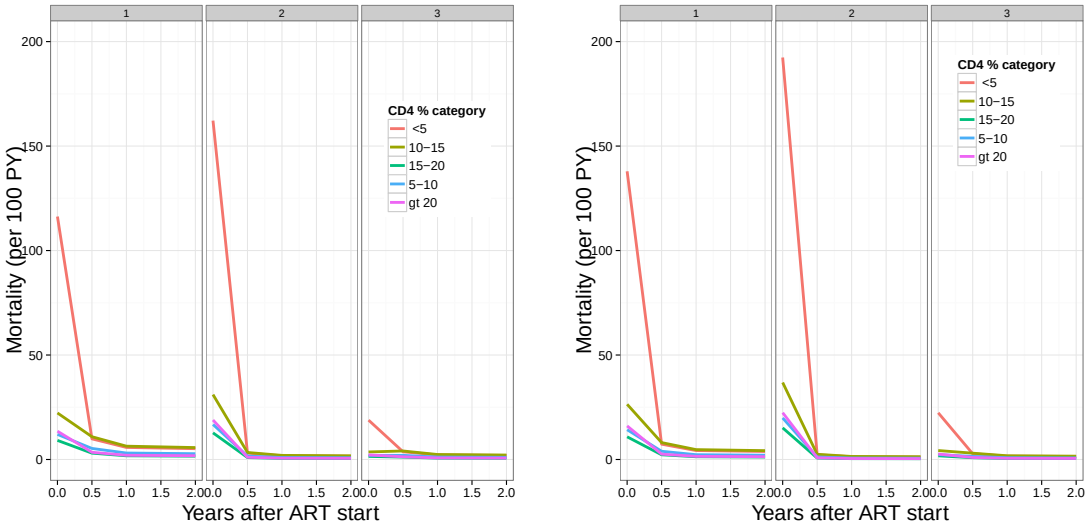



Figure 8: Estimated crude mortality by gender, age and CD4 count at ART initiation among children enrolled in Central Africa: Boys left, girls right)




and stabilizes to a low level thereafter with no evidence of re-emergence of mortality risk at least during the first two years after the initiation of ART. With respect to CD4

percent at the start of therapy, the results are consistent with expectation. Children who start therapy at lower CD4 percents, particularly $< 5\%$, have significantly higher mortality rates compared to those starting at CD4 percents above 10%.

Figure 9: Estimated crude mortality by gender, age and CD4 count at ART initiation among children enrolled in West Africa: Boys left, girls right)

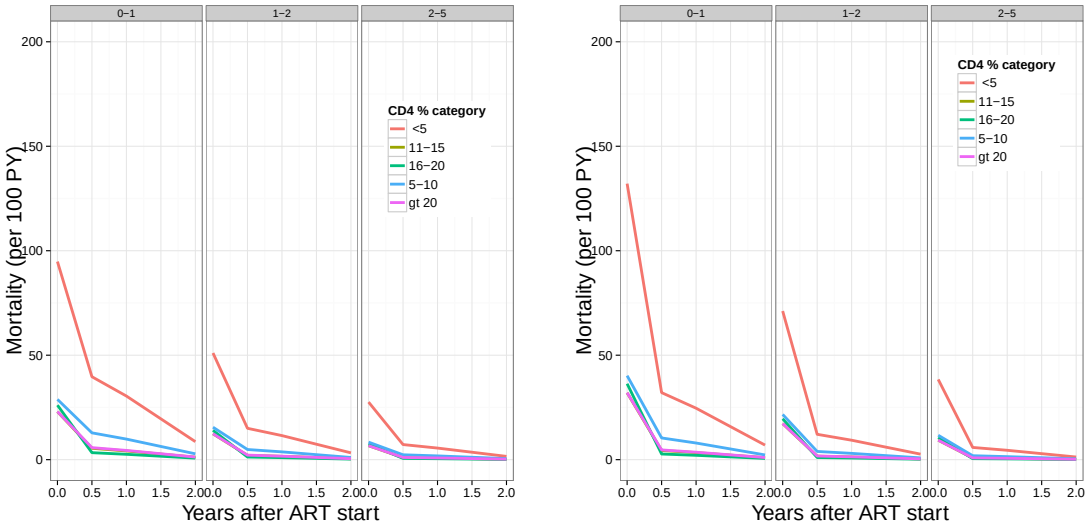



Figure 10: Estimated crude mortality by gender, age and CD4 count at ART initiation among children enrolled in the Southern Africa IeDEA region: Boys left, girls right)

Figure 11: Estimated crude mortality by gender, age and CD4 count at ART initiation among children enrolled in the Asia Pacific IeDEA region: Boys left, girls right)

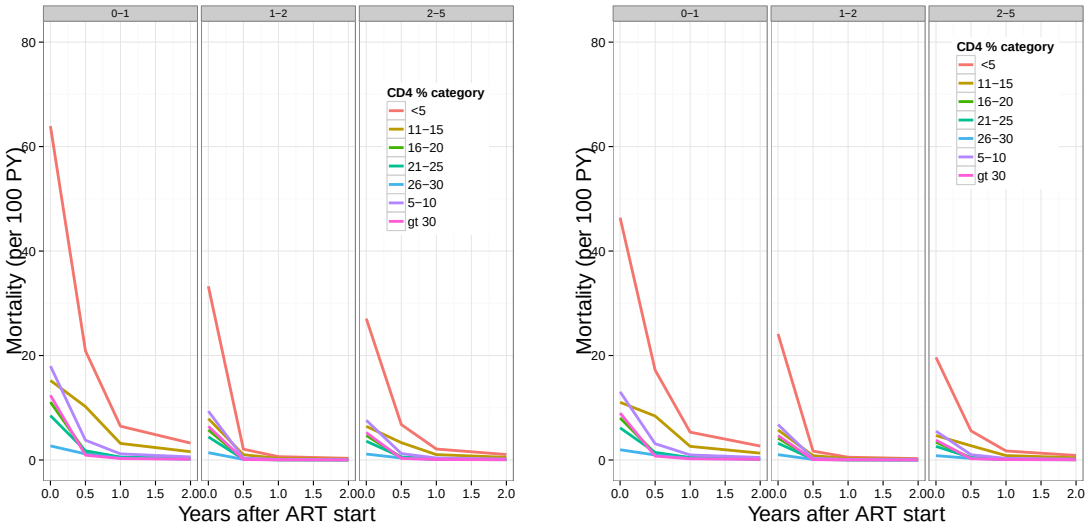



Figure 12: Estimated crude mortality by gender, age and CD4 count at ART initiation among children enrolled in Central South America and the Caribbean: Boys left, girls right)

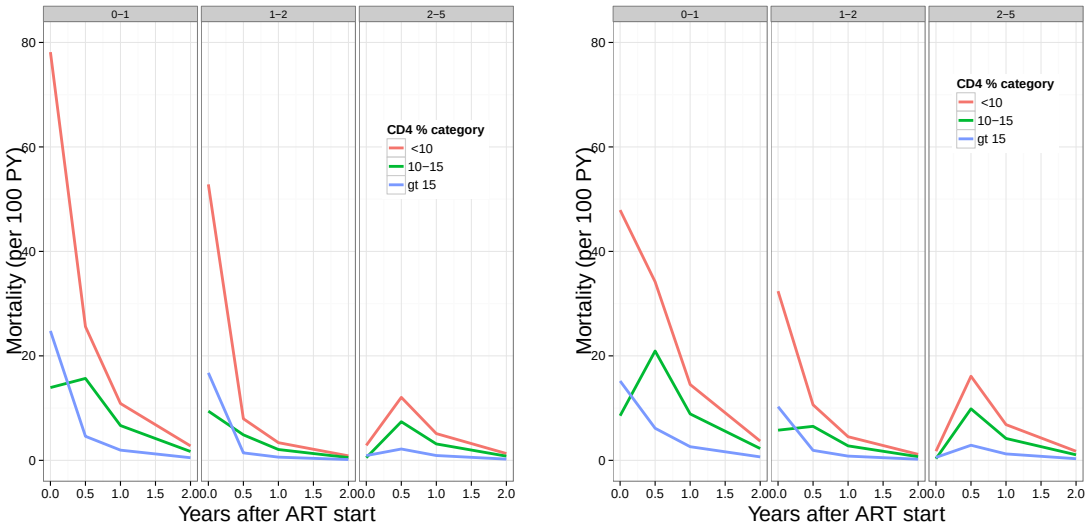


Table 5: Crude mortality estimates by CD4 percent and age for males enrolled in East Africa (corresponding to Figure 7 left panel)

| | Time from ART start (months) | | | |
|---|---|---|---|---|
| Age (years) | 0-6 | 6-12 | 12-24 | >24 |
| **CD4 percent <5** | | | | |
| 0-1 | 66.88 | 26.98 | 14.91 | 8.50 |
| 1-2 | 27.83 | 12.57 | 6.94 | 3.96 |
| 3-5 | 21.74 | 8.83 | 4.88 | 2.78 |
| **CD4 [percent 5-9** | | | | |
| 0-1 | 28.15 | 11.27 | 6.22 | 3.55 |
| 1-2 | 11.71 | 5.25 | 2.90 | 1.65 |
| 3-5 | 9.15 | 3.69 | 2.04 | 1.16 |
| **CD4 percent 10-14** | | | | |
| 0-1 | 16.99 | 5.05 | 2.79 | 1.59 |
| 1-2 | 7.07 | 2.35 | 1.30 | 0.74 |
| 3-5 | 5.52 | 1.65 | 0.91 | 0.52 |
| **CD4 percent 14-19** | | | | |
| 0-1 | 10.03 | 2.51 | 1.39 | 0.79 |
| 1-2 | 4.17 | 1.17 | 0.65 | 0.37 |
| 3-5 | 3.26 | 0.82 | 0.45 | 0.26 |
| **CD4 percent 20-24** | | | | |
| 0-1 | 18.89 | 5.35 | 2.96 | 1.69 |
| 1-2 | 7.86 | 2.49 | 1.38 | 0.79 |
| 3-5 | 6.14 | 1.75 | 0.97 | 0.55 |
| **CD4 percent 25-29** | | | | |
| 0-1 | 6.88 | 5.37 | 2.97 | 1.69 |
| 1-2 | 2.86 | 2.05 | 1.38 | 0.79 |
| 3-5 | 2.24 | 1.76 | 0.97 | 0.55 |
| **CD4 percent $\geq$ 30** | | | | |
| 0-1 | 5.66 | 6.15 | 3.40 | 1.94 |
| 1-2 | 2.35 | 2.87 | 1.58 | 0.90 |
| 3-5 | 1.84 | 2.01 | 1.11 | 0.63 |

Table 6: Place holder for a table of CD4 percent by age for females enrolled in East Africa (corresponding to Figure 7 left panel)

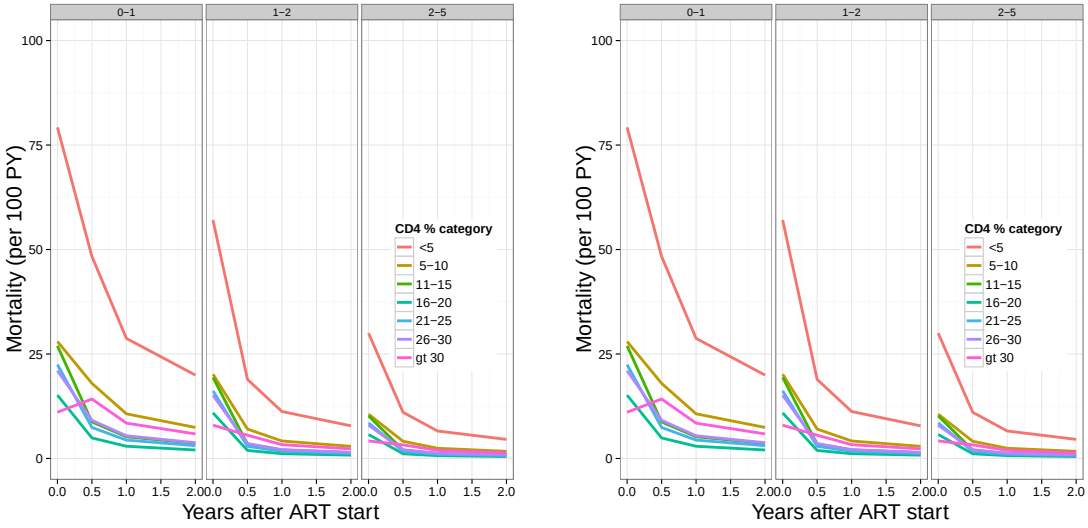
| | Time from ART start (months) | | | |
|---|---|---|---|---|
| Age (years) | 0-6 | 6-12 | 12-24 | >24 |
| **CD4 percent <5** | | | | |
| 0-1 | 54.94 | 21.95 | 12.13 | 6.92 |
| 1-2 | 22.86 | 10.23 | 5.65 | 3.22 |
| 3-5 | 17.86 | 7.18 | 3.97 | 2.26 |
| **CD4 [percent 5-9** | | | | |
| 0-1 | 23.13 | 9.17 | 5.06 | 2.89 |
| 1-2 | 9.62 | 4.27 | 2.36 | 1.35 |
| 3-5 | 7.52 | 3.00 | 1.66 | 0.95 |
| **CD4 percent 10-14** | | | | |
| 0-1 | 13.96 | 4.11 | 2.27 | 1.30 |
| 1-2 | 5.81 | 1.91 | 1.06 | 0.60 |
| 3-5 | 4.54 | 1.34 | 0.74 | 0.42 |
| **CD4 percent 14-19** | | | | |
| 0-1 | 8.24 | 2.04 | 1.13 | 0.64 |
| 1-2 | 3.43 | 0.95 | 0.53 | 0.30 |
| 3-5 | 2.68 | 0.67 | 0.37 | 0.21 |
| **CD4 percent 20-24** | | | | |
| 0-1 | 15.52 | 4.35 | 2.41 | 1.37 |
| 1-2 | 6.46 | 2.03 | 1.12 | 0.64 |
| 3-5 | 5.05 | 1.43 | 0.79 | 0.45 |
| **CD4 percent 25-29** | | | | |
| 0-1 | 5.65 | 4.37 | 2.41 | 1.38 |
| 1-2 | 2.35 | 2.04 | 1.12 | 0.64 |
| 3-5 | 1.84 | 1.43 | 0.79 | 0.45 |
| **CD4 percent $\geq$ 30** | | | | |
| 0-1 | 4.65 | 5.00 | 2.77 | 1.58 |
| 1-2 | 1.93 | 2.33 | 1.29 | 0.74 |
| 3-5 | 1.51 | 1.64 | 0.90 | 0.52 |

## 3.1 Sensitivity analysis

To assess the impact of death under-reporting due to loss to program on mortality rates, we used a sub-analysis involving data from East Africa, where vital status was ascertained on a subset of children who were lost to follow-up. We used the methods of Frangakis & Rubin [8, 1] which weight the hazard of mortality by the inverse probability of outreach (i.e., the inverse fraction of the children who were lost to follow-up and were subsequently traced through outreach). These methods have been used in a number of

papers [1, 9, 15] and, most recently, by Yiannoutsos and colleagues [17] while estimating survival of adult HIV patients. The adjusted mortality rates are shown in Figures 13 (males in the left panel and females in the right panel).

Figure 13: Estimated adjusted mortality by gender, age and CD4 count at ART initiation among children enrolled in East Africa: Boys left, girls right)




The mortality rates corresponding to Figure 13 are shown in Tables 7 for male children and 8 for female children.

Table 7: Adjusted mortality estimates by CD4 percent and age for males enrolled in East Africa (corresponding to Figure 7 left panel)

| | Time from ART start (months) | | | |
|---|---|---|---|---|
| Age (years) | 0-6 | 6-12 | 12-24 | >24 |
| **CD4 percent <5** | | | | |
| 0-1 | 58.83 | 52.57 | 31.24 | 21.07 |
| 1-2 | 42.35 | 20.56 | 12.22 | 8.49 |
| 3-5 | 22.26 | 12.02 | 7.14 | 4.96 |
| **CD4 [percent 5-9** | | | | |
| 0-1 | 20.78 | 19.55 | 11.62 | 8.07 |
| 1-2 | 14.96 | 7.64 | 4.54 | 3.15 |
| 3-5 | 7.86 | 4.47 | 2.65 | 1.84 |
| **CD4 percent 10-14** | | | | |
| 0-1 | 20.00 | 9.50 | 5.65 | 3.92 |
| 1-2 | 14.40 | 3.72 | 2.21 | 1.53 |
| 3-5 | 7.57 | 2.17 | 1.29 | 0.90 |
| **CD4 percent 14-19** | | | | |
| 0-1 | 11.25 | 5.34 | 3.17 | 2.20 |
| 1-2 | 8.10 | 2.09 | 1.24 | 0.86 |
| 3-5 | 4.26 | 1.22 | 0.73 | 0.50 |
| **CD4 percent 20-24** | | | | |
| 0-1 | 16.68 | 8.06 | 4.79 | 3.33 |
| 1-2 | 12.01 | 3.15 | 1.87 | 1.30 |
| 3-5 | 6.31 | 1.84 | 1.09 | 0.76 |
| **CD4 percent 25-29** | | | | |
| 0-1 | 15.58 | 9.93 | 5.90 | 4.10 |
| 1-2 | 11.22 | 3.88 | 2.31 | 1.60 |
| 3-5 | 5.90 | 2.27 | 1.35 | 0.94 |
| **CD4 percent $\geq$ 30** | | | | |
| 0-1 | 8.22 | 15.46 | 9.19 | 6.38 |
| 1-2 | 5.92 | 6.05 | 3.59 | 2.50 |
| 3-5 | 3.11 | 3.53 | 2.10 | 1.46 |

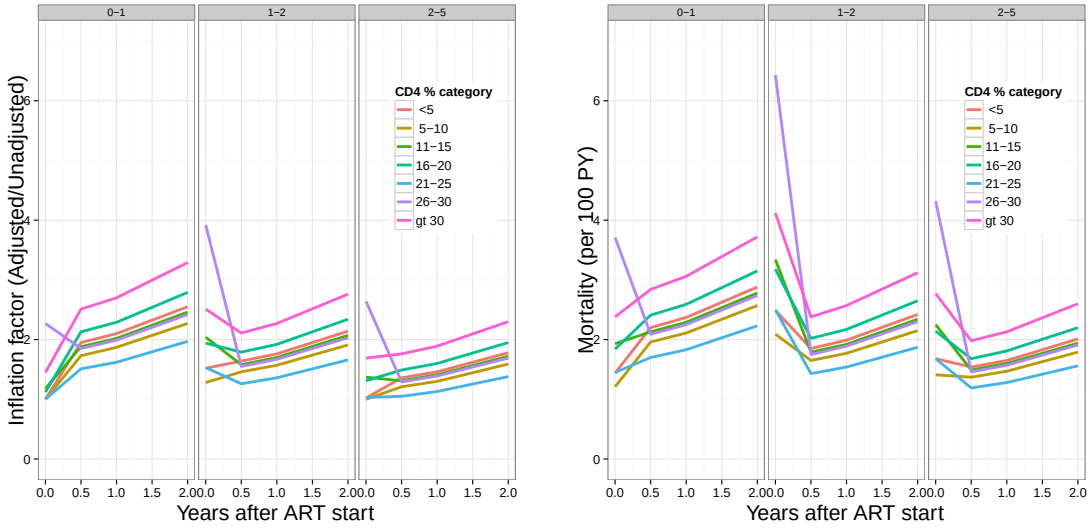
Table 8: Adjusted mortality by CD4 percent and age for females enrolled in East Africa (corresponding to Figure 7 left panel)

| | Time from ART start (months) | | | |
|---|---|---|---|---|
| Age (years) | 0-6 | 6-12 | 12-24 | >24 |
| **CD4 percent <5** | | | | |
| 0-1 | 79.23 | 48.34 | 28.73 | 19.95 |
| 1-2 | 57.04 | 18.91 | 11.23 | 7.80 |
| 3-5 | 29.98 | 11.05 | 6.57 | 4.56 |
| **CD4 [percent 5-9** | | | | |
| 0-1 | 27.99 | 17.97 | 10.68 | 7.42 |
| 1-2 | 20.15 | 7.03 | 4.18 | 2.90 |
| 3-5 | 10.59 | 4.11 | 2.44 | 1.70 |
| **CD4 percent 10-14** | | | | |
| 0-1 | 26.94 | 8.74 | 5.19 | 3.61 |
| 1-2 | 19.39 | 3.42 | 2.03 | 1.41 |
| 3-5 | 10.19 | 2.00 | 1.19 | 0.82 |
| **CD4 percent 14-19** | | | | |
| 0-1 | 15.15 | 4.91 | 2.92 | 2.03 |
| 1-2 | 10.9 | 1.92 | 1.14 | 0.79 |
| 3-5 | 5.73 | 1.12 | 0.67 | 0.46 |
| **CD4 percent 20-24** | | | | |
| 0-1 | 22.46 | 7.41 | 4.40 | 3.06 |
| 1-2 | 16.17 | 2.9 | 1.72 | 1.20 |
| 3-5 | 8.5 | 1.69 | 1.01 | 0.70 |
| **CD4 percent 25-29** | | | | |
| 0-1 | 20.99 | 9.13 | 5.43 | 3.77 |
| 1-2 | 15.11 | 3.57 | 2.12 | 1.47 |
| 3-5 | 7.94 | 2.09 | 1.24 | 0.86 |
| **CD4 percent $\geq$ 30** | | | | |
| 0-1 | 11.07 | 14.22 | 8.45 | 5.87 |
| 1-2 | 7.97 | 5.56 | 3.30 | 2.29 |
| 3-5 | 4.19 | 3.25 | 1.93 | 1.34 |

These mortality rates must be compared to the unadjusted ones presented in Tables 5 and 6 respectively. To summarize the difference, we present the inflation factors of mortality resulting from the adjustment in Figures 14. The inflation factors were calculated as the ratio of the adjusted to the unadjusted mortality rate. When inflation factors below one were truncated to one because the adjusted rate cannot be lower than the unadjusted rate (such an occurrence is rare but it is possible to occur when the sample size involved is limited). It is seen that the under-reporting of death due to loss to follow-up can be severe as the adjusted mortality can be up to seven times what is observed. It is also seen that death under-reporting increases as time since

ART initiation increases, and children with the highest CD4 percent levels have higher inflation factors, perhaps because they are less involved with the health care system as they may be less sick (so when they die, their death is more likely to go unreported).

Figure 14: Inflation factor of mortality due to unreported deaths by gender, age and CD4 count at ART initiation among children enrolled in East Africa: Boys left, girls right)




# 4 Conclusions

This analysis is the largest study of HIV-infected pediatric patients to date, involving more than XX,XXX children starting antiretroviral therapy from birth to 5 years of age in six regions around the world participating in the IeDEA worldwide collaboration. The data in this analysis span almost two decades in some cases and in all situations cover the first decade of ART scale-up around the world.

In every case we analyzed, despite the geographical diversity of the various regions, we observed very high mortality, particularly among the sickest infants and small children. On the positive side, mortality rates were reduced precipitously after ART initiation and stabilized afterwards, but there was a slight indication of an uptick in mortality after 2 years of follow-up.

We also observed serious death under-reporting due to loss to program in a sub-analysis involving data in a large site in East Africa where vital status was ascertained in a subset of children who were lost to program. The resulting inflation of the estimated mortality, up to seven times the observed mortality in some cases, was more pronounced

among less sick children and increased with increasing time after ART initiation. This observation, which is consistent with data from studies in adults (see for example [9, 15, 17]) focuses attention to the significant challenge that the epidemic poses on HIV care and treatment programs in this setting and, we suspect, all low and middle-income settings.

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# 5 Statistical appendix

We present here some mathematical details of the model used in the adjusted analyses. The general exponential regression model of survival is a proportional hazards model of the hazard (the instantaneous risk of death). The general proportional hazards model is as follows:

$$\lambda_i(t, \mathbf{x}_i) = \lambda_0(t) \exp\{\mathbf{x}_i \beta\}$$

where the vector $\mathbf{x}$ contains the measurements of interest (in our case, gender, and CD4 count and age category at ART initiation), and $\lambda_0(t)$ is the "baseline" hazard (the hazard of a person with all risk factors set at their reference values). The exponential survival model has the added simplification that $\lambda_0(t) = \lambda$ for all time points $t$ (constant hazards) so that the exponential model for the hazard is

$$\lambda_i(t, \mathbf{x}_i) = \lambda_0 \exp\{\mathbf{x}_i \beta\} \tag{A.1}$$

Since the constant-hazard assumption is rather restrictive, we fit a *piecewise* exponential model where $\lambda_0(t) = \lambda_j$ for $t$ in the time interval $[\tau_{j-1}, \tau_j)$ with $\tau_0 = 0, \tau_1 = 6, \tau_2 = 12, \tau_3 = 24, \tau_4 = \infty$ and $j = 1, 2, 3, 4$. Put more simply, we assumed that the baseline hazard of death is constant in the four time intervals (in months from ART start) $[0, 6), [6 - 12), [12 - 24)$ and $\geq 24$ months.

Clearly however, an adjustment needs to be made to account for the fact that a large proportion of the patient cohort, a subgroup including some patients with very adverse prognosis, has been lost from observation. To do this we consider the vital status ascertained on a subset of the lost patients (which we consider a random sample of all patient dropouts). In the case of the East African cohort, the vital status of this subset was located through patient outreach and was assumed to be successfully located was assumed to be representative (i.e., form a random sample) of the entire lost to follow-up cohort.