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ICCR ROTATION (AUG 7-25)
STUDY PROPOSAL

TITLE:

Prevention of mother-to-child transmission of HIV in Mozambique: efficacy of current antiretroviral prophylactic regimens and predictors of infant HIV-infection

BACKGROUND:

Mother-to-child transmission (MTCT) of the human immunodeficiency virus (HIV) is responsible for 15 percent of new infections each year, the majority of which occur in the developing world. Approximately 2-million children were living with HIV in 2007, the vast majority of whom contracted the disease via MTCT and live in sub-Saharan Africa[i]. In developed nations, effective antiretroviral prophylactic therapy combined with elective cesarean section and formula feeding of infants has drastically reduced MTCT. However, in resource-limited countries where the latter two of these prevention strategies are often not feasible due to lack of healthcare professionals and necessary resources, it remains a large public health problem.[ii,iii]

After the World Health Organization (WHO) set a goal of 20% reduction in MTCT by 2005,[1] a public health-based approach to the prevention of mother-to-child transmission (PMTCT) was instituted in many resource-poor areas to help abate this problem.[1,2,iv] The PMTCT program was chartered with four primary objectives: 1) Primary prevention of HIV infection. 2) Prevention of unintended pregnancies among women living with HIV. 3) Prevention of HIV transmission from mothers living with HIV to their infants. 4) Provision of treatment, care and support for mothers living with HIV, their children and families.[1,v] In practice, however, emphasis has historically been placed on the third component, as this situation presents the most alarming need for intervention considering the limited time to act with antiretroviral prophylaxis in pregnancy.[1,5]

In Sub-Saharan Africa, where there is a disproportionately high incidence of MTCT and little access to cesarean-section or formula feeds, PMTCT programs have focused on antiretroviral prophylactic therapies to prevent infant infection.[1,4,vi] In 1994, a clinical trial of Zidovudine (ZDV) showed 60-70 percent reduction in MTCT.[1,vii] Shortly thereafter, other trials demonstrated a 12% transmission rate with single-dose Nevirapine (SD-NVP) given at the onset of labor.[1,4,7,viii] This seemed a simple and cost effective means to greatly reduce MTCT, however, studies showed a high incidence of resistance to nevirapine and other non-nucleoside reverse transcriptase inhibitors after exposure in both mothers and infants after use of SD-NVP.[8,ix] The trials with short course use of ZDV were not associated with resistance, but the transmission rate was significantly higher so it was not a viable option.[1,7] Accordingly, combination regimens consisting of ZDV+SD-NVP or ZDV+Lamivudine (3TC), or ZDV+3TC+SD-NVP were tested in women living with HIV whose disease has not yet progressed to Acquired Immune Deficiency Syndrome (AIDS). These regimens showed transmission rates estimated at 2-4%.[7]

Based on these and other clinical trials, the current World Health Organization (WHO) recommendations for antiretroviral prophylaxis for PMTCT in patients with HIV but not AIDS, consist of ZDV beginning at 28 weeks gestation, SD-NVP at the initiation of labor and before rupture of membranes, followed by a 7-day ZDV+Lamivudine (3TC) tail course to prevent resistance to NVP. The newborn infant is to receive SD-NVP as soon as possible after birth followed by a 1 week course of ZDV (individual providers have the option of extending duration of ZDV prophylaxis in the infant if mother started ZDV after 28 weeks).[1]

In those patients who meet WHO criteria for a diagnosis of AIDS (clinical evidence of opportunistic infections, or CD4 cell count less than 200 cells/mm^3) HAART therapy is instead recommended for maternal benefit as well as PMTCT. This consists of daily, long-term, therapy with ZDV+NVP+3TC and has been shown to have transmission rates of less than 2 percent. Medications could potentially be substituted in this regimen to avoid harmful drug effects, however efficacy of therapy remains unchanged if patients are adherent.[1,7]

RATIONALE :

In Mozambique, HIV prevalence amongst adults is estimated to be 12-16 percent.[x,xi] Approximately 60 percent of those currently infected are women, making MTCT is a real concern in the country. Columbia University's International Center for AIDS Prevention and Treatment Programs (ICAP) supports 36 clinics in Mozambique, each of which is equipped for antenatal care (ANC) with staff trained in PMTCT guidelines. In the first quarter of 2008, over 15,500 women initiated care at ICAP-supported ANC clinics. Of these, approximately 2,500 tested HIV-positive and will require some means of ARV prophylactic therapy for PMTCT.

All ICAP clinics in Mozambique follow current WHO guidelines regarding PMTCT prophylactic regimens, providing pregnant women with ZDV from 28 weeks gestation to term as well as SD-NVP to take at the onset of labor. Still, for unclear reasons, a large number of these women either do not receive or do not take the prophylactic drugs provided. Women are encouraged to go to a medical facility for delivery of their babies, where, if they did not receive standard ICAP therapy, they are given SD-NVP. Those women who do not receive antiretroviral drugs (ARVs) from ANC and do not deliver in a medical facility, however, receive no prophylaxis at all. Despite the encouragement of ICAP staff, this situation is far more common than These women are encouraged to

LITERATURE REVIEW:

A review of PMTCT evaluations in resource-poor settings reveals a dearth of scientific literature evaluating efficacy of PMTCT programs.[xii] The majority of studies examine 18-month infant outcomes in breast-feeding populations.[3,4] One study examined the

efficacy of scARV vs HAART therapy for prophylaxis. An overall rate of MTCT of 2.2% was reported but no conclusions were drawn between the two study groups. The authors further speculated that the risk of premature birth and low-birth weight infants with HAART might outweigh its potential MTCT benefits.[xiii] Six-week infant HIV PCR testing can provide valuable insights into the effectiveness of ARV prophylactic regimens and PMTCT programs and need to be more closely studied.[12,xiv]

HYPOTHESES:

Null Hypothesis: MTCT occurs independent of ARV prophylaxis

Alternative Hypothesis: ARV prophylactic regiment and MTCT are associated

STUDY DESIGN:

This study is a prospective, observational study. All data necessary for analysis in this study are routinely collected upon enrollment and on subsequent care visits for each woman in ICAP-supported ANC clinics. Patients are assigned a unique ICAP identifier and upon entry into the study, all identifying information will be stripped from their record. The data is recorded by patient identifier in a secure electronic database and in confidential patient registers in the individual clinics.

The following data will be recorded from the electronic database and patient registers:

1. Maternal Prophylactic Regimen – None, SD-NVP, scARV or HAART
2. Infant HIV-PCR Outcome at 6 weeks
3. Maternal Data:
    a. CD4 count at initiation of prophylaxis
    b. Age
    c. Gravity
    d. Parity
    e. Distance from home to clinic
    f. Employment status
    g. Physical type and Location of residence
4. Infant Data:
    a. Sex
    b. Birth Weight
    c. Labor Complication

**All of this data is routinely recorded for every PMTCT patient in ICAP ANC clinics.*

The study period will be 24 months to allow for necessary subject recruitment. Subjects will be identified as eligible and then sorted into the appropriate study arm based on the prophylactic regimen they end up receiving. The relevant data mentioned above will be collected and their records will then be traced confidentially to look for pregnancy outcomes and infant PCR result at 6-weeks. We have elected to use the 6-week PCR result as the majority of women in this population breastfeed their infants, which confers

additional risk of MTCT after birth. By using the 6-week PCR test, we should be able to minimize the incidence of HIV infection via this route and look strictly at intrauterine and intrapartum transmission.

SAMPLE SIZE ESTIMATION:

Sample size calculations were calculated using Chi-square test of proportion on the two groups with the smallest effect size between them, scARV and HAART. MTCT is estimated in the literature at 4% with scARV. With HAART, it is thought to be between 0 and 1 percent. Accounting for the fact that there will be significantly fewer pregnancies available to recruit into the HAART study arm (4:1, scARV:HAART), different sample sizes were calculated for each group.

n_{HAART} = 233 pregnancies
n_{scARV} = 931 pregnancies
**Source: http://www.biomath.info/crc*

Based on this, we will also recruit 931 subjects each into the no treatment and the SD-NVP study groups, for a grand total (N) of 3026 subjects.

ANALYSES:

(For all analyses, Type I error (alpha) will be set at 0.05. Power (1-beta) will be set at 80%)

Estimating the Incidence of MTCT

Incidence of MTCT and 95% confidence intervals will be calculated for each of the four treatment arms using the following equation:

$$\text{Incidence of MTCT} = \frac{\text{\# of infants with positive HIV-PCR results for prophylaxis group}}{\text{Total \# of pregnancies in prophylaxis group}}$$

Hypothesis Testing

Data will also be fit into a 2x4 contingency table (below). Using Chi-squared analysis with 3 degrees of freedom, we will test the null hypothesis that MTCT and ARV prophylaxis regimen are independent.

MTCT	Prophylactic Regimen				Total
	None	SD-NVP	scARV	HAART	
Yes					
No					
Total	n = 931	n = 931	n = 931	n = 233	N = 3026

Analysis of Descriptive Statistics

All data will also be modeled using multiple logistic regression to determine the odds of MTCT when adjusting for other maternal and infant variables. Models will adjust for: MTCT prophylactic regimen, maternal CD4 count, infant birth weight, infant sex, maternal gravity and parity, distance from home to ANC clinic, type of residence.

A total of five models will be created, one for each of the four treatment arms, accounting for all of the other variables of interest and one inclusive model for data from all study arms, which also adjusts for prophylactic regimen.

STUDY SUBJECTS:

Inclusion Criteria: This study will enroll HIV-positive pregnant women who enroll in care at ICAP ANC clinics prior to their third trimester of pregnancy. Subjects must either be naive to ARV therapy or on long-term, continuous HAART therapy with no interruptions in their treatment or history of treatment resistance.

Exclusion Criteria: Women with a past history of discontinuous, interrupted, or non-adherence to HAART will be excluded from this study due to the risk of ARV resistance. Women with documented history of ARV resistant infection will be excluded as well. Women whose infants die before their HIV status is known will be accounted for in the results, but excluded from the analysis.

Recruitment: All study subjects will be drawn from the pool of HIV-positive, pregnant women enrolling in care at ICAP supported ANC clinics in Mozambique. As this is an observational, completely database and registry dependent study with no patient identifiers used except for an anonymously assigned record number, recruitment of subjects will be done via database survey and patients need not be officially enrolled in the study.

CONFIDENTIALITY OF STUDY DATA:

All identifying markers are stripped from patient records in the database. A secure identifier is assigned to each patient and serves as a means for tracking individual records throughout the databases and patient registers.

POTENTIAL RISKS:

Minimal

POTENTIAL BENEFITS:

None

ALTERNATIVES:

N/A

STUDY WEAKNESSES:

One potential flaw in this study design is in the measurement of patient adherence. ICAP has no formal measures of adherence to ensure that patients take the medicines they are dispensed. This relies solely on anecdotal, provider-initiated, reporting of adherence. Thus, for the purposes of this study, unless it is explicitly stated otherwise in a patient's record, we will assume that if they were dispensed a medication, that they took it. This could lead to potentially artificially increased estimates of MTCT in the prophylaxis arms as one would expect a higher rate of transmission if the medications are not actually being taken. Our hope, is that the distribution of medication non-adherence will be equal throughout the three therapeutic arms so that an association can be determined using the hypothesis test.

Inherent in any observational study is the possibility that the differences between arms could be due to confounders rather than the variable be measured (in this case ARV prophylaxis). In an ideal study, patients would be randomized to the various treatment arms, however, in the case of this disease, there is clear benefit to treatment vs. no treatment and an obvious need for HAART therapy in those women with AIDS. As such, it would be unethical to randomize patients into the individual study arms. We attempt to elucidate any such confounders with the multiple logistic regression analysis by prophylactic regimen. If there is a variable that we adjust for that independently effects MTCT outcome in one group more-so than the others, it should become evident during this analysis.

There is one study group where there will be a clear difference in the sample population. The HAART group will likely consist of sicker patients with lower baseline CD4 counts than the other three study arms. While the other three arms will likely have patients who qualify for HAART, the HAART study group will not have the same distribution of healthy and sick patients as the other groups. This could lead to confounding in the results as low CD4 count correlates with high viral load and increased MTCT in patients not on HAART therapy. We attempt to minimize this, however, by only enrolling

patients that receive at least 3 months (1 trimester) of HAART therapy prior to the birth of their infant.

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