

P24 antigen screening for early detection of HIV infection in discordant heterosexual couples in Africa

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Objective: The early infection period is of interest for studies of pathogenesis. Early detection is also critical as an endpoint in clinical trials of prevention interventions. Strategies to increase identification of new infections include shorter testing intervals and antigen detection methods.

Methods: HIV discordant couples are enrolled through a couples' VCT center and followed at 3-month intervals. The HIV negative partner is serologically tested with rapid HIV tests (Abbott Determine and Trinity Biotech Capillus), and plasma set aside for weekly p24Ag screening (Beckman-Coulter). Antibody positive patients are counseled and additional samples taken of blood and genital fluids from both partners. Antibody negative individuals that are p24Ag+ are called in for repeat testing and sample collection. The p24Ag is considered positive at 3x the calculated cutoff for the EIA run.

Results: The seroconversion rate in counseled HIV discordant Zambian couples is 7-8/100 PY. Of 106 seroconvertors identified in 30 months of the study, 24 (23%) were p24Ag+. Six of these were antibody positive with two rapid tests at the time p24Ag was detected, the remaining 18 were antibody negative. All 18 were antibody positive when they returned for repeat testing and sample collection, but only 1 of the 18 was still p24Ag+ at re-draw.

Conclusions: In a cohort with a seroconversion rate of approximately 2% per 3-month interval, one quarter of new infections can be identified during the early, p24Ag+ phase. The main obstacle to detection is the short duration of the antigen positive window, rather than the sensitivity of the antigen test. Because increasing the frequency of study visits would result in decreased retention, the best strategy for obtaining study samples in early infection is more frequent batching of p24Ag testing and same-day invitations for re-draw.

Pregnancy and breastfeeding challenges to volunteer recruitment for clinical trial in African Research settings

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Introduction: Most vaccine trials require that female participants do not bear a child and that male participants do not conceive during the trial for safety reasons. Likewise, women who breastfeed are excluded from participation. In Africa where cultural norms and limited access to family planning encourage large families, the recruitment of female volunteers is a challenge. After enrollment, the need for contraception remains in order to avoid dropout due to pregnancy.

Methods: Projet San Francisco (PSF), follows a cohort of HIV concordant negative and serodiscordant couples in a study on Heterosexual Transmission (HT) of HIV. These couples are recruited from Couple Voluntary Counseling Testing (CVCT) centers, and are potential volunteers for phase I, II and III vaccine trials.

Results: Twenty three percent of women coming to CVCT are pregnant and 33% are breastfeeding. Only 10% of women who were not pregnant or breastfeeding reported using a contraceptive method. At enrollment, 80% of couples stated that they did not intend to have more children but only 5% used a modern family planning method other than condoms.

Conclusion: In our study with limited selection criteria, pregnancy and breastfeeding are shown to be major impediments for referral in clinical trials. In vaccines trials that have more extended and stringent selection criteria, the search for women volunteers can be impeded by pregnancy and breastfeeding. An appropriate family planning service should be offered to avoid withdrawal of female volunteers by preventing unplanned pregnancy during trials.

Increase in referrals for Couples' VCT from PMTCT and ARV programs in Lusaka, Zambia

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Introduction: The Zambia-Emory HIV Research Project (ZEHRP) in Lusaka, Zambia provides couples' voluntary counseling and testing (CVCT) in order to recruit HIV discordant couples for prevention clinical trials. Recently, HIV prevalence and self report of prior testing have increased.

Methods: HIV prevalence and prior testing are described for 7774 couples attending ZEHRP CVCT between January 2002 and February 2005. All clients received HIV results, counseling, and condom skills training as a couple.

Results: From 1995-2000, 57% of couples were concordant negative (--), 20% discordant (+-), and 23% concordant positive (++). At two antenatal clinics in 2001, 3-8% of women reported previous HIV testing.

From 2002-2005, the proportion of concordant positive, discordant, and concordant negative couples was 36% (++), 18% (+-), and 46% (--) in 2005. The proportion of clients previously tested at non-ZEHRP clinics increased from 9% of women and 7% of men in 2002, to 28% of women and 17% of men in 2005. The proportion of couples with both partners previously tested increased from 4% to 14%, and the proportion with neither partner previously tested decreased from 87% to 62%. Many women reported previously testing at antenatal clinics. ARV programs opened at nearby government clinics in quarter four of 2004, and the proportion of couples with at least one HIV+ partner increased from 53% to 58% during that time.

Conclusions: At ZEHRP, the proportion of clients previously tested for HIV has steadily increased in the last 3 years. This corresponds with the introduction of PMTCT, VCT, and ARV programs, and confirms that these services are encouraging individuals to test with their spouses. Referrals between Couples' VCT, perinatal prevention, and HIV care programs ensures access to comprehensive treatment and prevention services. These strategies can assist with recruitment of discordant couple cohorts for HIV vaccine trials.

Clinical Laboratory Reference Ranges in Adults at Project San Francisco (PSF) in Kigali/Rwanda as Part of a Multi-Center Study (IAVI Protocol D) at Seven African Sites in Preparation for HIV Vaccine Efficacy Trials.

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Background

Studies have shown differences in clinical laboratory tests between Africans and Caucasians possibly due to endemic diseases, genetic, nutritional, environmental, or socioeconomic factors. Using laboratory reference ranges from Caucasians results in exclusion of volunteers from clinical trials and difficulties assessing adverse events or medical conditions.

Methods: PSF enrolled 400 clinically healthy, HIV uninfected adults (200 women and 200 men) between 18 and 60 years performed a comprehensive medical history and a complete physical examination, vital signs, weight and height. Volunteers were enrolled if they were clinically asymptomatic and a febrile, if female, excluded if they were pregnant or menstruating. Detailed socio-demographic data potentially relevant to clinical laboratory values were collected. Blood tests for HIV, syphilis, hepatitis B and C, hematology, biochemistry and CD4 counts were performed. Urine pregnancy tests and a urine dipstick (microscopy if abnormal) were performed. The number of volunteers per gender was sufficient to be 95% confident that the 2.5th and 97.5th percentiles will be within about 2 percentage points of the true percentiles.

Results:

Of 400 enrolled the analysis excluded 27 volunteers who were either pregnant (7), hepatitis B (13) or C (11) positive. The mean age was 27 for women and 32 years for men. Hemoglobin, (women only) and creatinine were lower whereas bilirubin, AST/ALT, eosinophils (%), amylase, total immunoglobulins, and CPK were higher than other published data (Washington manual, Massachusetts General Hospital).

Conclusions:

The lower levels of hemoglobin are probably due to nutritional factors, which may disproportionately affect women. Lower creatinine levels may be explained by lower body mass indexes that we see in Rwanda compared to Western countries. Higher eosinophils counts are probably due to chronic parasitic infections and elevated total immunoglobulins levels due to chronic immune stimulation due to endemic infections. These data provide guidance for future clinical trials.

Reasons for Screening Failures in a Cross-Sectional Study to establish Clinical Laboratory References Ranges in Adults in Kigali, Rwanda.

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Objective: To establish baseline clinical laboratory references ranges for the local population in the preparation for future preventive HIV vaccine trials as previous studies have shown differences in clinical safety and immunological laboratory values between Africans and Caucasians.

Methods: 400 a symptomatic men and women, who were not infected with HIV, between the ages of 16 and 60 are being recruited as part of a multi-center study in 2800 volunteers at 8 sites in 4 countries in Africa. Volunteers were prescreened by nurses using a questionnaire that contained the main inclusion and exclusion criteria. A complete medical history and a full physical examination were performed. Volunteers who were clinically well, afebrile and had no clinically significant findings on history or physical examination were enrolled. HIV tests, syphilis, hepatitis B and C serology, hematology, clinical chemistry and CD4 and CD8 T-cell count, urinalysis, pregnancy tests and stools for parasites were performed. Volunteers who were pregnant or had HIV infection, active syphilis, and viral hepatitis will be excluded from the analysis.

Results: To date 404 volunteers have been screened. Of the total 400 planned, 322 have been enrolled. Of the 82 excluded, 13 failed the informed consent assessment of understanding, 9 had a history of serious or chronic illness, 8 female volunteers were actively menstruating, 11 had a symptomatic acute illness, 5 were emaciated and 20 had a clinically significant physical abnormality of which splenomegaly was the most common.

Conclusions: Potential volunteers in developing countries may have greater baseline morbidity due to malaria, parasitic infestations, and malnutrition. Therefore a larger number of individuals may need to be evaluated to ensure that an adequate number of healthy volunteers are enrolled. A greater effort to educate potential volunteers in research will decrease the number of people who fail to understand the informed consent.

Overcoming language and literacy barriers for Low-literacy Audiences in the Informed Consent Process in African Research Environments: Case of projet San Francisco, Kigali. Rwanda

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Background: A sixth grade education level is recommended for all informed consent processes. The concept of "grade" however is not applicable to Africa where the majority of the population is illiterate. In addition most research is often developed in non-African languages. Specific terms like those related vaccine research lack direct equivalents and are the most difficult to translate. Standardization of the consent process can ensure that the meaning of the consent form is understood at all literacy levels.

Methods: Projet San Francisco (PSF) in Kigali, Rwanda first translated the informed consent for all study into Kinyarwanda, the main language spoken in Rwanda. Videos of counselors reading the consent in Kinyarwanda are shown during an interactive group session, written copies are given to participants to consult. Counselors stop the video between sections of the consent and invite questions that enhance the comprehension. An “understanding of informed consent” is administered to volunteers’. Results are provided using descriptive figures.

Results: More than 100 volunteers, many of whom are illiterate, go through the informed consent process each day at PSF’s four research sites. Ten percent are potential volunteers for a protocol establishing normal values laboratory values for Rwanda as part of preparedness activities for HIV vaccine clinical trials. Less than 5 % of 373 potential volunteers were eliminated because of poor comprehension of the informed consent.

Conclusions: Though informed consent is particularly challenging in African research settings, the use of audio-visual aids translated in the subjects’ language results in time saving, and prevents subtleties in communication from hindering comprehension. Standardized, the informed consent is more effectively communicated in the local language and at the appropriate literacy level of the population.

Recruitment and retention of an HIV discordant couple cohort in Kigali, Rwanda in preparation for vaccine efficacy trials

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Objectives: The Global HIV/AIDS Vaccine Enterprise identified “expanding access to large, well-defined populations of uninfected people at high risk of HIV infection” as a gap in the clinical trials capacity of developing countries. An estimated, 25.4 million people in Africa were living with HIV at the end of 2004. Cohabiting couples in Africa are the largest HIV risk group in the world. In Kigali, Rwanda, we have enrolled 800+ discordant couples (one partner HIV infected, one HIV uninfected) in preparation for HIV prevention trials.

Methods: Projet San Francisco maintains three Couples’ Voluntary Counselling and Testing (CVCT) Centers. HIV discordant couples, who have cohabitated for the last twelve months and live in Kigali are offered enrollment into a heterosexual transmission of HIV study. Follow-up is quarterly; study benefits include free family medical care and prescriptions, family planning, ARV screening and treatment and ongoing counseling.

Results: In 2004, PSF CVCT Centers tested 9770 couples. 513 (5.3%) discordant couples were invited to enroll in the follow-up study. 401 (78%) chose to screen and were enrolled. The majority of couples not enrolled were determined to be false couples by community workers and enrollment of truly eligible couples is 93%. The HIV incidence rate is 4% per year and retention is >90% at 12 months.

Conclusions: The establishment and retention of a well-defined, high-risk cohort in preparation for vaccine efficacy trials is possible in developing countries. A run-in design, using an existing cohort provides an accurate assessment of HIV incidence and allows the recruitment of volunteers with good follow-up and compliance. Further, the opportunity to determine contraceptive acceptability, an inclusion criteria of vaccine trials, is critical in countries like Rwanda, where up to 75% of eligible women are pregnant or breastfeeding. The limiting factor to the development of such cohorts is the commitment of funding.

Patterns of contraception choice to prevent unplanned pregnancies among HIV discordant infected couples in Zambia

Bellington Vwalika and the Rwanda/Zambia HIV Research Group

Background: Access to user-independent family planning methods is improving in Zambia, where the total fertility rate is 6.1. HIV discordant couples are ideal participants for HIV vaccine trials. Pregnancy incidence is 20-30%/year and results in exclusion and dropout from clinical trials of vaccine candidates.

Methods: HIV discordant couples (280 with HIV- men and HIV+ women, and 255 with HIV+ men and HIV- women) were recruited through our VCT centres in Lusaka and enrolled in a trial of family planning promotion interventions. Video messages were used in four study arms: method-focused, motivational, both, or neither (control). The methods video promoted user independent contraception while the motivational video encouraged planning activities such as will writing, naming a guardian, and making a financial plan. Videos were presented to couples in groups and followed by one-on one counseling with scripted messages to reinforce the videos. Couples were then offered their choice of family planning method.

Results: Fewer than 7% of couples randomized did not select any contraceptive method after the video sessions. Couples who viewed the methods video were 3-4 times as likely to choose IUD than those who did not (6-8% vs 2%). Selection of tubal ligation (2-3%), implant (9-15%), depo-provera (38%-44%) and oral contraception (34-38%) was similar in all groups. Preliminary analysis shows a significantly lower pregnancy incidence in intervention groups. Condom use in discordant couples did not differ among the different method users and non-users.

Conclusions: Many couples with HIV wish to limit fertility. Interventions that encourage user-independent contraceptive use can assist with prevention of unplanned pregnancies. Many clinical trials exclude pregnant women; effective contraceptive promotion can contribute to reduced dropout due to pregnancy.

Enrollment of heterosexual HIV discordant couples for HIV prevention trials in Zambia

Cheswa Vwalika and the Rwanda/Zambia HIV Research Group

Objective: Cohabiting couples with one HIV+ and one HIV- partner ("discordant couples") are the largest risk group in Africa. They are also ideal participants for clinical trials of prevention strategies for heterosexual transmission, including reduction of the 'contagion' of the HIV+ partner as well as reduction of 'vulnerability' of the HIV- partner.

Methods: Recruitment of HIV discordant couples is a challenge. Fewer than 1% of African couples have been tested together. The recent increase in VCT services prompted by PMTCT programs and ARV services have resulted in more individuals seeking testing, but past experience shows that more than half of married individuals who are tested alone share their results with their spouse. We provide Couples' VCT services and used a variety of community-based strategies to promote the services.

Results: From 2002-early 2005, 1388 discordant couples (794 with HIV- men and HIV+ women and 594 with HIV+ men and HIV- women) were identified at the CVCT center. Of those, 1098 (79%) met eligibility criteria for enrollment and 743 (68%) of those were enrolled. 114 seroconvertors (70 women and 44 men) have been identified during followup. As of Feb 8, 2005, 618 couples are actively enrolled.

	Male:Female HIV results				Discordant couples			Enrolled	Cohort size	Seroconversion		
	++	--	+-	+-	Eligible					F	M	Total
					+	-	Total					
2002												
Q1	89	40	39	24	24	38	62	12	218	4	3	7
Q2	126	233	44	34	34	41	75	30	287	4	1	5
Q3	185	379	84	57	48	64	112	56	343	3	1	4
Q4	219	477	92	56	40	73	113	118	444	4	4	8
2003												
Q1	295	564	122	77	71	99	170	111	532	4	6	10
Q2	177	279	50	44	39	42	81	84	582	8	3	11
Q3	144	205	32	36	32	27	59	59	596	7	7	14
Q4	168	244	54	47	34	34	68	53	600	7	4	11
2004												
Q1	161	236	56	47	40	38	78	48	606	9	5	14
Q2	134	166	42	26	24	32	56	43	591	5	1	6
Q3	261	366	85	59	40	60	100	49	605	8	2	10
Q4	313	346	64	66	45	37	82	39	600	4	4	8
2005												
-Feb 8	99	142	30	21	18	24	42	41	618*	3	3	6

Conclusions: It is possible to recruit and retain sufficient numbers of HIV discordant couples for Phase II-b clinical trials. Phase III trials will require substantial expansion of CVCT services.