

Investigating the Utility of the Anti-HIV-1 IgG Capture Enzyme Immunoassay (BED-CEIA) to Detect Early HIV Infections Using Known Incident Infection Panels from Lusaka, Zambia and Kigali, Rwanda

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360P

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Introduction

A safe, effective and accessible vaccine against HIV infection is important to controlling the global epidemic. Identification of populations with high HIV incidence suitable for HIV vaccine efficacy trials is therefore a priority (1). New assays are being developed that may allow estimation of incidence from prevalent specimens.

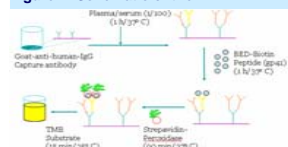
The BED IgG-Capture EIA (CEIA) is a commercially available EIA assay (Calypte® BED, Rockville MD, USA) containing recombinant gp41 sequences from B, E, and D subtypes. This assay measures HIV-specific IgG as a proportion of total IgG and has been tested in samples from the United States (subtype B), Thailand (subtype B, E), Ethiopia (subtype C), Zimbabwe (subtype C), Kenya (subtypes A, D) and against panels of known incident infections provided through the US Centers for Disease Control (2, 3). On the basis of these data, the assay was proposed as a method for identifying recent (incident) infection using antibody titer.

Methods

Two to eight specimens at different time points were tested from incident cases in two cohorts of HIV discordant couples from Rwanda and Zambia seen every three months (4, 5). Based on HIV antibody rapid test results, or p24 antigen ELISA (Coulter) for early detection of HIV infection, the date of infection for each volunteer was estimated at 14-45 days before their first positive result (antigen or antibody respectively). Specimens that were p24 antigen positive but antibody negative (n=6) were not tested with the BED (an antibody dependent assay).

All tests were carried out using the BED CEIA kit as per the manufacturer's instructions and CDC training module. A simplified schematic of the BED CEIA is shown in Figure 1. Test sera were initially tested singly, and median control values were used to calculate normalized OD (OD-n). Specimens with OD-n values ≤ 1.2 were retested in triplicate. If the mean OD-n on repeat testing was ≤ 0.8 , the volunteer was assumed to be recently (≤ 183 days) infected. Sensitivity and specificity were calculated for the full sample and using an equal number of data points from each volunteer to control for inter-volunteer variability

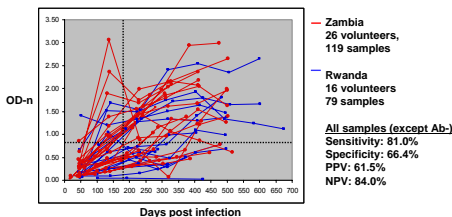
Figure 1: Schematic of the BED EIA



Results

Incident infection samples from 42 urban volunteers (16 Rwanda, 26 Zambia) infected every 3 months for up to 22 months representing 198 specimens (79 Rwanda, 119 Zambia) were evaluated. The BED results from the full sample are shown in Figure 2.

Figure 2: Normalized OD results by date of infection



For both Zambia and Rwanda the development of antibodies is noted to be slower than that published previously, such that based on the assay criteria for early infection almost 40% of the samples that scored under the OD cutoff (38/98) were from infections that exceeded 183 days. Thus the positive predictive value for the full sample was lower than expected at 61.5%.

Eleven volunteers (26%) never cross the OD cutoff at any time during the period of observation (range 275 to 479 days Figure 3). Limited viral load (copies/ml, n=3) data suggest that these volunteers are not individuals with very low viral loads, who might therefore develop lower antibody titers and appear as early infections by the BED assay.

Figure 3: Viral load data and BED trajectories of volunteers who do not cross the BED OD cutoff

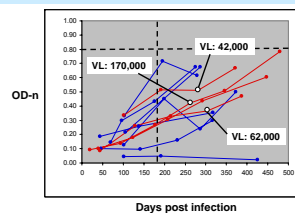
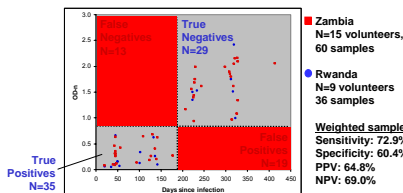
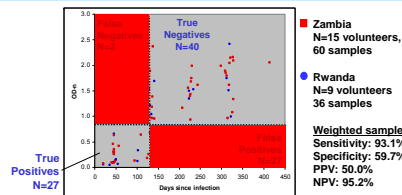


Figure 4: Weighted estimates of BED sensitivity, specificity



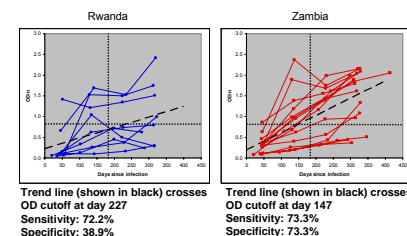
To control for inter-volunteer variability, the sensitivity and specificity of the BED assay was calculated using four data points per volunteer (N=24, n=96); two prior to the 183 day cutoff, and two after (Figure 4). These weighted estimates were lower than the estimates from the full sample (unweighted estimate). Due to a spike in false negatives detected between days 130 to 145, the sensitivity dropped to 72.9%. The specificity also remained low, at 60.4%. Using two data points (early mean 57 ± 24 days, late mean 310 ± 32 days), it was possible to increase the sensitivity of the assay to 95% but the specificity remained low at only 62.5%.

Figure 5: Reducing window period to 130 days improves sensitivity but not specificity



Reducing the window period from 183 to 130 days improved the sensitivity without significantly affecting the specificity (Figure 5). However, 50% of those called early infections (27/54) were from infections of duration longer than 130 days. This differential misclassification would inflate estimates of incidence taken from prevalent samples in these populations.

Figure 6: The weighted BED sensitivity and specificity by site



While the weighted BED sensitivity did not vary between Rwandan and Zambian samples (Figure 6), the specificity did vary significantly ($p=0.02$). Although there was considerable variability between volunteers at each site, plotting the trend line of the OD trajectories shows an elapse of 80 days from when the Zambian mean crosses the OD cutoff to when the Rwandan mean crosses the cutoff (227 days vs. 147 days, Figure 6).

Conclusions

In this population of well-characterized, known incident HIV infections, the BED assay had a low predictive value for detecting recent infections from HIV infected prevalent samples. This may in part be due to a large fraction of individuals (11/42) who never develop antibody titers above the cut-off. The differential misclassification would then result in an over estimation of incidence from older prevalent specimens. Previous work has demonstrated subtype-dependent variability in estimating the window period with subtype E virus reaching the OD threshold 20 days earlier than subtype B virus in Thailand (3). In our sample, HIV-specific IgG titers from samples from Rwanda (primarily subtype A) were significantly slower to develop than those from Zambia (subtype C).

This assay also overestimated the likely incidence in prevalent samples from four other East African cohorts (See Poster 327P), suggesting that additional approaches must be utilized to obtain accurate incidence estimates.

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Challenges to Female Volunteers Recruitment for Clinical Trials in African Research Settings: Pregnancy and Breastfeeding

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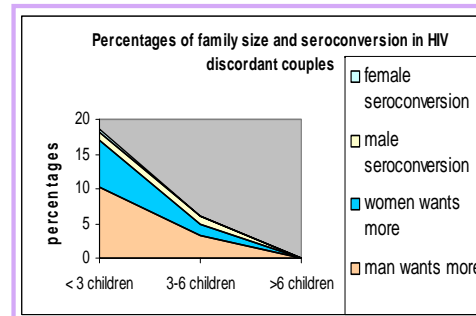
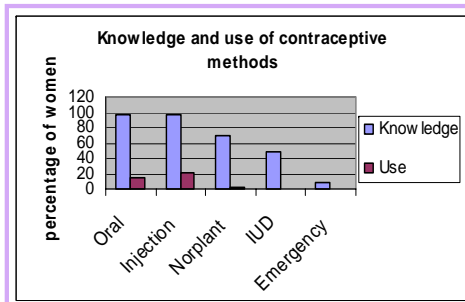
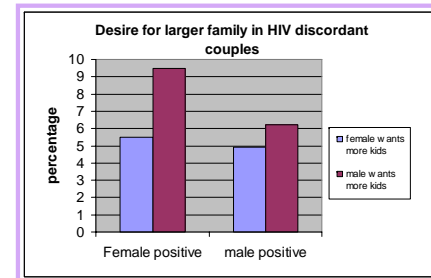
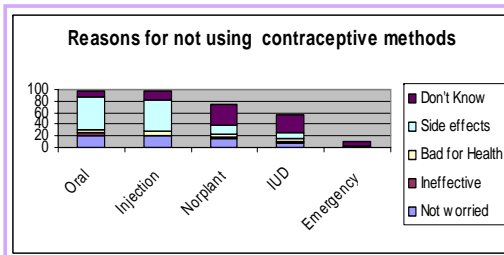
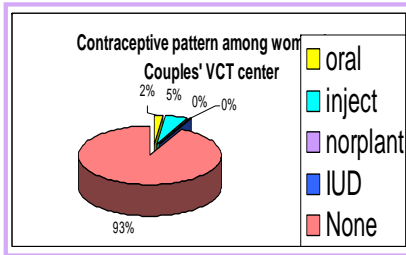
ABSTRACT

Objectives: Most clinical trials, particularly vaccine trials, require that female participants are not pregnant at the time of enrollment and do not become pregnant during the course of the trial for safety reasons. Women who are breastfeeding are also screened out for the same reasons. 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 Couples' 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.

Conclusions: In our study with limited selection criteria, pregnancy and breastfeeding are shown to be major impediments for referral in clinical trials. In vaccine 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.



Knowledge attitude and behavior toward contraceptive methods:

There is no correlation between couples knowledge about contraception and the actual use of a method. Over 95% of women within HIV discordant couples knew at least 2 modern contraceptive methods, but only 30% had used or were currently using any contraceptive method. Of those who used contraception in the past, 75% stopped because of side effects or the desire become pregnant. More than 60% of women who never used a contraceptive method did so because of misconceptions about the side effects.

Despite a good knowledge of contraceptive methods among couples, very few of them use modern family planning due to misconceptions about the side effects of these methods. Therefore, family planning counseling should discuss user-independent contraception and reassure couples about side effects.



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Increases in referrals for couples VCT from PMTCT and ARV programs in Lusaka, Zambia

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Poster 356P

Abstract

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 9218 couples attending ZEHRP CVCT between January 2002 and June 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 27% of women and 15% of men in 2005. The proportion of couples with both partners previously tested increased from 4% to 11%, and the proportion with neither partner previously tested decreased from 87% to 64%. 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.

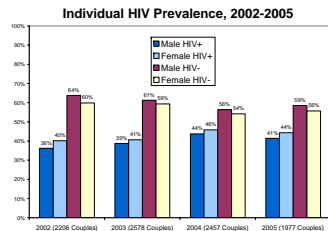
Conclusions: At ZEHRP, the proportion of clients previously tested for HIV has steadily increased in the last 3 years. This corresponds with the introduction of PMTCT, VCT, and ARV programs, and confirms that these services are encouraging individuals to test with their spouses. Referrals between Couples' 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.

Methods

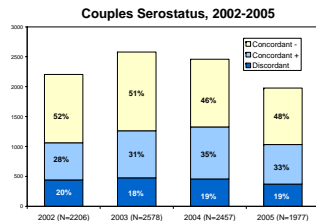
HIV prevalence and prior testing are described for 9218 couples attending ZEHRP CVCT between January 2002 and June 2005. This data is compared with nearly 10,000 couples tested from at ZEHRP from 1995-2000, and 665 couples tested at two antenatal clinics in 2001.

Results

Since 2002, the prevalence of HIV in men and women attending ZEHRP CVCT has increased. During the first half of 2005, 41% of men and 44% of women were HIV-positive, higher than the Lusaka general population prevalence estimate of 22%.



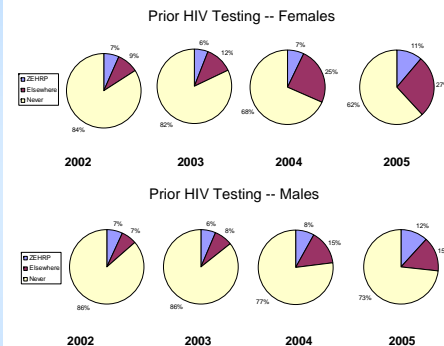
The serostatus of the couple has also changed over time. From 1994-2000, 57% of couples were concordant negative, 20% discordant, and 23% concordant positive. In 2002, 52% of couples were concordant negative, 28% concordant positive, and 20% discordant. In 2004 and 2005, for the first time at ZEHRP, there are more couples with HIV than couples without HIV. This peaked in the final quarter of 2004, with 56% of couples with one or both partners HIV+.



Results

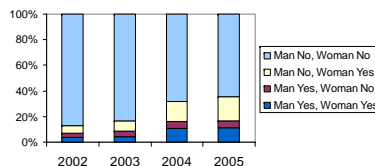
At two antenatal clinics in 2001, 3-8% of women who participated in the weekend CVCT program with their spouse reported they had ever been tested for HIV.

The proportion of clients previously tested at non-ZEHRP clinics increased from 9% of women and 7% of men in 2002, to 27% of women and 15% of men in 2005.



Excluding couples who had previously tested at ZEHRP, the proportion of couples with both man and woman previously testing for HIV before coming to ZEHRP increased from 4% to 11%. From 2002 to 2005, the number of couples with neither partner previously tested decreased from 87% to 64%.

Prior Testing in Couples, 2002-2005



Conclusion

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 couples for HIV vaccine trials.



Signpost, ZEHRP CVCT Center, Kanyama, Lusaka, Zambia. (photo, M. Price)



Mobile couples VCT unit, Project San Francisco, Kigali, Rwanda.

Acknowledgements

Thank you to the staff, interns, and couples of the Zambia Emory HIV Research Project, and to Project San Francisco, the sister research site in Kigali, Rwanda. This research is supported with funds from the National Institutes of Mental Health, the National Institutes of Child Health and Development, the International AIDS Vaccine Initiative, the Bill & Melinda Gates Foundation, and the Centers for Disease Control and Prevention.

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

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BACKGROUND

Access to user-independent family planning methods is improving in Africa. The total fertility rate in Zambia is 6.1. This is a concern for couples with HIV who must plan for their families if they fall ill or die.

METHODS

Concordant positive and discordant couples are identified at one of three ZEHRP CVCT centres in Lusaka.

After enrollment, couples with one or both partners HIV+ are randomized to one of four arms.

- **Methods Video:** user-independent methods placed at beginning of contraceptive message hierarchy (IUD, implant, depo-provera, oral contraceptives)
- **Motivational Video:** planning for consequences of illness and death (writing a will, appointing a guardian, education of children)
- **Methods + Motivational Videos:** both videos are viewed.
- **Usual Practice Video (control):** hand washing, other non-reproductive health issues.

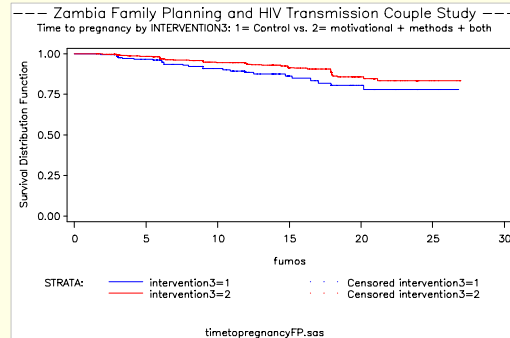
All couples are given condoms and provided with counseling to prevent HIV/STI transmission. Pregnant women receive nevirapine.

The primary endpoint is pregnancy. It is hypothesized that either intervention video will reduce pregnancy by 20%.

RESULTS

Fewer than 7% of 1037 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.

	Intervention arm-factorial design															
	Control				Motivational				Methods				Both			
	New	nuing	Tot	%	new	nuing	Tot	%	New	nuing	Tot	%	New	nuing	Tot	%
OC	71	24	95	37%	72	28	100	38%	77	21	98	37%	66	21	87	34%
INJ	82	16	98	38%	91	23	114	44%	83	17	100	38%	82	16	98	38%
NOR	37	1	38	15%	22	1	23	9%	27	3	30	11%	29	0	29	11%
IUD	5	1	6	2%	5	0	5	2%	14	3	17	6%	20	0	20	8%
BTL	7	0	7	3%	8	0	8	3%	3	0	3	1%	5	0	5	2%
NON	1	13	14	5%	0	10	10	4%	1	14	15	6%	0	17	17	7%



Kaplan-Meier analysis showed a significantly lower pregnancy incidence in the intervention groups compared with the control group (log rank and Wilcoxon rank sum tests $p < 0.05$). The impact of method and motivational interventions on patterns of contraceptive switching and attrition will be compared. Condom use in discordant couples did not differ among the different method users and non-users.

CONCLUSION

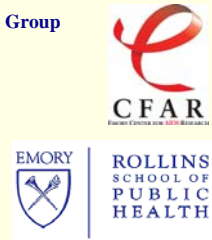
Many couples with HIV wish to limit fertility. Interventions that encourage user-independent contraceptive use can assist with prevention of unplanned pregnancies. Many clinical trials exclude pregnant women; effective contraceptive promotion can contribute to reduced dropout due to pregnancy.

ACKNOWLEDGEMENTS

Our deepest thanks to the staff and study participants of ZEHRP.

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Enrollment of HIV discordant couples for HIV prevention trials

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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.

Conclusion

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.

Acknowledgements

Thank you to the staff and study participants of ZEHRP. These studies are funded by the International AIDS Vaccine Initiative, the NIH, and the Bill & Melinda Gates Foundation.

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	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

Rwanda Zambia HIV Research Group



Since 1994 ZEHRP has offered CVCT services to over 20,000 couples in Lusaka Zambia. ZEHRP maintains 3 CVCT sites in different districts in Lusaka as well as a mobile unit which changes location monthly.

Couples enrolled in observational CVCT services to over 20,000 couples in Lusaka Zambia. ZEHRP maintains 3 CVCT sites in different districts in Lusaka as well as a mobile unit which changes location monthly.

As of June 2005, there are over 750 couples in the Lusaka discordant couples cohort.

Reasons for screening failure in a cross-sectional study to establish clinical laboratory references ranges in adults in Kigali, Rwanda

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Abstract

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 asymptomatic 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 of 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 504 volunteers have been screened and 400 have been enrolled. Of the 104 excluded at enrollment, 17 failed the informed consent assessment of understanding, 13 had a history of serious or chronic illness, 13 had a symptomatic acute illness, 12 were emaciated and 31 had a clinically significant physical abnormality of which splenomegaly was the most common. 27 volunteers with viral hepatitis or who were pregnant were excluded from the analysis after enrollment.

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.

Introduction

Clinical Laboratory references ranges have not been established in African populations. Clarifying these reference ranges and determining the reasons and frequency of conditions that would preclude enrolment of volunteers is an important step in the preparation for future clinical vaccine trials. We report the main reasons for screen failure and exclusion from analysis in a study to establish Clinical Laboratory Reference ranges conducted at Projet San Francisco in Kigali, the capital of Rwanda.

Methods

Volunteers were recruited from CVCT (Couples' Voluntary Counseling and Testing) Centers and a cohort of HIV sero-discordant couples at Projet San Francisco in Kigali. Clinically well candidates were referred to the study after a chart review. Entry requirements mandated that volunteers be males and females between 16 and 60 years of age, clinically asymptomatic, without a fever or known infection with HIV or syphilis. Pregnant women were excluded and menstruating female volunteers were rescheduled for another screening visit. Eligible volunteers were invited to participate in the study. After watching a video of the informed consent form and participating in group and individual discussions, they were individually assessed to determine comprehension of study information using a standardized Assessment of Understanding of Informed Consent Questionnaire. Only those individuals who completed the assessment correctly were invited to sign the informed consent form. No data collection or procedures for this study were done prior to consent. Basic demographic information and a comprehensive medical history were obtained. A complete physical examination was performed and the Body Mass Index (BMI) was calculated. Blood was taken for hematology, chemistry, HIV, syphilis and hepatitis B and C serology and CD4 count. Urine was examined by dipstick for chemistry and pregnancy. Urine microscopy was performed when there was a dipstick abnormality. Three stools were examined for the presence of parasites.

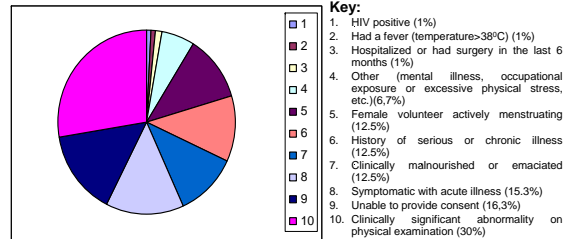
Map: Rwanda Zambia HIV Research Group



Results

504 volunteers (242 males, 262 females) were screened between 04 December 2004 and 03 June 2005 (average 19 per week); 400 volunteers (200 males and 200 females) were enrolled during this time (15 per week). 104 (20.6%) volunteers were screened out for the reasons shown below (some volunteers had more than one reason for exclusion).

Figure: Screen Failures



Female volunteers who were menstruating were rescreened and enrolled at a later date. The median age was 31 years for males and 27 years for women. Twenty seven volunteers were enrolled, but excluded from the analysis due to pregnancy and viral hepatitis (see Table, below). Of 504 volunteers who were screened for this study, 373 (74.0%) will be considered in the final analysis.

Table: Excluded from Analysis

Reasons for early termination	Male	Female
Positive Hepatitis B	11	2
Positive Hepatitis C	6	4
Pregnant	--	4



Discussion

A clinically significant abnormality on physical examination was the major cause of exclusion. The most common abnormality was splenomegaly, probably due to the high prevalence of malaria. The second most common was cardiac abnormalities (murmurs); an abnormality that often goes unnoticed due to a low level of health care coverage.

Sixteen percent of the excluded volunteers were unable to demonstrate proper understanding of the consent form. Most of the volunteers excluded on the basis of acute illness at the time of enrollment were suffering from upper respiratory tract infection. Twelve percent of those screened out were either clinically malnourished or emaciated, reflecting the difficult social conditions affecting a significant proportion of the population.

Conclusions

The pre-screening by chart review underestimates the true morbidity in the population in developing countries due to malaria, parasitic infestations and malnutrition. Therefore a much larger total number of individuals will need to be evaluated to ensure recruitment of healthy volunteers in future clinical vaccine trials. Over a quarter of those screened for enrollment were not eligible for analysis.

A greater effort to educate potential volunteers in research coupled with efforts to simplify the consent process will reduce the number of people who fail to understand informed consent

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