Co-factors in Seroconversion to AIDS-associated Retrovirus among Homosexual Men in San Francisco

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Introduction:

Antibodies to the AIDS-associated retrovirus (ARV) are used as markers of past or current infection in epidemiologic studies of ARV transmission. These seroepidemiological studies have implicated a number of modes of transmission. Sexual intercourse with infected persons, especially receptive anal intercourse (1,2), parenteral contact with contaminated needles (3), infusions with contaminated blood products (4), and in utero exposure to the virus (5) have been established as modes of transmission of ARV. This study examines some host factors and infectious co-factors which may enhance or diminish the probability of ARV infection and antibody response following exposure via homosexual intercourse.

The process of ARV transmission via sexual intercourse involves many steps each of which may be affected by unique factors. Current information allows the construction of the following scenario for seroconversion. The process begins in the partner when infected lymphocytes or free virus are secreted into the seminal fluid. The infected seminal fluid is brought into contact with the uninfected partner through deposition on an epithelial surface. Because the epithelial cells do not appear to be permissive for viral replication (6,7), the virus must traverse the epithelial barrier to gain access to susceptible cells in the new host. The virus passes through the epithelial lining, penetrates a permissive cell, uncoats, replicates, matures, and is released from the cell by budding through the

membrane or through direct cell to cell contact (7). At some point in this process, the host's cellular mediated immune system recognizes the viral antigens as foreign and stimulates the B cells to produce antibodies specific to ARV antigens.

This simple scenario illustrates that sexual contact with an infected person is necessary, but hardly sufficient, for the development of antibodies in the sexually exposed host. The characteristics of the virus, the infected partner, and the exposed host must be permissive for transmission, colonization, and a humoral immune response in the newly infected host.

Some of the characteristics of the host that determine risk for viral infection and/or seroconversion may be epidemiologically important. It has been suggested that inflammation of the mucous membranes may facilitate viral penetration through the epithelial lining (6). There have been a number of reports of associations between past history of sexually transmitted diseases and positive ARV antibody status (8,9). Finally, reports of a prolonged ARV positive, antibody negative state (10,11,12,13) indicate that there is a role for host immune factors in determining the serological response to ARV infection.

In this report, an epidemiologic model of the seroconversion rate in the San Francisco Men's Health Study cohort will be presented to help evaluate the hypothesis that host factors and coinfections influence efficiency of transmission and serologic response to the ARV. In addition, the history of sexually

transmitted diseases, and serologic findings of viral coinfections are analyzed to determine if these factors increase risk for seroconversion to ARV independently of exposures to numbers of sexual partners, types of sexual practices, and sharing needles.

Materials and Methods:

The study subjects analyzed here are participants of the San Francisco Men's Health Study (SFMHS) cohort. As described elsewhere (2,14), the SFMHS is a prospective cohort study of 1034 single men ages 25 to 55 selected from the 19 census tracts of San Francisco that had the highest incidence of AIDS prior to 1984 when the cohort was established. The cohort was obtained by randomly selecting residential blocks within each of which all eligible men were asked to participate in the study. Approximately 60% of those eligible for the study were recruited and examined at the baseline. At six month intervals, information regarding sexual practices and medical history is obtained through structured interviews. In addition, a medical examination, skin testing, a complete blood count, lymphocyte subset counts, and ARV antibody tests were performed as described elsewhere (15).

At the first examination, there were 212 men who described their sexual behavior as "exclusively heterosexual." These men, none of whom had any serologic evidence of ARV infection, have been excluded from all of the analysis in this report.

A seroconversion is here defined as a positive test for antibodies to ARV in a man who did not have detectable antibodies at an earlier point in the study. All positive IFA tests of initially IFA negative individuals are confirmed using Western Blots.

Cohran-Mantel-Haenszel methods for stratified analysis and multivariate-logistic regression were used to examine the associations between the history of sexually transmitted diseases and ARV antibody status at the baseline examination.

A nested case-control study of serologic status to a panel of micro-organisms was performed on paired samples of frozen serum from the first ten men to develop antibodies to ARV during the prospective follow-up of the cohort. Paired samples from 30 persistently seronegative matched controls were also tested. Serologic tests were done by the Viral and Rickettsial Disease Laboratory, California Department of Health Services. Matching was on number of male intercourse partners in the year prior to the first positive ARV serologic test in the case. All of the cases and the controls had described their behavior as homosexual or bisexual at every examination cycle and all denied ever having shared needles. This data was analyzed using contingency tables of matched sets (16).

MODEL OF SEROCONVERSION RATES

During the fall of 1985, 11 (3.2%) of the 341 initially seronegative homosexual and bisexual men seroconverted to ARV after the first six months of follow-up. The question relevant to the issue of co-factors in seroconversion is whether this low seroconversion rate is due only to reductions in numbers of sexual partners or changes in the types of sexual practices or whether the low seroconversion rate represents an accumulation of resistant men among those who have remained seronegative through a number of years of the epidemic. To address this issue, an epidemic model of seroconversions was developed to calculate the infectivity of the virus during two different periods of the epidemic.

The "null" hypothesis under which this model was developed was that exposure alone determines whether a person will develop antibodies to the ARV. The number of seroconversions over the six month period is written as a function of the number of male intercourse partners each seronegative man had, the population prevalence of antibodies to the virus, and the infectivity of the virus. The model will then be solved for infectivity using data from the SFMHS to estimate the other parameters of the model.

Low infectivity rates calculated using the "exposure-alone" model would suggest that factors other than sexual exposure are required for transmission of the virus. For example, an infectivity of 1% would mean that 99% of sexual contacts with seropositive men somehow fail to transmit the virus. If an

infectivity rate of only 1% were found, the search for factors which determine which contacts transmit the virus would be promising. In contrast, very high infectivity rates indicate that the factors included in the "exposure-alone" model are sufficient to explain the observed rates of transmission.

The following "exposure-alone" model was derived in collaboration with James Wiley using the following assumptions:

1. The probability that one randomly selected seropositive intercourse partner will transmit the virus to his seronegative partner is constant over all pairs of men. This probability is defined as the infectivity (f).
2. In 1985, ARV is only transmitted among gay and bisexual men of this cohort through sexual intercourse including insertive and receptive, oral and anal intercourse. The infectivity of the virus does not depend on the type of intercourse or the number of sexual episodes occurring with any given partner over a six month period.
3. Seronegative men select their partners at random with respect to ARV antibody status. Under this assumption, each seronegative man is assumed to select his partners from a population whose seroprevalence is the same as the seroprevalence in the population of all homosexual and bisexual men. The population seroprevalence (p) is estimated by the observed seroprevalence among all gay and bisexual men in the cohort.

4. There have been a number of reports of extended periods of time between exposure and seroconversion (10,11,12,13). The implications of these reports for this model are that some seroconversions that occur over the period of observation will be due to sexual contact that occurred prior to that period of observation. Further, sexual exposure occurring during the period of observation may cause some seroconversions to occur after the end of the period of observation. This model adequately accounts for latency to seroconversion when the number of seroconversions due to prior (unobserved) exposure equals the number of seroconversions that occur after the end of the period of observation but which are due to observed exposure. This condition is met when the latency to seroconversion and the period of observation are short relative to the rate of decrease in sexual practices that pose a high risk for ARV transmission.

The population seroprevalence and infectivity can be written as probabilities:

f = p(seroconversion ¢ one seropositive partner)

and p = p(a randomly selected partner is seropositive).

The probability that sexual intercourse with a male partner will cause seroconversion is the joint probability of the

seroprevalence and the infectivity. This can be written assuming that selection of partners is random with respect to ARV antibody status:

$$p(\text{seroconversion } ¢ \text{ one partner}) = pf.$$

The probability that seroconversion will not occur from any given partner is one minus the above:

$$p(\text{no seroconversion } ¢ \text{ one partner}) = 1 - pf.$$

The probability that no seroconversion will occur after n partners is obtained by the joint probability of each partner not transmitting the virus. This joint probability can be written under the assumption that the infectivity is independent of the number of partners:

$$p(\text{no seroconversion } ¢ \text{ n partners}) = (1 - pf)^n.$$

The probability of seroconversion after n partners is just one minus the above:

$$p(\text{seroconversion } ¢ \text{ n partners}) = 1 - (1- pf)^n.$$

The number of seroconversions (S) expected given N seronegative men, each of which has n_i number of male sexual intercourse

partners, is the sum of the probabilities of seroconversion over all initially seronegative men:

$$S = \sum_{i=0}^{N} (1-(1-pf)^{n_i})$$

where S = number of seroconverters
n_i = number of male intercourse partners
p = population seroprevalence
f = infectivity
N = number of men initially seronegative and tested 6 months later.

The data from the cohort provides the following observations for the first six months of follow-up: There were 11 seroconversions (S = 11). The population seroprevalence was .48 (p = .48). There were 341 men who were initially ARV antibody negative and who were tested at the next examination cycle (N = 341). And each of these seronegative men had a known number of male intercourse partners (n_i = 0, . . . , 150).

The equation is solved for infectivity by numerical means, ie: a value of infectivity is sought such that the predicted number of seroconversions is equal to the observed number. Tables 1 and 2 illustrate the last iteration of this calculation for the first and second six months of follow-up respectively. For the first period, the expected number of seroconverters converged with the observed number when the infectivity was set equal to 1.8% (f = .018). The infectivity for the second period was found to be 1.1% (f = .011).

These rates, obtained by fitting the calculated and the observed marginal number of seroconversions, can be compared to

the rates obtained by using maximum likelihood estimation and the same model to fit each subject's expected probability of conversion with his observed seroconversion status. The maximum likelihood estimates of the infectivities are 1.56 (95% confidence interval: .64 - 2.47) and 1.07 (95% confidence interval: .14 - 1.99) for the first and second periods of follow-up respectively. The maximum likelihood estimates are within 10% of the estimates derived by fitting the marginal number of seroconversions.

The infectivity rate calculated by this model is small compared to other infectivity rates (for example, 30% for heterosexual syphilis transmission [17], 22% for female to male gonorrhea transmission [18], and 64% for heterosexual genital wart transmission [19]). Indeed, infectivities of 1.8% and 1.1% suggest that exposure to the virus via sexual intercourse is not the only factor involved in the transmission of the ARV. If the assumptions given above are correct, there may be something which protects a sizeable portion of sexually active seronegative men.

At least one assumption given above is not correct however. Analysis of the baseline data of the San Francisco Men's Health Study (2,20) indicated that risk of transmission due to male sexual intercourse depended on the type of sexual intercourse. Oro-genital contact and insertive anal intercourse involve little or no risk and receptive anal intercourse involves relatively high risk. Therefore, the model developed above incorrectly

pooled highly infectious exposures with relatively safe exposures thus giving a spuriously low estimate of infectivity.

If we conclude from baseline analysis that only receptive anal intercourse involves a risk for seroconversion, the number of receptive anal intercourse partners should be substituted for $n_{i\cdot}$. As depicted in Table 3, a problem arises with this substitution in that 2 of 11 and 3 of 5 seroconversions in the first and second periods of follow-up ocurred in men who denied having any receptive anal intercourse in the 6 months prior to their first positive antibody test. For this analysis, it is assumed that these men became infected by receptive anal intercourse occurring prior to the respective periods of observation. Under this assumption, fitting the marginal numbers of seroconversions is valid if the number of seroconversions due to unobserved exposure is similar to the number of unobserved seroconversions that will occur due to observed exposure (assumption #4). In other words, fitting the marginal numbers of seroconversions allows previously exposed seroconversions to "represent" the seroconversions occurring among men who were exposed during the observation period but who will not develop antibodies until later.

Maximum likelihood estimates were not calculated for the model based on receptive anal partners because the values for infectivity would be spuriously low. According to the model, men who did not have receptive rectal intercourse in the 6 months prior to their first positive antibody test have no risk of

seroconversion. Thus, fitting each subject's probability of seroconversion (given the model) with his observed seroconversion status would disregard seroconversions among men with no recent receptive anal partners. Consequently, the model would be fit to only a fraction of the observed number of seroconversions.

Table 3 shows the last iteration of the calculation of the model using only receptive anal contact as the exposure and the marginal number of seroconversions as the fitting criteria. The infectivity over the first 6 months of follow-up was 9.1%. Over the subsequent 6 months of follow-up there were 5 seroconversions and a considerable reduction in the numbers of receptive anal intercourse partners. Furthermore, the infectivity for this later period dropped to 5.8%.

The number of seroconversions in the second period expected given the infectivity of the first period is 7.7. This is not significantly more than the observed number of 5 ($p = .2$, one-tailed binomial test). Thus, the decline in infectivity from 9.1% to 5.8% could be explained by chance alone.

A number of phenomena could account for the relatively low infectivity calculated from this model. For example, Levy et al reported isolating virus from only 4 (21%) of 19 samples of semen taken randomly from seropositive men (21). This low rate of shedding into semen can be incorporated into the model by redefining infectivity as the probability of seroconversion given receptive anal intercourse with a seropositive man <u>who is shedding virus in his semen</u>. The new equation is the following:

$$S = \sum_{i=0}^{N} (1-(1-prf)^{n_i})$$

where S = number of seroconverters
n_i = number of male receptive anal intercourse partners
p = population seroprevalence
f = infectivity
r = viral recovery rate from semen of seropositive men
N = number of men seronegative initially and tested 6 months later.

As depicted in Table 4, the infectivity rates of this model are 43% and 27% for the first and second 6 month periods of follow-up respectively. These much higher infectivity rates indicate that transmission of the virus is very likely given exposure by receptive anal intercourse to male partners who are shedding virus in their semen.

Model of Seroconversion Rates: Discussion

According to this model, the probability that receptive anal intercourse with a single seropositive partner will transmit ARV is approximately 5% to 10%. Low rates of viral shedding in semen protects many of the remaining 90% of receptive anal contacts which escape seroconversion. Partner factors, such as urethral inflammation, may determine whether a seropositive man is shedding virus. Host resistance factors may be explain the 57% to 73% of receptive anal contacts that fail to transmit the virus even when the partners are shedding virus into their semen. These factors may involve, for example, a healthy mucosal barrier or poorly-permissive lymphocytes. Alternatively, the relatively infrequent failure of virus transmission observed in this cohort

could be entirely explained by "chance" events that are too diverse to be characterized as "factors."

The declining infectivity rate, if real, may indicate an accumulation of resistance among men who have remained seronegative through at least 5 years of experience with the AIDS epidemic in San Francisco. As more direct estimates of the infectivity of the ARV become available, the "exposure-alone" model developed above can be more directly tested. Also, if models of seroconversions in populations with less experience with the selection pressures of the epidemic show that infectivity is much higher than 10%, the existence of host resistance factors would be strongly suggested.

Sexually Transmitted Diseases: Results

Table 5 indicates that histories of sexually transmitted diseases were frequently reported in this cohort of homosexual and bisexual men. Furthermore, the ARV antibody positive group gave histories of these diseases 1.2 to 3.5 times more frequently than their ARV antibody negative counterparts. Table 6 indicates that 68% of ARV antibody positive men reported having had 3 or more episodes of selected sexually transmitted diseases in their lifetimes. Only 6% of these men denied any episode of these diseases.

The odds ratios in Table 5 describe the observed positive association between history of a given disease and ARV antibody status. These unadjusted odds ratios were significantly greater

than one for all the sexually transmitted diseases queried except scabies, genital herpes and the "other parasite" categories ($p = .05$).

The history of hepatitis was determined by medical history and not confirmed serologically. The similarity of the odds ratios for serum and infectious hepatitis (2.50 and 2.53 for Hepatitis B and Hepatitis A respectively) is consistent with a prevalent clinical impression that the various types of hepatitis cannot be reliably distinguished by interview alone. Because serological confirmation was not available at the time of this writing, the various types of hepatitis will not be distinguished in the following analysis.

A multivariate-logistic regression model was developed to control for confounding with numbers of sexual intercourse partners, types of sexual practices, and history of multiple sexually transmitted diseases. Earlier analysis of this cohort showed that insertive anal intercourse and oro-genital contact were not associated with an increased risk for seropositivity after controlling for numbers of receptive anal intercourse and numbers of partners (2). In accordance with these findings, this multivariate logistic-regression model was based on an index of the number of receptive anal partners that each subject reported in the 2 years prior to the baseline interview and serological assessment. As described in Table 7, the index is the reported number of all male sexual intercourse partners multiplied by an estimate of the proportion of the male intercourse partners with

whom the participant had receptive anal intercourse. The numerical value of the proportion is estimated from a five level qualitative response to an interview item. Thus, the receptive anal partner index is an approximation of the real number of receptive anal partners.

The assumption that other sexual intercourse practices do not involve an increased risk for seropositivity in this cohort was checked by entering dichotomous terms for other sexual practices after fitting the receptive anal partner index. Corroborating the earlier findings (2), insertive anal intercourse and oro-genital contact did not significantly improve the fit of the model. Further, a dichotomous term representing over 10 female intercourse partners in the 2 years prior to the interview did not fit into the model.

Also as reported earlier (2), rectal douching before intercourse was associated with an increased risk of seropositivity. Sharing needles in the five years prior to the interview also fit into the logistic model. Drug use with sexual partners, however, did not have an independent effect on risk however. Specifically, the use of marijuana, poppers, cocaine, hallucinogens, amphetamines, barbiturates, and MDA during sexual episodes were not independently associated with positive ARV antibody status.

Table 8 describes the logistic model of risk factors for positive serostatus that best fit the data. The number of receptive anal intercourse partners is clearly the most important

risk factor in this cohort giving a cumulative odds ratio of 8.94 for more than 50 receptive anal partners ($OR^{levels} = 1.55^5 = 8.94$). Douching and sharing needles also involved considerable risk as reported elsewhere (2).

Table 8 also indicates that a history of syphilis, rectal or urethral gonorrhea, genital and anal warts, and hepatitis are independently associated with positive ARV antibody status. The odds ratios given by this model are substantially less than the unadjusted odds ratios given in Table 5 indicating that the effects of sexually transmitted diseases originally observed were confounded somewhat by numbers of sexual partners and types of sexual intercourse. This model indicates, however, that a history of gonorrhea, syphilis, warts, and hepatitis increases risk for seropositivity independently of all the sexual and drug practices that have been identified as risk factors for seropositivity in this cohort.

No three-way interaction was substantial or significant. The two-way interaction terms that substantially affected the fit of the model and/or the main effects terms were douching & rectal gonorrhea, syphilis & sharing needles, and warts & urethral gonorrhea. All the interaction coefficients were negative yielding odds ratios less than one. The interaction odds ratios can be interpreted as in the following example: Men who both douched and had rectal gonorrhea are at a greater risk of being seropositive but the increased risk is less than would be expected given the risk associated with douching and rectal

gonorrhea when they occur separately. The negative interactions have similar interpretations for the men with both a history of syphilis and who had shared needles, and for men who had histories of both genital-anal warts and urethral gonorrhea.

Since the medical and sexual histories for this analysis were obtained solely by interview, the effects of misclassification were examined. Non-differential misclassification of the exposure variables (eg: sexually transmitted diseases) is expected to produce a conservative bias of the odds ratios, ie: the observed odds ratios will be closer to one than the true odds ratios (22). Thus, the significant associations observed between the sexually transmitted diseases and ARV antibody status are more striking when the probable misclassification of histories of sexually transmitted diseases is considered.

In contrast, non-differential misclassification of a covariate can bias estimates of risk away from the null (23). The importance of misclassification in this analysis can not be known without information about the accuracy of the sexual history obtained. Nevertheless, the potential magnitude of the problem was assessed using a model, described in Table 9, based a stratified analysis of the association between the history of syphilis and positive ARV antibody status. A series of tables (one table for each strata of the receptive anal partner index) was created using observed strata frequencies, and the hypothesis that there is no association between syphilis and ARV antibody

status. These tables represent the "true" distribution of risk under the hypothesis that all of the observed association between syphilis and ARV antibody status is due to non-differential misclassification of the number of partners. Misclassification between strata was set at a given level and the model was fit by selecting "true" odds ratios for the associations between partners & syphilis and partners & ARV antibody status such that the corresponding odds ratios after misclassification were similar to those observed in the cohort. The amount of association between syphilis and ARV antibody status created by the misclassification was then measured and expressed as Cochran-Mantel-Haenszel summary odds ratios. Table 9 indicates that the amounts of misclassification that might occur in the receptive anal partner index (20% to 40%) could create only small associations (odds ratios of 1.07 and 1.21 respectively). Further, the observed association between syphilis and ARV antibody status could not be explained by misclassification even if all of the subjects were misclassified into adjacent categories.

There is no reason to suspect differential misclassification in the data being used in this analysis. Nevertheless, certain types of differential misclassification in any of the data could create spurious associations.

The possible detrimental effect of sexually transmitted diseases on immune status was examined using skin testing to 7 antigens and T helper cell counts as measures of cell-mediated-

immunity. As depicted in Table 10, a history of urethral gonorrhea was associated with fewer T helper cells (p = .008) among seropositive men. The seropositive men reporting a history of genital-anal warts had a mean skin test score that was significantly lower than the mean skin test score of men denying such history (p=.007). In addition, skin test score decreased with more recent history of syphilis (p = .09). Neither skin test score nor counts of T helper cells were associated with a history of any of the other sexually transmitted diseases, including hepatitis.

Sexually Transmitted Diseases: Discussion

The logistic model of risk factors for seropositivity is consistent with earlier reports (8,9). As in this paper, Kriess et al modeled risk factors using multivariate-logistic regression and found odds ratios of 3.80, 3.31, and 2.52 for laboratory confirmed gonorrhea, genital ulcers, and syphilis respectively. Given the differences in the populations studied (Kriess studied female prostitutes in Nairobi and this study is of male homosexual and bisexual men in San Francisco), the odds ratios observed in Africa are remarkably similar to those observed in this study.

The factors that continued to be associated with ARV antibody status after using multivariate-logistic regression to adjust for confounding and interactions were related to anal intercourse. Syphilis, rectal gonorrhea, and genital-anal warts

are all more common in men practicing anal intercourse (24). The importance of urethral gonorrhea suggests that insertive intercourse may increase risk for ARV transmission when the host is made susceptible by an underlying urethral inflammation. Sexually transmitted diseases associated with oral routes of entry, such as giardia, shigella, and salmonella were not independently associated with ARV antibody status. These findings are consistent with previous analysis of this cohort which found that anal intercourse was the most important mode transmission of ARV and that oro-genital and oro-anal contact involved little or no risk (2,20).

The elevated risks associated with the history of sexually transmitted diseases must be interpreted in light of the negative interactions. No behavioral or biological interpretation seems apparent for any of interaction terms that were included in the multivariate-logistic model but the following speculations are germane. The risk factors involved in negative interactions (douching, warts, syphilis, and gonorrhea) may represent, in part, a common risk factor that has not been measured in this study. This would account for the negative interaction in that people with more than one of the above characteristics (eg: people who douche and have rectal gonorrhea) have only one dose of the common factor. Thus, the risk of having two of the modeled risk factors (but only one dose of the common factor) is only slightly higher than having only one of the modeled factors either of which represents the presence of the common factor.

This common factor could be behavioral, epidemiological, or biological. In terms of behavior, the common factor may involve a pattern of sexual practice that was not measured or otherwise cannot be modeled. This seems improbable given that the information gathered for this study of the natural history of AIDS was exhaustive. Further, present and earlier (2) efforts to model patterns of sexual behavior using available data failed to show important sexual practices other than numbers of receptive anal intercourse partners and douching.

An epidemiological explanation for the common factor involves postulating that there are two circles of comparably active homosexual and bisexual men in San Francisco. According to this theory, the prevalence of STD's (including ARV infection) is considerably higher in one circle relative to the other. Given these two circles, the history of syphilis, gonorrhea, and/or warts would represent membership status in the STD infected circle. This theory is not probable in that the two circles would have to be rather completely segregated to prevent inoculation and subsequent spread of STD's into the previously non-STD circle. Cultural and sociological evidence for what would have to be a marked segregation is lacking.

The common factor may represent some biological characteristic such as an STD associated impairment of host defence that precedes and facilitates ARV infection. Such impairments of host defence may involve altered cellular mediated immunity as suggested by Table 10. The associations between

history of warts and syphilis and low skin test score are consistent with in vitro studies that found that lymphocytes taken from women with recalcitrant condylomata acuminata (25) and syphilis patients (26) were less responsive to mitogen stimulation. Perhaps, genital-anal warts and syphilis increase permissiveness for ARV infection by impairing the host's cellular mediated immunity. Alternatively, gonorrhea, syphilis, and genital-anal warts could compromise the mucosal barrier of the rectum or the urethra. A mucosal injury from a syphilitic chancre, genital-anal warts, and/or gonococcal infection could facilitate the penetration of the ARV through the non-permissive epithelial cell layer.

Serological Panel: Results

Serological tests for the micro-organisms listed in Table 11 were performed on paired samples from the first ten seroconverters and 30 persistently seronegative matched controls. One of the ARV seroconverters concomitantly seroconverted to influenza type A. One of the controls seroconverted to herpes simplex virus and another seroconverted to cytomegalovirus. There was a greater than 1.5 times increase in the ELISA test for measles in one control and for varicella-zoster in another control. All subjects had stable IgG antibody titres to Epstein-Barr VCA.

The associations between baseline serostatus to the panel of organisms and ARV seroconversion are described in Table 12. None

of the associations were statistically significant due to the small numbers of people studied. Further, odds ratios could not be calculated for adenovirus and cytomegalovirus due to the lack of data. The largest odds ratios were for chlamydia and mycoplasma (OR = 2.42 and 2.64 respectively).

Serological Panel: Discussion

These studies indicate that the poly-clonal activation that has been observed among AIDS patients (27,28) has not yet ocurred in this group of recently infected men. The rising antibody titre to influenza type A in the one ARV seroconverter probably represents co-infection by two highly prevalent viruses. The seroconversions and rising titres among the persistently ARV seronegative controls probably represent new infections, reactivation of old infections, or measurement error.

The odds ratios for prior chlamydia infection and prior mycoplasma infection were large although not statistically significant. Both of these organisms are thought to be involved in non-gonococcal urethritis which involves lymphocytic infiltration of the urethral mucosa. This process would tend to enhance the number of lymphocytes available to transmit or receive ARV. Further serological studies of incident seroconverters to ARV will help evaluate the significance of these findings.

Conclusion

The epidemic model of seroconversion indicated that few, if any, of the sexually active homosexual and bisexual men in the San Francisco Men's Health Study are protected by host resistance factors. The low rates of seroconversion in this cohort are largely attributable to the adoption of "safe-sex" practices including fewer partners and less anal intercourse with potentially infected men.

Certain sexually transmitted diseases may facilitate ARV transmission by impairing mucosal integrity or cellular mediated immunity in the susceptible host or the infected partner. Further study of the association between sexually transmitted disease and ARV infection is warranted. Analysis of these issues requires rigorous control of confounding to separate the independent effects of sexually transmitted diseases from their effects as markers of high risk sexual behavior. Confounded or not, this study's findings further demonstrate the need for medical and educational services for those at risk for both AIDS and the older sexually transmitted diseases.

Why some people remain seronegative even after prolonged ARV infection is not understood. Although this study provides no evidence of viral interactions in the process of seroconversion to ARV, such interactions have not been excluded. Other viruses, such as Epstein-Barr virus and cytomegalovirus, may be inducers or inhibitors of the humoral immune response to ARV. Immunological and serological assessment of ARV-positive antibody-negative subjects will address this issue more directly.

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TABLE 1

CALCULATIONS OF THE SEROCONVERSION MODEL
USING TOTAL MALE INTERCOURSE PARTNERS
IN THE FIRST 6 MONTHS OF FOLLOW-UP AS THE EXPOSURE

seroprevalence (p) = 0.48
infectivity (f) = 0.018

Male Intercourse Partners (n)	Number of seronegative men (k_n)	Probability of Seroconversion $p(S) = 1 - (1 - pf)^n$	Number of Seroconverters	
			Expected $p(S)k_n$	Observed
0	47	.00	0.00	
1	108	0.01	0.92	
2	50	0.02	0.85	3
3	40	0.03	1.02	
4	17	0.03	0.57	1
5	15	0.04	0.63	2
6	13	0.05	0.65	
7	5	0.06	0.29	
8	6	0.07	0.40	
9	1	0.07	0.07	
10	8	0.08	0.66	1
11	1	0.09	0.09	1
12	4	0.10	0.39	1
14	1	0.11	0.11	
15	8	0.12	0.97	
16	1	0.13	0.13	
18	2	0.14	0.29	
20	5	0.16	0.79	1
25	2	0.19	0.39	1
30	1	0.23	0.23	
35	1	0.26	0.26	
40	2	0.29	0.58	
50	2	0.35	0.70	
150	1	0.72	0.72	
Total	341		11.00	11

TABLE 2

CALCULATIONS OF THE SEROCONVERSION MODEL
USING TOTAL MALE INTERCOURSE PARTNERS
IN THE SECOND 6 MONTHS OF FOLLOW-UP AS THE EXPOSURE

seroprevalence (p) = 0.50
infectivity (f) = 0.011

Male Intercourse Partners (n)	Number of seronegative men (k_n)	Probability of Seroconversion $p(S) = 1 - (1 - pf)^n$	Number of Seroconverters	
			Expected $p(S)k_n$	Observed
0	60	0.00	0.00	
1	99	0.01	0.55	3
2	46	0.01	0.51	1
3	31	0.02	0.51	
4	21	0.02	0.46	
5	13	0.03	0.35	
6	6	0.03	0.20	
7	1	0.04	0.04	
8	4	0.04	0.17	
9	2	0.05	0.10	
10	5	0.05	0.27	1
12	2	0.06	0.13	
13	1	0.07	0.07	
14	1	0.07	0.07	
15	4	0.08	0.32	
16	1	0.08	0.08	
18	1	0.09	0.09	
20	1	0.10	0.10	
25	1	0.13	0.13	
35	1	0.18	0.18	
50	1	0.24	0.24	
96	1	0.41	0.41	
Total	303		5.00	5

TABLE 3

CALCULATIONS OF THE SEROCONVERSION MODEL
USING MALE RECEPTIVE ANAL INTERCOURSE PARTNERS

FIRST SIX MONTHS

seroprevalence (p) = 0.48
infectivity (f) = 0.091

Receptive Anal Intercourse Partners (n)	Number of seronegative men (k_n)	Probability of Seroconversion $p(S) = 1 - (1 - pf)^n$	Number of Seroconverters	
			Expected $p(S)k_n$	Observed ---
0	193	.00	.00	2
1	95	0.04	4.16	1
2	30	0.09	2.57	4
3	11	0.13	1.38	1
4	4	0.16	0.66	
5	2	0.20	0.40	2
6	2	0.24	0.47	
7	1	0.27	0.27	
10	3	0.36	1.08	1
Total	341		11.00	11

SECOND SIX MONTHS

seroprevalence (p) = 0.50
infectivity (f) = 0.058

Receptive Anal Intercourse Partners (n)	Number of seronegative men (k_n)	Probability of Seroconversion $p(S) = 1 - (1 - pf)^n$	Number of Seroconverters	
			Expected $p(S)k_n$	Observed ---
0	190	.00	.00	3
1	82	0.03	2.38	1
2	19	0.06	1.09	1
3	4	0.08	0.34	
4	5	0.11	0.55	
6	1	0.16	0.16	
7	1	0.19	0.19	
12	1	0.30	0.30	
Total	303		5.00	5

TABLE 4

INFECTIVITIES USING RECEPTIVE ANAL INTERCOURSE PARTNERS PER 6 MONTH PERIOD OF FOLLOW-UP

Period	Seroprevalence at beginning of the period	No. (%) with > 1 partners	Number of Seroconverters Observed	Infectivity	
				Sero (+)*	Shedding§
First 6 Months	.48	53 (16%)	11/341 (3.2%)	.091	.43
Second 6 Months	.50	31 (10%)	5/303 (1.6%)	.058	.27

*Infectivity = probability that receptive anal intercourse with a random seropositive man will cause seroconversion.

§Infectivity = probability that receptive anal intercourse with a random seropostive man who is shedding the virus will cause seroconversion.

TABLE 5

LIFE HISTORY OF SEXUALLY TRANSMITTED DISEASES*
AMONG HOMOSEXUAL AND BISEXUAL MEN IN
SAN FRANCISCO BY ARV ANTIBODY STATUS

	Homosexual and Bisexual ARV antibody: Negative (N=410)	Positive (N=381)	Unadjusted odds ratio
Gonorrhea			
Urethral	199 (48%)	270 (68%)	2.25
Oral	22 (5%)	44 (11%)	2.26
Rectal	89 (22%)	205 (52%)	3.99
NGU	137 (33%)	193 (50%)	1.86
Syphilis	69 (17%)	163 (41%)	3.63
Amoeba	56 (14%)	99 (25%)	2.05
Shigella or Salmonella	16 (4%)	55 (14%)	4.01
Giardiasis	16 (4%)	57 (14%)	3.71
Genital Warts	114 (28%)	188 (47%)	2.27
Herpes			
Facial	155 (38%)	187 (47%)	1.49
Genital	40 (10%)	51 (13%)	1.38
Anal	19 (5%)	47 (12%)	2.71
Hepatitis B	79 (19%)	145 (37%)	2.50
Hepatitis A	30 (7%)	64 (16%)	2.53

*History of sexually transmitted diseases was obtained by interview.

TABLE 6

FREQUENCY OF OCCURRENCE OF SELECTED SEXUALLY TRANSMITTED DISEASES AMONG ARV ANTIBODY POSITIVE HOMOSEXUAL AND BISEXUAL MEN (N = 381)

	number of disease episodes		
	0	1 or 2	≥ 3
Syphilis	221 (59%)	132 (35%)	22 (6%)
Urethral Gonorrhea	121 (32%)	116 (31%)	143 (37%)
Rectal Gonorrhea	182 (48%)	125 (33%)	71 (19%)
Genital-Anal Warts	203 (53%)	162 (42%)	16 (5%)
Any of the above	24 (6%)	101 (26%)	256 (68%)

TABLE 7

METHOD FOR CALCULATING INDEX OF NUMBERS OF MALE RECEPTIVE ANAL INTERCOURSE PARTNERS

Reported number of male intercourse partners:			(A)		
Reported proportion of partners with whom the respondent had receptive anal intercourse:	none	one	some	most	all
			(B)		
Value assigned to response (B):	0	1	33%	67%	100%
			(C)		
Receptive anal intercourse partner index:			(A) * (C) = index		

TABLE 8

LOGISTIC REGRESSION MODEL OF RISK FACTORS FOR POSITIVE ARV ANTIBODY STATUS AMONG HOMOSEXUAL AND BISEXUAL MEN

Risk Factor	χ^2	p =	Odds ratio	95% Conf. Int.
Male receptive anal partners*	40.5	<.0001	1.55	1.35 - 1.77
Douche§	25.8	<.0001	3.46	2.14 - 5.59
Sharing Needles§	7.6	.006	6.66	1.73 - 25.60
Syphilis§	18.4	<.0001	2.57	1.67 - 3.96
Rectal Gonorrhea§	7.6	.006	2.07	1.23 - 3.46
Urethral Gonorrhea§	13.3	.0003	2.45	1.51 - 3.96
Genital-anal Warts§	13.0	.0003	2.98	1.64 - 5.40
Hepatitis§	13.4	.0003	2.01	1.38 - 2.91
Douche * Rectal GC	1.4	.2	.63	
Syphilis * Needles	5.8	.02	.12	
Warts * Urethral GC	6.5	.01	.37	

*Coded as: 0 = no partners, 1 = one partner, 2 = 2 to 4 partners, 3 = 5 to 19 partners, 4 = 20 to 49 partners, 5 = $\geq$ 50 partners.

§Coded as 1 if the risk factor was present, 0 otherwise.

TABLE 9

THE EXPECTED EFFECT OF MISCLASSIFICATION OF NUMBERS OF RECEPTIVE ANAL PARTNERS ON THE ASSOCIATION BETWEEN SYPHILIS AND POSITIVE ARV ANTIBODY STATUS

Proportion of misclassification	Expected odds ratio of syphilis and arv antibody status	95 % confidence interval
0	1.00	.71 - 1.43
20%	1.07	.75 - 1.53
40%	1.21	.85 - 1.73
60%	1.63	1.22 - 2.37
80%	2.21	1.46 - 3.36
100%	2.27	1.47 - 3.50
observed	2.81	1.94 - 4.08

TABLE 10

IMMUNE STATUS BY HISTORY OF SELECTED

SEXUALLY TRANSMITTED DISEASES

	TIMING OF EPISODE OF STD WITH THE INTERVIEW AND IMMUNOLOGIC TESTING							
	Never	prior to 6 months	within the last 6 months		Never	prior to 6 months	within the last 6 months	
	Mean Skin Test Score (N)				Mean T Helper Cell Count (N)			
Syphilis	11.4 (193)	10.3 (124)	7.5 (11)	p = .09 *	538 (212)	577 (139)	599 (12)	N.S.
Urethral Gonorrhea	10.6 (105)	11.0 (220)	12.0 (6)	N.S.	610 (119)	531 (239)	408 (7)	p = .008
Rectal Gonorrhea	11.3 (160)	10.5 (154)	14.4 (5)	N.S.	590 (177)	520 (183)	628 (5)	p = .031
Warts	12.0 (174)	9.7 (115)	9.6 (42)	p = .007	575 (195)	532 (127)	532 (44)	N.S.
Hepatitis	11.1 (94)	10.9 (209)	10.7 (11)	N.S.	565 (107)	554 (230)	517 (10)	N.S.

* Differences between means were tested using ANOVA.

TABLE 11

LIST OF SEROLOGICAL TESTS

AND SUBJECTS WITH RISING TITRES

Organism	Test	ARV Seronegative (N = 30)	ARV Seroconverters (N = 10)
		No. with rising titres/ No. of subjects with valid results from both samples	
Mycoplasma	CF	/25	/9
Clamydia	CF	/25	/9
Influenza B	CF	/26	/9
Influenza A	CF	/26	1/9 *
Mumps	CF	/25	/10
Adenovirus	CF	/25	/9
Cytomegalovirus	EIA	1/30 §	/10
Herpes-Simplex	EIA	1/30 §	/10
Varicella-Zoster	EIA	1/29 *	/10
Measles	EIA	1/30 *	/10
Epstein-Barr VCA	IFA	/30	/10
Q fever	CF	/29	/10

* Significant rise in titre.

§ Seroconversion.

TABLE 12

MATCHED ANALYSIS OF SEROSTATUS TO A NUMBER OF VIRUSES AT WAVE 1 AND RISK OF ARV SEROCONVERSION

	ARV Seronegative (N = 30)	ARV Seroconverter (N = 10)	odds ratio	χ^2 *
	No. with valid result (% positive)			
Mycoplasma	26 (38%)	9 (67%)	2.64	.43
Clamydia	28 (21%)	10 (60%)	2.42	.91
Mumps	26 (50%)	10 (60%)	.73	.00
Adenovirus	26 (88%)	9 (100%)	---- §	.40
Influenza B	27 (70%)	9 (78%)	1.22	.05
Influenza A	27 (74%)	9 (100%)	1.67	.00
Cytomegalovirus	30 (90%)	10 (100%)	---- §	.11
HSV	30 (87%)	10 (90%)	1.39	.08
Varicella-Zoster	30 (100%)	10 (100%)		
Measles	30 (100%)	10 (100%)		
Epstein-Barr VCA	30 (100%)	10 (100%)		
Q fever	29 (0%)	10 (0%)		

* None of the associations were significant at $\alpha = .2$.

§ Odds ratio not calculable.