MATHEMATICAL BIOSCIENCES
AND ENGINEERING
Volume **??**, Number **0??**, ???? **2005**

http://www.mbejournal.org/

pp. **1–9**

MODELING THE POTENTIAL IMPACT OF RECTAL MICROBICIDES TO REDUCE HIV TRANSMISSION IN BATHHOUSES

Romulus Breban

Department of Biomathematics, David Geffen School of Medicine at UCLA
Los Angeles, California, 90024 USA

Ian McGowan

Center for HIV and Digestive Diseases, Division of Digestive Diseases, & the UCLA AIDS Institute, David Geffen School of Medicine at UCLA
Los Angeles, California, 90020 USA

Chad Topaz

Department of Mathematics, UCLA, Los Angeles, California, 90020 USA

Elissa J. Schwartz

Department of Biomathematics and Department of Biostatistics, David Geffen School of Medicine at UCLA
Los Angeles, California, 90020 USA

Peter Anton

Center for HIV and Digestive Diseases, Division of Digestive Diseases, & the UCLA AIDS Institute, David Geffen School of Medicine at UCLA
Los Angeles, California, 90020 USA

Sally Blower[1]

Department of Biomathematics & the UCLA AIDS Institute, David Geffen School of Medicine at UCLA
Los Angeles, California, 90024 USA

2000 *Mathematics Subject Classification.* 92D30.

Key words and phrases. anal intercourse, rectal microbicide, HIV-1, transmission, bathhouse, mathematical model, MSM.

[1]Corresponding author

Abstract. We evaluate the potential impact of rectal microbicides for reducing HIV transmission in bathhouses. A new mathematical model describing HIV transmission dynamics among men who have sex with men (MSM) in bathhouses is constructed and analyzed. The model incorporates key features affecting transmission, including: sexual role behavior (insertive and receptive anal intercourse acts), biological transmissibility of HIV, frequency and efficacy of condom usage, and, most pertinently, frequency and efficacy of rectal microbicide usage. To evaluate the potential impact of rectal microbicide usage, we quantify the effect of rectal microbicides (ranging in efficacy from 10% to 90%) on reducing the number of HIV infections in the bathhouse. We conduct uncertainty analyses to assess the effect of variability in both biological and behavioral parameters. We find that even moderately effective rectal microbicides (if used in 10% to 50% of the sex acts) would substantially reduce transmission in bathhouses. For example, a 50% effective rectal microbicide (used in 50% of sex acts) would reduce the number of secondary infections by almost 13% at disease invasion . Our modeling analyses show that even moderately effective rectal microbicides could be very effective prevention tools for reducing transmission in bathhouses, and also potentially limit the spread of HIV in the community.

1. **Introduction.** There is a critical need to develop new HIV prevention strategies. Lately, developing topical microbicides for the prevention of vaginal or rectal transmission of HIV has become an area of increasing interest. The profound differences in anatomy, histology, and microbiology between the vagina and rectum suggest that site-specific microbicides might be required. It is possible that a product that could be used with impunity in the vaginal cavity may damage the vulnerable lining of the intestinal tract and could actually increase the risk of HIV transmission if used as a rectal microbicide. To date, there have been only three human rectal microbicide studies in men who have sex with men (MSM); all the studies evaluated the safety and acceptability of N-9[1, 2, 3]. In the first study[1], 35 seroconcordant couples received escalating doses of N-9 for up to 6 weeks without obvious toxicity, although minor histological abnormalities were common in both N-9 and placebo recipients. In a second smaller study[2], the use of N-9 products resulted in significant rectal epithelial damage within 15 minutes of administration. This observation was subsequently confirmed in a third larger study by the same group[3]. Additional human vaginal[4] and animal rectal studies[5, 6] with N-9 have demonstrated limited efficacy and a potential for significant mucosal toxicity. Therefore, this product is now contraindicated for rectal use. Despite these disappointing results, the feasibility of preventing rectal transmission has been recently demonstrated using cyanovirin in the SIV/macaque model[7]. Whilst these data are encouraging, the technical challenges in developing a similar product for use in humans are considerable. In addition, it is currently unclear which elements of the intestinal mucosa are the initial targets of infection[8] and also which region of the colon needs protection. As rectal microbicides are developed there is an urgent need to evaluate their potential impact on HIV transmission.

The majority of MSM practice insertive or receptive anal intercourse (AI)[9], and this activity occurs within a community with a considerable prevalence of HIV infection[9, 10]. Within the MSM community there are high-risk sexual zones (such as bathhouses) where MSM congregate for sexual activity[11, 12, 13], and where the frequency of unprotected AI is likely to be particularly high. Bathhouses are a feature of most major North American and European cities. These facilities provide

both communal and private spaces where MSM can engage in sexual activity with multiple partners[12, 14]. There are approximately 80 such venues in the United States of America (USA)[13, 15]. Almost all bathhouses provide condoms and lubricants, and some have sexually transmitted diseases and HIV testing facilities for patrons[15]. Despite the availability of these products, it is estimated from one study that at least 10.7% of patrons have unprotected AI in the bathhouse setting[11]. As a consequence, bathhouses are high-risk zones for HIV transmission and, therefore, should be used for targeting prevention strategies and health education for MSM[16, 17]. The purpose of our study is to evaluate the potential impact of rectal microbicides for reducing HIV transmission in bathhouses.

2. **Methods.** *Mathematical Model.* We develop an ordinary differential equation (ODE) model describing HIV infection amongst an MSM population in a bathhouse. We assume that the bathhouse is permanently open, and that the population is large and well mixed (i.e., we assume mass action mixing) such that an ODE model is appropriate. The total number of MSM in the bathhouse at any time, $N(t)$, is subdivided into three groups: susceptible (i.e., uninfected) men, $S(t)$, and HIV-infected men, $I(t)$, and the HIV-exposed men $E(t)$; thus, $N(t) = S(t) + I(t) + E(t)$. The population dynamics of the three groups S, I and E are modeled by the equations

$$\begin{cases} \frac{dS}{dt} = \pi - \beta \frac{SI}{N} - \mu S \\ \\ \frac{dI}{dt} = \rho - \mu I \\ \\ \frac{dE}{dt} = \sigma + \beta \frac{SI}{N} - \mu E. \end{cases} \tag{1}$$

These three equations track the inflow and outflow of MSM into the bathhouse. The inflow rates of susceptible, infected MSM, and exposed MSM are, respectively, π, ρ, and σ. The average time spent in the bathhouse by MSM is $1/\mu$. Within the bathhouse, we assume that HIV transmission takes place exclusively though AI (both receptive and insertive acts occur); transmission is modeled by the term $\beta \frac{SI}{N}$. The probability of HIV transmission (β) through either insertive or receptive AI is given by

$$\beta = c_i \beta_i (I - \eta^c \psi_i^c)(1 - \eta^m \psi_i^m) + c_r \beta_r (1 - \eta^c \psi_r^c)(1 - \eta^m \psi_r^m)$$

The probability of HIV transmission through insertive AI depends on three quantities: the rate of formation of AI partnerships where the insertive is susceptible (c_i), the probability of transmission in one act of insertive AI (β_i), and the level of protection against HIV infection due to microbicide usage or condom usage. If microbicides are used, HIV transmission is decreased by a factor of $(1-\eta^m \psi_i^m)$, where η^m is the microbicide efficacy and ψ_i^m is the frequency of microbicide use. Similarly, if condoms are used, HIV transmission is decreased by a factor of $(1 - \eta^c \psi_i^c)$, where η^c is the condom efficacy and ψ_i^c is the frequency of condom use. Likewise, HIV transmission through receptive AI is characterized by c_r, β_r, and the type of protection utilized, $(1 - \eta^m \psi_r^m)(1 - \eta^c \psi_r^c)$. Once MSM are infected with HIV they do not immediately become infectious, and they enter the exposed class. Since the average interval of time spent in the exposed class is much larger than the average duration of bathhouse visits, we assume that no exposed MSM become infectious in the bathhouse.

Parameter Definition	**Symbol**	**Minimum**	**Maximum**
Average length of bathhouse visit (hours)	$1/\mu$	1	7
Viral transmission probability per insertive partnership (insertive is HIV-)[2][31, 32]	β_i	0.0003	0.01
Viral transmission probability per receptive partnership (receptive is HIV-)[2][31, 32]	β_r	0.0006	0.02
Number of insertive partnerships per hour[3]	c_i	0.14	5
Number of receptive partnerships per hour[3]	c_r	0.14	5
Number of insertive partnerships per bathhouse visit	C_i	1	5
Number of receptive partnerships per bathhouse visit	C_r	1	5
Number of bathhouse visits per year	ν	1	2
Years that an MSM visits bathhouses	N	10	30
Total number of bathhouse visits[4]	n	10	60
Condom efficacy	η^c	0.8	0.95
Frequency of condom use when HIV- is insertive	ψ_i^c	0	0.3
Frequency of condom use when HIV- is receptive	ψ_r^c	0	0.2
Microbicide efficacy[5]	η^m	0.1	0.9
Frequency of microbicide use when HIV- is insertive[5]	ψ_i^m	0.1	0.5
Frequency of microbicide use when HIV- is receptive[5]	ψ_r^m	0.1	0.5

TABLE 1. Parameters of the bathhouse model: parameter definition, symbol, minimum, maximum.
[2]The broad range in β accounts for the fact that patrons can be newly or chronically infected.
[3]Calculated as $c_{i,r} = C_{i,r}\mu$.
[4]Calculated as $n = N\nu$.
[5]Study variable.

Model Analysis. We analyze our model to obtain an expression for the average number of secondary HIV infections within the bathhouse (which we denote by R) assuming that virtually all MSM in the bathhouse are susceptible. For our particular model, this concept is very much related to that of the basic reproduction ratio, R_0[18], except that since exposed MSM do not become infectious in the bathhouse, there is no tertiary HIV transmission in the bathhouse during one visit. Thus, for the HIV transmission in a bathhouse when there are no infected entrants ($\rho = 0, \sigma = 0$) we have $R = \beta/\mu$[18] per bathhouse visit. If n visits are considered, then $R = n\beta/\mu$. It is very important to note that R describes disease invasion (where the number of susceptible MSM is much larger than that of HIV infected

MSM). Clearly, R also plays an important role in disease eradication where again the condition of the number of susceptible MSM being much larger than that of HIV infected MSM is met. However, the current situation with HIV is far from invasion or eradication; rather, HIV is approaching an endemic equilibrium of constant incidence and prevalence. In this context, R is used as a measure of the severity of the HIV epidemic.

Parameter Values. In order to account for uncertainty in estimating the values of the parameters, we use uncertainty analysis[19, 20] and sample from probability distributions to predict R and its variability; see Table 1 for ranges and probability distributions for each of the biological and behavioral parameters. In the absence of detailed data that would allow the precise estimation of all of the parameters in Table 1, we choose conservative ranges for these parameters in order to illustrate the potential minimum impact of microbicides on HIV transmission in bathhouses. For most parameters given in Table 1[19, 20], we sample uniform probability distributions 40000 times in order to predict the distribution of R. Two parameters (microbicide efficacy and usage) are study variables and vary from 0 to 1. For the convenience of a two-dimensional plot, we choose the same level of microbicide use for both receptive and insertive AI, i.e., $\psi_i^m = \psi_r^m$.

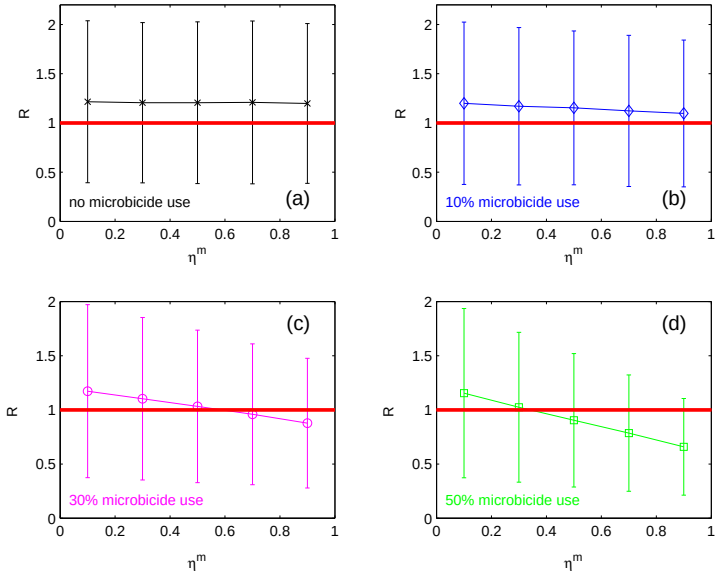

FIGURE 1. The potential impact of rectal microbicides use on HIV transmission in a bathhouse. The panels (a), (b), (c), and (d) show the average number of secondary infections per infected individual per bathhouse visit (R) considering a bathhouse full of susceptibles versus the microbicide efficacy (η^m) for 0%, 10%, 30%, and 50% microbicide use. The bars represent the standard deviation of the average values.

3. **Results.** Our results in Fig. 1 show the levels of microbicide efficacy and usage that are necessary in order to decrease R. For low microbicide use (i.e., 10%), R

decreases slowly with increasing microbicide efficacy. However, for fairly modest microbicide use (between 30%-50%), R becomes lower than 1 when microbicide efficacy is greater than 30%. Therefore, our results imply that even if microbicide use in bathhouses was fairly modest, microbicide efficacy would only need to exceed 30% in order to have a significant impact and decrease R below 1. Furthermore, a 50% effective rectal microbicide (used in 50% of sex acts) would reduce the number of secondary infections at disease invasion (R) by almost 13%.

4. **Discussion.** The sexual behavior and condom usage of MSM attending bathhouses are critical determinants of HIV transmission rates. Unfortunately, detailed data are limited. For our current analyses we assumed relatively low condom use rates and high rates of receptive and insertive AI in order to reflect sexual activity in a high-risk setting. Our results clearly demonstrate that even modest usage of moderately effective rectal microbicides by MSM could have a substantial impact on reducing HIV transmission within bathhouses. In addition, these products would be of benefit in other high-risk environments such as circuit parties where high levels of unprotected AI is known to occur[21]. Assuming that most of the transmission of HIV in the USA MSM population occurs in high risk venues (such as bathhouses, sex clubs, etc.), our results imply that microbicides could potentially have a significant impact on the overall MSM HIV epidemic.

Whether moderately effective rectal microbicides can be developed remains to be seen. However, if they are developed there is little doubt that these products would be used by MSM[22, 23] many of whom are currently practicing unprotected AI[24, 25, 26]. Feasibility studies have determined both the need for rectal microbicides for MSM, as well as the willingness of this group to participate in rectal microbicide trials[27]. In a recent study of MSM in San Francisco, 41% of the men interviewed had used a nonoxynol-9 (N-9) containing gel believing that N-9 would prevent HIV infection[22]. A product with a good acceptability profile and a formulation that does not interfere with AI is likely to increase microbicide use by MSM[28]. The first generation of microbicides will likely be distributed in unit doses of lubricant in foil packets (like Neosporin ointment). These could be made as readily available as condoms are. Clients could be encouraged to use microbicides as standard lubricant during sex.

MSM may not be the only target group for rectal microbicides. Preliminary data suggest that 5-20% of heterosexuals engage in AI[29, 30], thus it is possible that a fraction of the heterosexual population may also decrease their transmission risk through the use of rectal microbicides. Our modeling analyses clearly show that development of rectal microbicides may provide another opportunity for HIV prevention in at-risk populations. We have shown that even moderately effective microbicides could prevent new HIV infections in bathhouses, and perhaps could even be instrumental in helping stem the spread of HIV infection into the community. However, it should be noted that all our analyses have been based on the assumption that risk behavior will not change. Obviously, if risk behavior decreases, microbicides are likely to have an even greater impact in reducing transmission. Conversely, if risk behavior increases when microbicides are introduced, then it is possible that a perverse outcome will result; HIV transmission will increase rather than decline. Perverse outcomes have previously been shown to be possible as a result of introduction of imperfect HIV vaccines and/or antiretrovirals[34, 35].

Therefore, risk behaviors should be monitored when microbicides become readily available.

Acknowledgments. The authors acknowledge Trista Bingham, MPH for discussions about Los Angeles bathhouses. The authors thank Erin Bodine and Tara L. Martin for assistance with the manuscript. SB, RB and EJS acknowledge financial support from NIH/NIAID AI 041935. EJS also acknowledges support from NIH/NIAID Biostatistics Training Grant for AIDS Research (5 T32 AI 107370, to WG Cumberland). IM and PA were financially supported by NIH AI 28697 and the Macy's Foundation; PA was also supported by NIH AI 01610. CT was supported by NSF VIGRE grant DMS-9983726.

REFERENCES

[1] S. R. Tabet, C. Surawicz, S. Horton, M. Paradise, A. S. Coletti, M. Gross, T. R. Fleming, S. Buchbinder, R. C. Haggitt, H. Levine, C. W. Kelly, and C. L. Celum, Safety and toxicity of Nonoxynol-9 gel as a rectal microbicide. Sex Transm Infect 26 (1999) 564-571.

[2] D. M. Phillips, C. L. Taylor, V. R. Zacharopoulos, and R. A. Maguire, Nonoxynol-9 causes rapid exfoliation of sheets of rectal epithelium. Contraception 62 (2000) 149-154.

[3] D. M. Phillips, K. M. Sudol, C. L. Taylor, L. Guichard, R. Elsen, and R. A. Maguire, Lubricants containing N-9 may enhance rectal transmission of HIV and other STIs. Contraception 70 (2004) 107-110.

[4] L. Van Damme, G. Ramjee, M. Alary, B. Vuylsteke, V. Chandeying, H. Rees, P. Sirivongrangson, L. Mukenge-Tshibaka, V. Ettiegne-Traore, C. Uaheowitchai, S. S. Karim, B. Masse, J. Perriens, and M. Laga, Effectiveness Of Col-1492, A Nonoxynol-9 vaginal gel, on HIV-1 transmission in female sex workers: A randomised controlled trial. Lancet 360 (2002) 971-977.

[5] D. M. Phillips and V. R. Zacharopoulos, Nonoxynol-9 enhances rectal infection by herpes simplex virus in mice. Contraception 57 (1998) 341-348.

[6] D. L. Patton, Y. T. Cosgrove Sweeney, L. K. Rabe, and S. L. Hillier, rectal applications of Nonoxynol-9 cause tissue disruption in a monkey model. Sex Transm Dis 29 (2002) 581-587.

[7] C. C. Tsai, P. Emau, Y. Jiang, B. Tian, W. R. Morton, K. R. Gustafson, and M. R. Boyd, Cyanovirin-N gel as a topical microbicide prevents rectal transmission of SHIV89.6P in macaques. AIDS Res Hum Retroviruses 19 (2003) 535-541.

[8] R. J. Shattock and J. P. Moore, Inhibiting sexual transmission of HIV-1 infection. Nat Rev Microbiol 1 (2003) 25-34.

[9] B. A. Koblin, M. A. Chesney, M. J. Husnik, S. Bozeman, C. L. Celum, S. Buchbinder, K. Mayer, D. McKirnan, F. N. Judson, Y. Huang, and T. J. Coates, High-risk behaviors among men who have sex with men in 6 us cities: Baseline data from the explore study. Am J Public Health 93 (2003) 926-932.

[10] D. H. Osmond, K. Page, J. Wiley, K. Garrett, H. W. Sheppard, A. R. Moss, L. Schrager, and W. Winkelstein, HIV infection in homosexual and bisexual men 18 to 29 years of age: The San Francisco young men's health study. Am J Public Health 84 (1994) 1933-1937.

[11] C. A. Van Beneden, K. O'Brien, S. Modesitt, S. Yusem, A. Rose, and D. Fleming, Sexual behaviors in an urban bathhouse 15 years into the HIV epidemic. J Acquir Immune Defic Syndr 30 (2002) 522-526.

[12] W. J. Woods and D. Binson, Public health policy and gay bathhouses. J Homosex 44 (2003) 1-21.

[13] W. J. Woods, D. Tracy, and D. Binson, Number and distribution of gay bathhouses in the united states and canada. J Homosex 44 (2003) 55-70.

[14] R. M. Shilts, And the band played on: Politics, people, and the AIDS epidemic. 1 (1987)

[15] W. J. Woods, D. K. Binson, T. J. Mayne, L. R. Gore, and G. M. Rebchook, HIV/sexually transmitted disease education and prevention in us bathhouse and sex club environments. AIDS 14 (2000) 625-626.

[16] D. Binson, W. J. Woods, L. Pollack, J. Paul, R. Stall, and J. A. Catania, Differential HIV risk in bathhouses and public cruising areas. Am J Public Health 91 (2001) 1482-1486.
[17] F. Spielberg, B. M. Branson, G. M. Goldbaum, A. Kurth, and R. W. Wood, Designing an HIV counseling and testing program for bathhouses: The seattle experience with strategies to improve acceptability. J Homosex 44 (2003) 203-220.
[18] Anderson R.M. and May R.M., Infectious diseases of humans. 1 (1992)
[19] S. M. Blower and Dowlatabadi H., Sensitivity and uncertainty analysis of complex models of disease transmission: an HIV model, as an example. Int Stat Rev 2 (1994) 229-243.
[20] M. A. Sanchez and S. M. Blower, Uncertainty and sensitivity analysis of the basic reproductive rate. Tuberculosis as an example. Am J Epidemiol 145 (1997) 1127-1137.
[21] G. Mansergh, G. N. Colfax, G. Marks, M. Rader, R. Guzman, and S. Buchbinder, The circuit party men's health survey: Findings and implications for gay and bisexual men. Am J Public Health 91 (2001) 953-958.
[22] G. Mansergh, G. Marks, M. Rader, G. N. Colfax, and S. Buchbinder, Rectal use of Nonoxynol-9 among men who have sex with men. AIDS 17 (2003) 905-909.
[23] M. Gross, C. L. Celum, S. R. Tabet, C. W. Kelly, A. S. Coletti, and M. A. Chesney, Acceptability of a bioadhesive Nonoxynol-9 gel delivered by an applicator as a rectal microbicide. Sex Transm Dis 26 (1999) 572-578.
[24] G. Mansergh, G. Marks, G. N. Colfax, R. Guzman, M. Rader, and S. Buchbinder, BarebackingÏn a diverse sample of men who have sex with men. AIDS 16 (2002) 653-659.
[25] P. N. Halkitis, J. T. Parsons, and L. Wilton, Barebacking among gay and bisexual men in New York City: Explanations for the emergence of intentional unsafe behavior. Arch Sex Behav 32 (2003) 351-357.
[26] S. Y. Chen, S. Gibson, D. Weide, and W. McFarland, Unprotected anal intercourse between potentially HIV-Serodiscordant men who have sex with men, San Francisco. J Acquir Immune Defic Syndr 33 (2003) 166-170.
[27] M. Gross, S. P. Buchbinder, C. Celum, P. Heagerty, and G. R. Seage, III, Rectal microbicides for U.S. gay men. Are clinical trials needed? Are they feasible? HIVnet vaccine preparedness study protocol team. Sex Transm Dis 25 (1998) 296-302.
[28] M. Rader, G. Marks, G. Mansergh, N. Crepaz, L. C. Miller, P. R. Appleby, and S. Murphy, Preferences about the characteristics of future HIV prevention products among men who have sex with men. AIDS Educ Prev 13 (2001) 149-159.
[29] L. Misegades, K. Page-Shafer, D. Halperin, and W. McFarland, Anal intercourse among young low-income women in California: An overlooked risk factor for HIV? AIDS 15 (2001) 534-535.
[30] P. I. Erickson, R. Bastani, A. E. Maxwell, A. C. Marcus, F. J. Capell, and K. X. Yan, Prevalence of anal sex among heterosexuals in California and its relationship to other AIDS risk behaviors. AIDS Educ Prev 7 (1995) 477-493.
[31] E. Vittinghoff, J. Douglas, F. Judson, D. McKirnan, K. MacQueen, and S. P. Buchbinder, Per-contact risk of human immunodeficiency virus transmission between male sexual partners. Am J Epidemiol 150 (1999) 306-311.
[32] N. Padian, L. Marquis, D. P. Francis, R. E. Anderson, G. W. Rutherford, P. M. O'Malley, and W. Winkelstein, Jr., Male-to-female transmission of human immunodeficiency virus. JAMA 258 (1987) 788-790.
[33] T. C. Porco, J. N. Martin, K. A. Page-Shafer, A. Cheng, E. Charlebois, R. M. Grant, and D. H. Osmond, Decline in HIV infectivity following the introduction of highly active antiretroviral therapy. AIDS 18 (2004) 81-88.
[34] S.M. Blower, H.B. Gershengorn and R.M. Grant, A tale of two futures: HIV and antiretroviral therapy in San Francisco. Science 287 (2000) 650-654.
[35] S.M. Blower and A.R. McLean, Prophylactic vaccines, risk behavior change & the probability of eradicating HIV in San Francisco. Science 265 (1994) 1451-1454.

E-mail address: breban@ucla.edu
E-mail address: IMcGowan@mednet.ucla.edu
E-mail address: topaz@ucla.edu
E-mail address: es@ucla.edu
E-mail address: PAnton@mednet.ucla.edu
E-mail address: sblower@mednet.ucla.edu