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行政院衛生署疾病管制局九十二年度科技研究發展計畫

台灣地區愛滋病流行病學之數學及統計研究

研 究 報 告

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目　　錄

一、中文摘要

1．利用近年來臺北市同志三溫暖愛滋病篩檢數據以及統計貝氏分析，來估計臺北市同志三溫暖常客中愛滋病被感染者的總數，並可進而推算臺北地區同志三溫暖常客等高危險族群之總人數。

2．利用近年來臺灣地區愛滋病感染者追蹤治療病毒量數據資料,估計愛滋病感染者病毒量增減之 viral trajectory，以了解雞尾酒療法(HARRT)對臺灣地區愛滋病感染者之療效，而我們的結果顯示雞尾酒療法具有壓抑病毒量之功效。

3．利用近年來臺灣地區愛滋病感染者相關追蹤治療數據資料，估計臺灣地區愛滋病感染者愛滋病診斷到愛滋病發(ADI)時間及愛滋病發(ADI)到死亡時間(survival time)。以了解雞尾酒治療法**(HAART)**對臺灣地區愛滋病感染者之療效，而我們的結果顯示雞尾酒療法具有顯著延緩發病及死亡之功效。

關鍵詞：愛滋病流行病學、數學模式、經驗貝氏分析、高危險族群、雞尾酒治療法

二、英文摘要

1. To estimate the number of HIV-infected persons in hard-to-count, high-risk Men who have Sex with Men (MSM) groups from data of a voluntary HIV serotesting program targeted at the high-risk group of gay saunas patrons in Taipei area.
2. Using longitudinal viral load data from a clinical study of HIV-infected patients in Taiwan, we described the viral trajectories by applying a nonparametric mixed-effects model. We were then able to compare the efficacies of highly active antiretroviral therapy (HAART) and conventional therapy by using Young and Bowman's (1995) test.
3. Using longitudinal data from a clinical study of HIV-infected patients in Taiwan, we estimate the survival time to ascertain the efficacy of highly active antiretroviral therapy (HAART).

Keyword: HIV/AIDS, Mathematical model, generalized removal model, HAART, empirical Bayesian analysis

三、前言

我國衛生署疾病管制局多年來收集了完整的臺灣地區愛滋病相關數據，但尚未進一步分析研究如臺灣地區愛滋病潛伏期等議題。本計畫將收集整理衛生署疾病管制局現有臺灣地區愛滋病相關資料及近年來臺灣地區愛滋病感染者相關追蹤治療數據資料，來估計臺灣地區愛滋病潛伏期(incubation period)、viral progression等重要流行病參數。

研究計劃以數學及統計分析兩大方面進行臺灣地區愛滋病流行病學之研究。主要三項成果將分述於以下”**方法、結果與參考文獻**”部分。

四、方法、結果與參考文獻

1. Estimating the HIV-infected Population Size in Hard-to-count Men Who have Sex with Men groups: the case of gay saunas patrons in Taipei

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ABSTRACT

Objectives: To estimate the number of HIV-infected persons in hard-to-count, high-risk Men who have Sex with Men (MSM) groups from data of a voluntary HIV serotesting program targeted at the high-risk group of gay saunas patrons in Taipei area.

Methods: From August of 1999, voluntary HIV and syphilis tests were conducted at five gay saunas in Taipei. The HIV-serotesting results were subsequently used to estimate the number of HIV-positive population among men having sex with men (MSM) who are frequent customers of the gay saunas by utilizing the Generalized Removal Model for Open Populations (GERMO). Correction for data measurement error was performed to alleviate the effect of an anonymous HIV quick test program, initiated in 2001, in close proximity to the area where the gay saunas are situated.

Results: The median estimates for the number of HIV-positive persons among patrons of the five gay saunas in Taipei increase from 120 during the first half of 2000 to 224 for the second half of 2002.

Conclusion: The result indicates steady two-fold increase in the number of HIV-infect persons among these gay sauna patrons during the three-year period from 2000 to 2002. Given that dozens of similar gay saunas are scattered in every metropolitan area in Taiwan, it is clear that: (i) The gay sauna patrons are, without a doubt, a prominent high-risk group in Taiwan for

the spread of HIV/AIDS; (ii) This serotesting program is highly effective in detection and prevention of additional cases.

Key words: HIV/AIDS, MSM, generalized removal model, serotesting, gay sauna, measurement error correction, Taiwan.

Introduction

Male-male sexual activity has existed across cultural barrier throughout the history of mankind. However, due to traditional social norms, the men who have sex with men (MSM) population has been elusive and difficult to track. In many countries around the world, the incidence of Human Immunodeficiency virus (HIV) infections and Acquired Immunodeficiency Syndrome (AIDS) is most prevalent among MSM population [1-6]. Indeed, when the illness was first identified in 1981, it was termed as Gay-Related Immune Deficiency (GRID) for its initial prevalence in the gay community in United States. Due to traditional cultural norms and social stigma in many countries, the MSM population has always been effusive and hard to count. Consequently, regardless of the degree of openness of the society in question, the greatest difficulty in determinating the HIV prevalence in a certain MSM population is often the lack of knowledge concerning the actual size of that population group [7-9]. Fining a solution to this endeavor is especially crucial given that the MSM population is often used as a sentinel population for HIV epidemiology [7,10].

Recently, an estimation method named “Generalized Removal Model for Open populations”, or GERMO, was proposed to estimate the HIV-infected population size among specific population groups such as intravenous drug users (IVDU), sex workers, and sexually active individuals in a society [11-14]. Moreover, the results from the estimation procedure can be used to estimate the size of that hard-to-count, high-risk population group [15], which is crucial for the purpose of public health intervention measures. The method requires two or more random samples of serotesting of the given population group carried out at different sampling time. In this work, we will implement the procedure to determine the HIV-infected population size among the gay sauna patron population in Taipei area.

Since the first HIV/AIDS case in 1984, Taiwan has had a comparatively small HIV incidence. Through the end of 2002, there were a total of 4373 Taiwanese nationals infected with HIV/AIDS. Out of which 4055 (92.7%) were males. Moreover, 2152 (49.2%) were reported to be homosexual/bisexual persons. Therefore, MSM account for almost half of the HIV-infected population in Taiwan. There are three main types of MSM populations in Taiwan distinguished by their meeting places: gay saunas, gay bars, and public parks, with very little interaction between the three groups [16]. By its nature, saunas provide a more convenient location for sex to take place. Consequently the gay sauna patrons conceivably are more sexually active and at higher-risk than the other groups. In August of 1999, a voluntary HIV serotesting program was launched aiming at the customers of five gay saunas in Taipei, mainly in the Shi Meng Ding District. During the three years from 2000-2002, 81 HIV-positive

cases were detected through this program. It is worthwhile to note that during this same time period, the total number of new HIV/AIDS cases is 1955, which means that 4.14% of all new HIV cases in Taiwan during these three years came from the customers of these five gay saunas in Taipei (Table 1). Moreover, the prevalence rate of this gay sauna serotesting program over the same time period is 7.00% (81 out of 1191), much higher than that of any other risk group in Taiwan [17].

In a related study [18] of 589 gay sauna patrons in Taiwan, including those taking part in the gay sauna serotesting program in Taipei, responses to questionnaire on sexual behavior from the 589 participants have also shown that the 21.7% of those participated in the program frequented the gay saunas at least once a week, 79.7% visited the saunas at once a month, and 91.7% of all participants have sex in the gay saunas with at least 1-2 persons during each visit. Moreover, only 43.5% of the participants always or often bring their own condoms when they visit the gay sunas and, despite of all these gay saunas having free condoms available on demand, almost half (46.6%) of all participants never asked for condoms even though 48.3% of them practice anal sex at least occasionally. Clearly, these are strong indications that safe sex is not being practiced in these establishments.

To gain insight into the true extension of HIV prevalence among the gay sauna patron population while the population size is unknown, we make use of the serotesting result to estimate the number of HIV-infected persons among the men having sex with men who frequent the five saunas in Taipei by utilizing the

GERMO model. The idea is to consider the serotesting data as random samples from the gay sauna patrons of the MSM group in Taipei area. The result will give indications on the level of underreporting in this concentrated, effusive population, as well as estimates for its size.

Materials and Methods

Study subjects

To provide anonymous HIV-1 antibody and syphilis tests, together with pre-test counseling and condoms, a team comprised of a researcher, a nurse, and peer educators paid regular visits to five gay saunas in Taipei starting August of 1999. The visits were under prior consent from the gay sauna owners, and usually with posters at the entrances announcing the visits. Moreover, announcement was made over public announcement system of the establishments to encourage voluntary participation. In addition to taking blood samples, the participants were also encouraged, but not required, to fill in a questionnaire. The antibody and syphilis testing were done at Taipei Municipal STD Control Center (TSTDCC). The subjects would contact by phone in two weeks to learn the test results, with those tested positive being provided the full opportunity for clinical healthcare at a clinic of his choice. The result of the serotests for HIV-1 and syphilis in six-month periods from August 1999 to the end of 2002 is given in Table 2.

However, starting in 2001, an anonymous quick HIV-testing program was launched at TSTDCC, located in the busy Shi Meng Ding District of Taipei where four of the five gay saunas are located. Person taking the quick test can

come to TSTDCC voluntarily for blood sample and call back a week later to learn the testing result. Comparing the serotesting results of 2000 and 2001 in Table 2 shows that, from the half year prior to the initiation of the quick testing program (July-December, 2000) to the first half year of the quick test (January-June, 2001), there is a sharp decrease in the number of tests taken, as well in the number of HIV-positive tests and the prevalence rate. Since several of the gay saunas taking part in the gay sauna testing programs are within short walking distance from TSTDCC, those who are more inclined to participate in the program are also more likely to want to take the voluntary quick test at TSTDCC. It is then intuitive that the quick test program at TSTDCC has affected the data collected from the gay sauna testing program by detecting some HIV-positive persons who otherwise might have been tested and detected through the gay sauna testing program. Unfortunately, due to the anonymous nature of both programs, we are unable to identify the overlapping population. However, the quick test program has detected many HIV-positive persons who are MSM. From the follow-up (also voluntary) questionnaire for the HIV-positive persons, the quick test program has identified at least 21 HIV-positive MSM's during January-November of 2001 – more than the number of HIV-positive persons detected through the gay sauna testing program during the same period. Although there is no data on how many of these 21 persons were in fact gay sauna patrons, it appears safe to assume that this program has had some effect on the gay sauna testing. We will propose a method to rectify this problem in the next section.

Correction for measurement error

We will consider the effect of quick test on the gay sauna serotesting data as a measurement error occurred at the time of data collection. Moreover, the measurement error problem may be considered as an extreme case of the missing data. Data measured with error are very common in epidemiological studies. The regression calibration method is a useful tool in the missing data and measurement error problem [19]. It is a type of imputation, or a replacement of a missing data. In medical studies, this method is often used for correction of measurement error in covariates.

The association between HIV infection and sexual-transmitted diseases (STD), in particular syphilis (STS) and gonorrhea, is well-documented [20-24]. Therefore we will make use of the syphilis serotesting data in our effort to correct measurement errors in the HIV serotesting data caused by the initiation of the quick test program after 2001, by assuming that the HIV quick test program has no affect on the syphilis test results. We let V_{i1}, V_{i2}, and V_{i3} denote the respective numbers of seropositive tests taken at gay saunas, those tested HIV-positive, and those tested STS-positive at time i. We use the scatter plot and the Spearman's ρ correlation test to examine the linear relationship between those tested HIV-positive and those tested STS-positive. The plots show that there is a strong positively linear relationship between V_{i1} and V_{i2}, as well as between V_{i2} and V_{i3}. The estimates of Spearman's ρ correlation coefficients and p values of $H_0: \rho = 0$ for any two variables are

given in Table 3. The details of the method and the scatter plots (Figures 1-2) are given in Appendix I.

The predicted value of V_{32} from the correction of measurement error is

$$\hat{V}_2 = .65943V_3$$

with V_3=17. Consequently we use $\hat{V}_{32}$=11 to correct for measurement error in replacement of V_{32}=6 for the estimation procedure using GERMO.

Statistical Method: Generalized removal model for open populations (GERMO)

In our model, we make an assumption that the probability of HIV infections in *j*th sample is proportional to the *j*th sample size of serotests. We let N_j be the total number of subjects in HIV-infected population just before time t_j. Suppose u_j the number of distinct HIV-infected detected in the first *j*th sample. Therefore, $M_{j+1} = u_1 + \cdots u_j$ is the number of observed HIV-infected individuals in the first *j* samples.

The estimation procedures of Bayesian analysis are outlined as follows:

Step 1: Choose the prior distribution $p(\Theta)$ given by:

$$\pi(\Theta) = \pi(N, p) = \pi(\underset{\sim}{N}_1, N_2, ..., N_s)\pi(p),$$

where $\pi(p) = I(\frac{\alpha}{4} < p < \frac{7\alpha}{4})$.

$I(\cdot)$ is the indicator function with $I(A) = 1$ if the event A is true, α is determined empirically [11].

Step 2: Sample iteratively from $p(\Theta \mid U)$, $U = (u_1, u_2, ...u_s)$, to generate a posterior sample $\Theta^1, ..., \Theta^n$, where n is set at 9,000. The sampling is done in two blocks, including $(N_1, N_2, ..., N_s)$ and p.

Step 3: Form $\hat{\Theta}$, the point estimate of Θ, as the sample mean of the posterior sample:

$$\hat{\Theta} = \frac{1}{n-m} \sum_{k=m+1}^{n} \Theta^k ,$$

where m = 3,000 is the number of burn-in iterations to attain convergence. More details of the above procedures are presented in Appendix II.

We assume that the natural mortality rate of the sexually active population during this time period is small compared to the AIDS-related death rate, since the majority (93%) of the subjects in question are of age 20-48 when the natural mortality is low. Moreover, small variation in natural mortality does not affect the result of our estimation [12]. The convergence of the Gibbs samplers are monitored by examining a procedure developed in Raftery and Lewis [25].

Results and Discussions

Using GERMO, we estimated number of HIV-infected persons among the gay

sauna patrons in Taipei during the half-year periods from 2000 to 2002. The result of our estimation procedure is given in Table 4. The median estimates give the estimated number of HIV-positive persons among the patrons of these five gay saunas in Taipei during the half-year periods. As there are dozens of similar gay sauna scattered in every metropolitan area in Taiwan, it is clear that: (i) The gay sauna patrons are, without a doubt, a prominent high-risk group in Taiwan for the spread of HIV/AIDS; (ii) This serotesting program has been highly effective in detection of new cases, with 4.14% of all new HIV cases in Taiwan detected through this program during 2000-2002, and subsequently the prevention of additional cases. Furthermore, it provides useful data to carry out studies which enhance our understanding of this highly effusive and hard-to-count but at the same time important population group for surveillance and intervention purposes.

To gauge the information provided by this estimation procedure, we further compute the estimated number of undetected HIV-positive persons during each half-year, by subtracting the number of detected HIV cases in Table 2 (with corrected data $\hat{V}_{32}$=11) from the median estimates of HIV-infected population in Table 4. The result is given in Table 5. The result shows a steady increase of the undetected HIV-positive persons among the gay sauna patrons, almost doubling in three years. There are alarmingly high percentages (almost half) of persons who do not use condoms and persons who engage in anal sex in the gay saunas [17]. Moreover, almost one out of three HIV-positive gay sauna patrons participated in a related study [17] describe themselves as bi-sexual while 35%

of all participants in the same study are of age 29 or under, with 82.6% of these people still unmarried. Clearly, the gay sauna patron group is potentially a core group for the spread of HIV/AIDS in the community, as well as being a high-risk group. The present result highlights the need for public health officials to target the concentrated group of gay sauna customers for prevention measures, prominent among which are education programs on the danger of HIV transmission given their current sexual behavior and the importance of practicing safe sex.

One can further make use of the estimated number of HIV-positive persons in a population group to make estimates of the actual population size by simply dividing the estimated number of HIV-infected person by the HIV seroprevalence rate [15]. However its accuracy is highly dependent on the data available for the estimation. Seasonality in data might also be a factor, as the estimates for second half-years are always much higher than those of the first half-years.

As with any estimation methods, there are limitations to our procedure. Detailed discussions are given in [12]. For the present work, inconsistencies in the estimates as a result of the random sampling assumptions are very likely to occur, due to the use of data from the voluntary serotesting program. Any improvement in this direction, however, is difficult since data of this nature (i.e. data of hard-to-count populations) is difficult to obtain.

Appendix I. Correction of measurement error

Let V_{i1}, V_{i2}, and V_{i3} denote the respective numbers of seropositive tests taken at gay saunas, HIV+, and STS+ at time i. The pairs plot for the data is given in Figure 1 with the pairs plot for the data for time $i = 3$ deleted in Figure 2.

The plots show that there is a strong positively linear relationship between V_{i1} and V_{i2}, as well as between V_{i2} and V_{i3}.

The estimates of Spearman's ρ correlation coefficients and p values of $H_0: \rho = 0$ for any two variables are as given in Table 3. There is strongly significant linear relationship between any pair of two variables, (V_{i1}, V_{i2}) and (V_{i2}, V_{i3}). The existence of high correlations between the independent variables in a regression model is known as multicolinearity. There is highly positive correlation between V_1 and V_3 ($\hat{\rho} = .943$). The major concern is that the stability of the regression coefficients is affected by multicolinearity. To avoid serious multicolinearity, the variation of V_{i2} is explained by a simple regression line with an explanatory variable, V_3. Consequently, we assume a simple linear regression model:

$$E(V_{i2} \mid V_{i1}, V_{i3}) = \beta_0 + \beta_1 V_{i3}. \qquad (1)$$

Moreover, β_0 is not significant from zero. Equation (1) then reduces to

$$E(V_{i2} \mid V_{i1}, V_{i3}) = \beta_1 V_{i3}. \qquad (2)$$

We use the notation V_{32}^* for the indicator of observing V_{32}. We consider the case that V_{32} is missing completely at random due to the newly implemented quick test program.

We have $V_{31} = 139$ and $V_{33} = 17$ which are the numbers of individuals tested and those with STS+, respectively at time *i=3*. Instead of observing V_{32}, the data point V_{32} is treated as a missing value. We use the conditional expectation to estimate it. The information of $V_{32} \geq V_{32}^*$ is useful. We use $\max\{\hat{\beta}_1 V_{i3}, V_{32}^*\}$ as a predicted value for V_{32} where $\hat{\beta}_1$ is the least squared estimate which are obtained from $(V_{i2}, V_{i3}),\ \ i = 1,3,4,5,6$ using least square method.

Appendix II. The generalized removal model for open populations (GERMO)

We consider a sequence of *s* samples taken from the seroprevalence data of gay saunas in Taipei. Let t_j be the time when the *jth* sample is taken and let B_j be the number of HIV-infected individuals newly infected sexually between time t_j and time t_{j+1}. We define N_j to be the total number of subjects in HIV-infected population just before time t_j, and $N_j = B_0 + \ldots + B_{j-1}$. Assume that the prevalence rate of HIV infections in *j*th sample is proportional to the

*j*th sample size of serotests. Define $e_j = e_j^* / e_1^*$, j=1, 2, …, s where e_j^* denotes the number of individuals taken a serotest in the *jth* sample. Suppose that *P* denotes the prevalence rate in the first sample. Then pe_j is the prevalence rate in the *jth* sample.

The likelihood function can be obtained as follows:

$$L(B,P\,|\,D) \propto \left\{ \prod_{j=1}^{s} \binom{N_j - M_j}{u_j} (pe_j^*)^{u_j} (1-pe_j^*)^{N_j - M_{j+1}} \right\},$$

where D $= \{u_1, \cdots, u_s\}$, B = $(B_0, \cdots, B_{s-1})$, and u_j the number of distinct HIV-infected found in the *j*th sample. Therefore, $M_{j+1} = u_1 + \cdots u_j$ is the number of observed HIV-infected individuals in the first *j* samples. We call this model a generalized removal model for open populations due to the removal of the observed HIV-infected individuals from the (open) sexually active population, M_j, *j*=1, 2,…, in each sampling occasion.

Suppose that the prior distribution of (N, P) where $\mathbf{N} = (N_1, \cdots N_s)$ is given by $\pi(\mathbf{N},\mathbf{P}) = \pi(N_1, \cdots N_s)\pi(\mathbf{P})$. This asserts that N and P are *a priori* independent. We assume that $\pi(p) = I(\frac{\alpha}{4} < p < \frac{7\alpha}{4})$, I (·) is an indicator function that I (*A*) = 1 if the event *A* is true. The value of α is determined by solving the equation $\alpha = E(pe_1) \approx 1 - \{E(u_2)e_1\}/\{E(u_1)e_2\}$. Suppose that

$$\pi(N_1,\cdots,N_s) = I(N_1 \le \cdots \le N_s)$$

Such priors lead to conditional posteriors of the forms:

$$\pi(P \mid \mathrm{N}, D) \propto P^{u_1+\ldots+u_s} \prod_{j=1}^{s} (1-pe_j)^{N_j - M_{j+1}} \tag{3}$$

$$\pi(N_j \mid \mathrm{N}_{(-j)}, P, D) = \frac{\binom{(N_j - M_{j+1} + (u_j+1)) - 1}{u_j} (pe_j)^{u_j} (1-Pe_j)^{N_j - M_{j+1}}}{\sum_{N_j = \max\{N_j, R_j, M_{j+1}\}}^{N_{j+1}} \binom{(N_j - M_{j+1}) + (u_j+1) - 1}{u_j} (Pe_j)^{u_j} (1-Pe_j)^{N_j - M_{j+1}}} \tag{4}$$

where $\mathrm{N}_{(-j)}$ denotes the vector N with the N_j deleted. $(N_j - M_{j+1})$ follows a truncated negative binomial distribution. Subsequently one can easily implement the Gibbs sampler to generate $(N_j - M_{j+1})$ from the truncated negative binomial in Equation (4), and therefore the estimates of N_j can be obtained.

Since there are AIDS-related deaths during the process, we define the yearly survival rate specific to an HIV-infected individual between the (j-1)th and jth sample to be ϕ. The conditional expectations of M_{j+1} and N_{j+1} for (j+1)th sample given M_j (the number of distinct HIV-infected individuals captured in the first j-1 samples) and N_j (the total number of subjects in HIV-infected population just before time t_j), respectively, are

$$E(M_{j+1} \mid M_j) = \phi M_j + u_j \quad \text{and} \quad E(N_{j+1} \mid N_j) = \phi N_j + B_j \,. \qquad (5)$$

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Table 1. The number of new HIV/HIV cases in Taiwan from 1997 to 2002, and the number of new cases detected through the gay sauna testing program in Taipei.

Year	# of new HIV/AIDS cases in Taiwan	# of new AIDS cases in Taiwan	# of HIV cases from gay sauna testing in Taipei (starting in August of 1999)
`1997	350	134	0
1998	402	152	0
1999	478	176	3
2000	534	177	31
2001	652	158	18
2002	769	176	32

Table 2. The serotesting result from the gay sauna testing program in Taipei from August 1999 to the end of 2002.

Time Period	# tested	# of HIV+	% of HIV+	# of STS+	% of STS+	# of HIV+ and STS+
1999, Aug-Dec	58	3	5.17	9	15.51	1
2000, Jan-Jun	63	7	11.11	7	11.11	3
2000, Jul-Dec	273	24	8.79	36	13.19	7
2001, Jan-Jun	139	6	4.32	17	12.23	1
2001, Jul-Dec	178	12	6.74	14	7.87	4
2002, Jan-Jun	213	19	8.92	23	10.80	7
2002, Jul-Dec	265	13	4.91	28	10.57	10

Table 3: The estimates of Spearman's ρ correlation coefficients. The values in parentheses are the p values for $H_0: \rho = 0$.

		V_1	V_2	V_3
N=6	V_1	1.000*	.886*	.943*
		(.0000)	(.019)	(.005)
	V_2	.886*	1.00*	.771*
		(.019)	(.0000)	(.072)
	V_3	.943*	.771*	1.000*
		(.005)	(.072)	(.0000)
N=5	V_1	1.000*	.900*	1.000*
(without i=3)		(.0000)	(.037)	(.0000)
	V_2	.900*	1.000*	.9000*
		(.037)	(.0000)	(.037)
	V_3	1.000*	.9000*	1.000*
		(.0000)	(.037)	(.0000)

"*" denotes the value being significant at 5%.

Table 4. Summary statistics of the total number of HIV-infected gay sauna patrons in Taipei during 2000-2002. For the median estimates, fractions are taken to be 1.

Time Period	median	mean	SD	95% C.I. lower bound	95% C.I upper bound.
2000, Jan-Jun	120	118.5	21.4	76.5	159.0
2000, Jul-Dec	150	149.5	18.0	111.5	180.5
2001, Jan-Jun	166	164.6	18.6	124.5	197.0
2001, Jul-Dec	186	184.4	19.4	142.5	217.0
2002, Jan-Jun	207	206.1	20.7	159.5	243.0
2002, Jul-Dec	224	222.7	22.9	171.0	265.5

Table 5. The estimated number of undetected HIV-positive gay sauna patrons in Taipei during 2000-2002.

Time Period	# of undetected HIV-positive persons	95% C.I. lower bound	95% C.I upper bound.
2000, Jan-Jun	113	70	152
2000, Jul-Dec	126	88	157
2001, Jan-Jun	155	114	186
2001, Jul-Dec	174	131	205
2002, Jan-Jun	188	141	224
2002, Jul-Dec	211	158	253

Figures

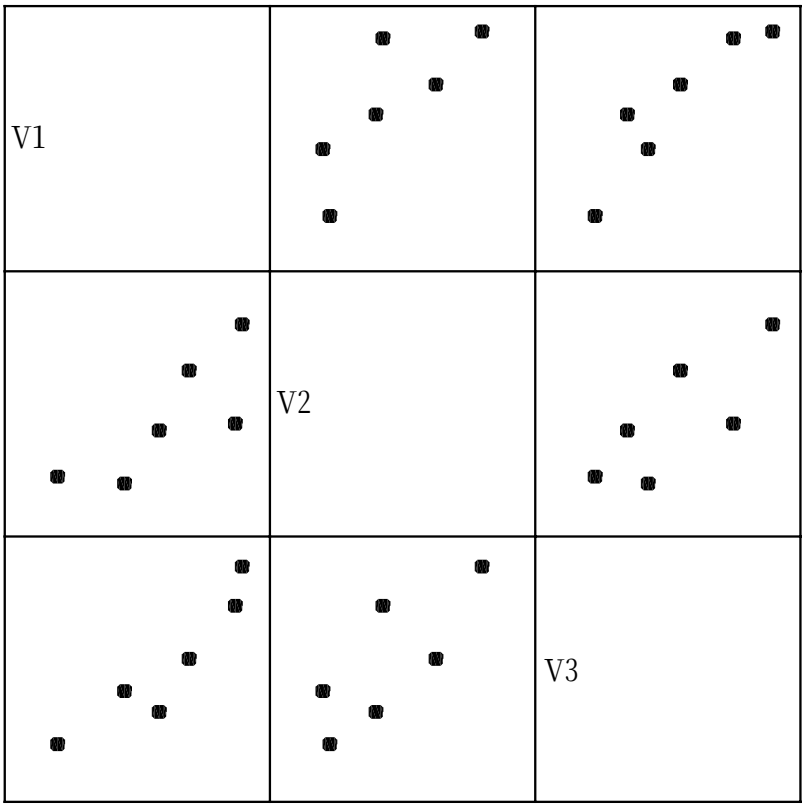

Figure 1. Pairs plot for the Taipei gay saunas HIV serotesting data in Table 2. V_1, V_2, and V_3 denote the columns and rows with for gay saunas, HIV+, and STS+, respectively.

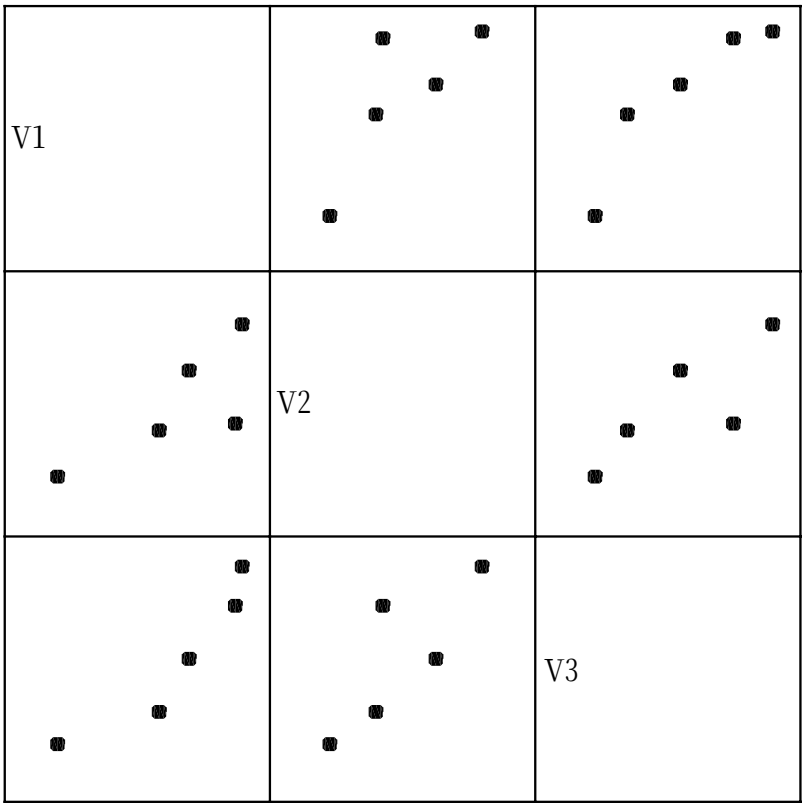

Figure 2. Pairs plot for the Taipei gay saunas HIV serotesting data in Table 2 with the data for time $i = 3$ deleted. V_1, V_2, and V_3 denote the columns and rows with for gay saunas, HIV+, and STS+, respectively.

2.Comparison of viral trajectories in AIDS Studies by using nonparametric mixed-effects models

(accetped manuscript)

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Summary. The efficacy of antiretroviral therapies for human immunodeficiency virus (HIV) infection can be assessed by studying the trajectory of the changing viral load with treatment time, but estimation of viral trajectory parameters by using the implicit function form of linear and nonlinear parametric models can be problematic. Therefore, using longitudinal viral load data from a clinical study of HIV-infected patients in Taiwan, we described the viral trajectories by applying a nonparametric mixed-effects model. We were then able to compare the efficacies of highly active antiretroviral therapy (HAART) and conventional therapy by using Young and Bowman's (1995) test.

Keywords: AIDS clinical trial; HIV dynamics; Longitudinal data; Kernel regression; Nonparametric mixed-effects model; viral load trajectory.

Short title: Study of Viral Trajectory

1 Introduction

Surrogate viral markers, such as the amount of HIV RNA in the plasma (the amount of HIV RNA in the patient's plasma represents the patient's viral load), currently play important roles in clinical research evaluating antiviral therapies for the acquired immunodeficiency syndrome (AIDS). Before HIV RNA assays were developed in mid-1990s, CD4+ cell counts served as the primary surrogate marker in AIDS clinical trials. Later, the amount of HIV RNA in the patient's plasma (viral load, measured as the copy number of the viral RNA) was shown to better predict the clinical outcome (Mellors *et al.*, 1995; Mellors *et al.*, 1996; Saag *et al.*, 1996), and thus replaced CD4+ cell counts as the primary surrogate marker used in most AIDS clinical trials. It is, therefore, important to characterize the trajectory that describes the change in viral load that occurs during antiviral treatment, because it is this trajectory that is commonly used to evaluate the efficacy of the treatment. For example, if the viral load reduces, we may infer that the treatment has successfully suppressed the replication of the virus. The differences between the viral loads resulting from different antiviral treatments may be used to compare the antiviral activities of the treatments. Appropriate analysis of the viral load is therefore very important in HIV/AIDS drug development. In general, it is believed that the replication of the virus is suppressed at the beginning of an antiviral treatment, but recovery of the virus (called rebound) can occur in later stages of treatment, because of drug resistance or treatment failure. Some parametric models have been developed to describe the progression of AIDS phenomenologically; among the best known of these models are the exponential models (Ho *et al.*, 1995; Wei *et al.*, 1995). More recently, biomathematicians and biologists have proposed a variety of complicated models that include the use of differential equations. The

use of these models has led to a deeper understanding of the pathogenesis of AIDS (e.g., Perelson and Nelson, 1999; Wu and Ding, 1999). In recent years, the necessity for appropriate models has gained more importance with the widespread use of highly active antiretroviral therapy (HAART) to treat HIV/AIDS (Ghani *et al.*, 2003). Numerous studies have shown that HAART is effective in extending the time taken from the diagnosis of HIV-infection to AIDS or death in HIV-infected patients (e.g., Detels *et al.*, 1998; Tassie *et al.*, 2002) as well as reducing the likelihood of perinatal HIV transmission (Cooper *et al.* 2002). However, in many clinical practices, combination antiviral therapy has failed to completely and durably suppress HIV replication (e.g., Deeks *et al.*, 1999).

To determine the efficacy of treatments in suppressing HIV replication in patients, the present study focuses on the following questions: (i) Given longitudinal viral load data, how can one identify a common feature of the antiviral activities of each treatment? (ii) How can we compare the antiviral efficacies of two different treatments? If we can answer question (ii), we may be able to demonstrate that the better treatment should be evaluated in a large-scale clinical study. However, it may be difficult to answer these questions by using existing parametric or semiparametric methods. To sufficiently consider all of the information available from the observations, and to avoid the misspecification of parametric modeling, we will use a nonparametric mixed-effects model to analyze the longitudinal viral load data, and we will incorporate the local linear approximation technique developed by Wu and Zhang (2002). The test statistic proposed by Young and Bowman (1995) will then be used to answer question (ii).

The remainder of this paper is organized as follows. In Section 2, we give details of the proposed model, with the method of estimation, and use the test statistic of Young and Bowman (1995) to determine whether

there is a difference between the effects of two treatments. In Section 3, we illustrate the use of the proposed methodology with longitudinal viral load data from 30 HIV-infected patients treated with HAART alone and another 30 patients treated with monotherapy or dual therapy. Some discussion is given in Section 4.

2 Nonparametric models and estimation methods

We fit the viral load trajectory data for treatment by using a nonparametric mixed-effects (NPME) model:

$$y_i(t) = \log_{10}\{V_i(t)\} = \eta(t) + v_i(t) + \varepsilon_i(t), \quad i = 1, 2, \cdots, n, \qquad (2.1)$$

where $V_i(t)$ is the number of copies of HIV-1 RNA per mL of plasma at treatment time t for the ith patient and $Y_i(t)$ is the corresponding value in $\log_{10}$ scale. $\eta(t)$ describes the population mean function, also called the fixed-effects or population curve. We are mainly concerned with the estimation of the fixed-effect (population) curve $\eta(t)$, which is very important because it reflects the overall trend or progress of the treatment process in an HIV-infected population and can provide an important index of the population's response to a drug or treatment in a clinical or biomedical study. $v_i(t)$ model individual curve variations from the population curve $\eta(t)$ and these variations are called random-effects curves, and $\varepsilon_i(t)$ are measurement errors. $v_i(t)$ and $\varepsilon_i(t)$ are assumed to be independent; $v_i(t)$ can be considered as realizations of a mean 0 process with a covariance function $\gamma(s,t) = \mathrm{E}(v_i(s)v_i(t))$, and $\varepsilon_i(t)$ can be considered as realizations of an uncorrelated mean 0 process with variance $\sigma^2(t)$. In addition, an individual curve $s_i(t) = \eta(t) + v_i(t)$ can represent an individual's response to a treatment in a study, so a good estimate of $s_i(t)$ would help the investigator to make better decisions about an individual's treatment management

and would enable us to classify subjects on the basis of individual response curves. Similar models have been proposed by Shi *et al.* (1996) and Zeger and Diggle (1994) to describe CD4+ cell counts.

Let t_{gij}, $j = 1, 2, \ldots, n_{gi}$, be the design time points for the ith individual in treatment group g. Then, NPME model (2.1) becomes

$$\begin{aligned} & y_{gi}(t_{gij}) = \eta_g(t_{gij}) + v_{gi}(t_{gij}) + \varepsilon_{gi}(t_{gij}), \\ & j = 1, 2, \ldots, n_{gi}; i = 1, 2, \ldots, n_g; g = 1, 2. \end{aligned} \tag{2.2}$$

Here, n_g is the number of subjects in treatment group g, and n_{gi} is the number of measurements made from subject i in treatment group g. We now wish to estimate $\eta_g(t)$ and $v_{gi}(t)$ simultaneously, via a local approximation of the NPME model (2.2), by using the local linear mixed-effects model approach of Wu and Zhang (2002), which combines linear mixed-effects (LME) models (Laird and Ware, 1982) and local polynomial techniques (Fan and Gijbels, 1996). For this purpose, we assume the existence of the second derivatives of $\eta_g(t)$ and $v_{gi}(t)$ at t, which are then approximated locally by a polynomial of order 2 as follows:

$$\eta_g(t_{gij}) \approx \eta_g(t) + \eta_g'(t)(t_{gij} - t) \equiv X_{gij}^T \boldsymbol{\beta}_g$$

and

$$v_{gi}(t_{gij}) \approx v_{gi}(t) + v_{gi}'(t)(t_{gij} - t) \equiv X_{gij}^T \mathbf{b}_{gi},$$

where $X_{gij} = (1, (t_{gij} - t))^T$, $\boldsymbol{\beta}_g = (\eta_g(t), \eta_g'(t))^T$, and $\mathbf{b}_{gi} = (v_{gi}(t), v_{gi}'(t))^T$. Consequently, the NPME model (2.2) can be approximated by the following model:

$$\begin{aligned} & y_{gij} = X_{gij}^T(\boldsymbol{\beta}_g + \mathbf{b}_{gi}) + \varepsilon_{gij}, \\ & j = 1, 2, \ldots, n_{gi}; i = 1, 2, \ldots, n_g; g = 1, 2, \end{aligned} \tag{2.3}$$

which is called a LME model. Note that, for simplicity of notation, $y_{gij} = y_{gi}(t_{gij})$, $\varepsilon_{gij} = \varepsilon_{gi}(t_{gij})$, $\boldsymbol{\epsilon}_{gi} = (\varepsilon_{gi1}, \ldots, \varepsilon_{gin_{gi}})^T \sim N(\mathbf{0}, \boldsymbol{\Sigma}_{gi})$, and $\mathbf{b}_{gi} \sim N(\mathbf{0}, D_g)$ for $\boldsymbol{\Sigma}_{gi} = \mathrm{E}(\boldsymbol{\epsilon}_{gi}\boldsymbol{\epsilon}_{gi}^T)$ and $D_g = \mathrm{E}(\mathbf{b}_{gi}\mathbf{b}_{gi}^T)$.

We are interested in the estimate of $\eta_g(t)$, which is the first element of the estimate $\boldsymbol{\beta}_g$. Estimation of $\eta_g(t)$ can be accomplished under the standard normality assumptions for $\mathbf{b}_{gi}$ by minimizing the following objective function:

$$\sum_{i=1}^{n_g} \Big\{ \left(\mathbf{y}_{gi} - \mathbf{X}_{gi}(\boldsymbol{\beta}_g + \mathbf{b}_{gi})\right)^T \mathbf{K}_{gih}^{1/2} \boldsymbol{\Sigma}_{gi}^{-1} \mathbf{K}_{gih}^{1/2} \left(\mathbf{y}_{gi} - \mathbf{X}_{gi}(\boldsymbol{\beta}_g + \mathbf{b}_{gi})\right) + \mathbf{b}_{gi}^T D_g^{-1} \mathbf{b}_{gi} + \log|D_g| + \log|\boldsymbol{\Sigma}_{gi}| \Big\},$$

where $\mathbf{y}_{gi} = (y_{gi1}, \ldots, y_{gin_{gi}})^T$; $\mathbf{X}_{gi} = (X_{gi1}, \ldots, X_{gin_{gi}})^T$; $\mathbf{K}_{gi\lambda} = \text{diag}\{K_\lambda(t_{gij} - t), \ldots, K_\lambda(t_{gin_{gi}} - t)\}$ is the kernel weight of the residual term for $K_\lambda(\cdot) = K(\cdot/\lambda)/\lambda$, in which $K(\cdot)$ is a kernel function; h is a bandwidth selected by a leave-one-subject-out cross-validation approach (Wu and Zhang, 2002); and the term $\mathbf{b}_{gi}^T D_g^{-1} \mathbf{b}_{gi}$ is a penalty term to account for the random effects $\mathbf{b}_{gi}$, taking between-subject variation into account. Thus, for given $\boldsymbol{\Sigma}_{gi}$ and D_g, the resulting estimators can be obtained as follows:

$$\begin{aligned} \widehat{\boldsymbol{\beta}}_g &= \left(\sum_{i=1}^{n_g} \mathbf{X}_{gi}^T \boldsymbol{\Omega}_{gi} \mathbf{X}_{gi} \right)^{-1} \left(\sum_{i=1}^{n_g} \mathbf{X}_{gi}^T \boldsymbol{\Omega}_{gi} \mathbf{y}_{gi} \right) \\ \widehat{\mathbf{b}}_{gi} &= \left(\mathbf{X}_{gi}^T \mathbf{K}_{gih}^{1/2} \boldsymbol{\Sigma}_{gi}^{-1} \mathbf{K}_{gih}^{1/2} \mathbf{X}_{gi} + D_g^{-1} \right)^{-1} \\ &\qquad \mathbf{X}_{gi}^T \mathbf{K}_{gih}^{1/2} \boldsymbol{\Sigma}_{gi}^{-1} \mathbf{K}_{gih}^{1/2} (\mathbf{y}_{gi} - \mathbf{X}_{gi} \widehat{\boldsymbol{\beta}}_g), \end{aligned} \tag{2.4}$$

where $\boldsymbol{\Omega}_{gi} = \mathbf{K}_{gih}^{1/2} (\mathbf{K}_{gih}^{1/2} \mathbf{X}_{gi} D_g \mathbf{X}_{gi}^T \mathbf{K}_{gih}^{1/2} + \boldsymbol{\Sigma}_{gi})^{-1} \mathbf{K}_{gih}^{1/2}$. As a result, the estimators of $\eta_g(t)$ and $v_{gi}(t)$ are $\hat{\eta}_g(t) = (1,0)\widehat{\boldsymbol{\beta}}_g$ and $\hat{v}_{gi}(t) = (1,0)\widehat{\mathbf{b}}_{gi}$. The unknown variance-covariance parameters in D_g and $\boldsymbol{\Sigma}_{gi}$ can be estimated by using maximum or restricted maximum likelihood, implemented by using the EM algorithm or the Newton-Raphson method (Davidian and Giltinan, 1995; Vonesh and Chinchilli, 1996).

Of particular interest are the comparative effects of the two treatments. Therefore, we need to compare the equality of the two population curves $\eta_1(t)$ and $\eta_2(t)$. To do this, we fit the model $\eta_c(t) + v_{cgi}(t)$ to all data, where $\eta_c(t)$ is the fixed-effect (population) curve for the data and $v_{cgi}(t)$ are

random-effects curves that deviate from $\eta_c(t)$. As is done when estimating $\eta_g(t)$ and $v_{gi}(t)$, we can use the local linear approximation approach of Wu and Zhang (2002) to obtain the estimators, $\hat{\eta}_c(t)$ and $\hat{v}_{cgi}(t)$, of $\eta_c(t)$ and $v_{cgi}(t)$.

Our main concern is how to justify that the difference between the two population curves is statistically significant. To compare the effects of two treatments, we apply the following test statistic (Young and Bowman, 1995):

$$\texttt{TS} = \sum_{g=1}^{2} \sum_{j \in T_g} \frac{\{\hat{\eta}_g(t_{gj}) - \hat{\eta}_c(t_{gj})\}^2}{\hat{\sigma}^2}, \tag{2.5}$$

where $T_g = \{\text{all distinict times } t_{gj} \text{ in treatment } g\}$ and $\hat{\sigma}^2 = \sum_{g=1}^{2} \sum_{i=1}^{n_g} (n_{gi} - 1)\hat{\sigma}_{gi}^2 / (n - \sum_{g=1}^{2} n_g)$ is an estimator of the variance of the measurement error with $n = \sum_{g=1}^{2} \sum_{i=1}^{n_g} n_{gi}$; $\hat{\sigma}_{gi}^2$ are obtained by using the first-order difference approach proposed by Rice (1984), as follows:

$$\hat{\sigma}_{gi}^2 = \frac{1}{2(n_{gi} - 1)} \sum_{j=1}^{n_{gi}-1} (y_{gi[j+1]} - y_{gi[j]})^2, \ i = 1, 2, \ldots, n_g; g = 1, 2.$$

If the two population curves are equal; that is, under the null hypothesis $H_0 : \eta_1(t) = \eta_2(t)$, the distribution of the test statistic TS in (2.5) is then approximated by $a\mathcal{X}^2(b) + c$, where $\mathcal{X}^2(b)$ is a chi-squared distribution with b degrees of freedom. Moreover, a, b, and c are constants such that the mean, variance, and skewness of $a\mathcal{X}^2(b) + c$ are equal to the corresponding quantities of the test statistic TS, which can be calculated directly. The distribution of $a\mathcal{X}^2(b) + c$ is then used to calculate the p-value. The standard error of the difference between the estimates for the two population curves can be computed as

$$\text{se}_{\text{diff}}(t) = \text{se}\{\hat{\eta}_1(t) - \hat{\eta}_2(t)\} = \sqrt{\text{se}_1^2(t) + \text{se}_2^2(t)},$$

where $\text{se}_1(t) = \text{se}\{\hat{\eta}_1(t)\}$ and $\text{se}_2(t) = \text{se}\{\hat{\eta}_2(t)\}$ are the standard errors of the estimates of the population curves, respectively. A reference band

whose width is centered at the average of the two estimated curves $\pm 2 \times \text{se}_{\text{diff}}(t)$ can be used to see how much difference there is between the two treatment groups (Young and Bowman, 1995).

3 The analysis of longitudinal viral load data

In this section, we illustrate the practical use of the proposed methodology with longitudinal viral load data from HIV-infected patients. The data set we are using includes the longitudinal viral load data obtained from 30 HIV-infected patients who received monotherapy or dual therapy and 30 HIV-infected patients who received HAART in several hospitals in Taipei, Taiwan, between 1997 and 2002. These data are subsets of data from a much larger cohort data of 1,195 HIV-infected patients in Taipei. We chose to use data from the patients treated with HAART who had never been given any other treatment regimen and non-HAART patients who had never been treated with HAART, to ensure the validity of the comparison. Treatment durations varied, because patients began receiving treatment at different times during the study period. Figure 1 presents scatter plots of viral load (in $\log_{10}$ scale) against treatment durations for the HIV-1-positive patients.

Place Figure 1 here

After excluding missing data, we have 208 complete viral load observations in the HAART group, of which 108 have a value less than 400; and we have 164 complete viral load observations in the non-HAART group, of which 69 have a value less than 400. If we use the criterion that a treatment is considered successful in its antiviral effect when the viral load is

below 400, the success rates in the HAART and non-HAART groups are 51.9% and 42.1%, respectively.

For data analysis, we used the quartic kernel, $K(u) = (15/16)(1 - u^2)^2 I_{(|u|\leq 1)}$. The estimates of the two population curves are depicted in Figure 2. From Figure 2, we can see that the estimates of the two population curves have different patterns although both decrease at the beginning of treatment. The estimated curve for the HAART group shows that the viral load is maintained at a constant level until the end of the treatment, whereas that for the non-HAART group shows that the viral load decreases sharply during the first 480 days, reaching its lowest point on day 480. However, after 480 days, the viral load increases, remains constant for a short time, and increases again at the end of the treatment.

A chi-squared test for the success rates of the two treatments gives a p-value of 0.07. It is hard to say that there is a significant difference between the effects of the two treatments, although the success rate in the HAART group is greater than that in the non-HAART group. Therefore, to look more closely at the difference between the effects of the two treatments, we use the principle described in Section 2. The p-value obtained by using this method is less than 10^{-4}, which indicates that the two population curves for each treatment are substantially different. To confirm this conclusion, we obtained a range of reference values and plotted them with our viral load trajectory estimates in Figure 2. The two estimated population curves deviate from the reference band, and the efficacy of the HAART is seen to be almost significantly superior to that of the conventional therapy that does not include HAART.

4 Discussion

1. To determine the efficacy of antiviral treatments by using longitudinal viral load data, we applied nonparametric mixed-effects models to estimate the patterns of the viral trajectories in the two sampled populations. This approach avoids misspecification and, thus, the occurrence of an artifical bias. By combining the between-subject and within-subject information, the models we have proposed can parsimoniously capture the features of viral response to an antiviral therapy, such that the estimated curve is able to show common features of the antiviral activity.

2. In implementing the estimation of population curves, we used local linear regression and the bandwidth selection method proposed by Wu and Zhang (2002) to select the bandwidth. Besides the local linear methods applied in this article, the methods of regression splines and smoothing splines may also be implemented for parameter estimation. The approach of regression splines transforms the models to standard linear mixed-effects models and is easy to implement by using existing software such as SAS and SPLUS. However, the method of regression splines can not capture the locality as kernel regression methods are able.

3. The result of our illustrative example indicates that HAART has effects that are significantly different from those of treatment that did not include HAART. At the beginning of treatment, non-HAART has strong antiviral activity, which is lacking with HAART. However, during the course of the treatment, the superiority of non-HAART lessens, and this therapy ultimately fails, whereas HAART maintains a constant effect throughout treatment. This maintenance of the viral load

at a constant level confirms previous findings and is preferable to the fluctuation of load resulting from non-HAART. This result confirms that HAART is worth continuing, despite its inability to suppress viral replication completely (Deeks and Martin 2001).

4. Finally, the reference band covers a wider range of viral loads at the end of treatment, despite the increasing difference between the two estimated curves. This is not surprising because of the smaller sample size resulting from a shorter treatment duration for some patients at that time.

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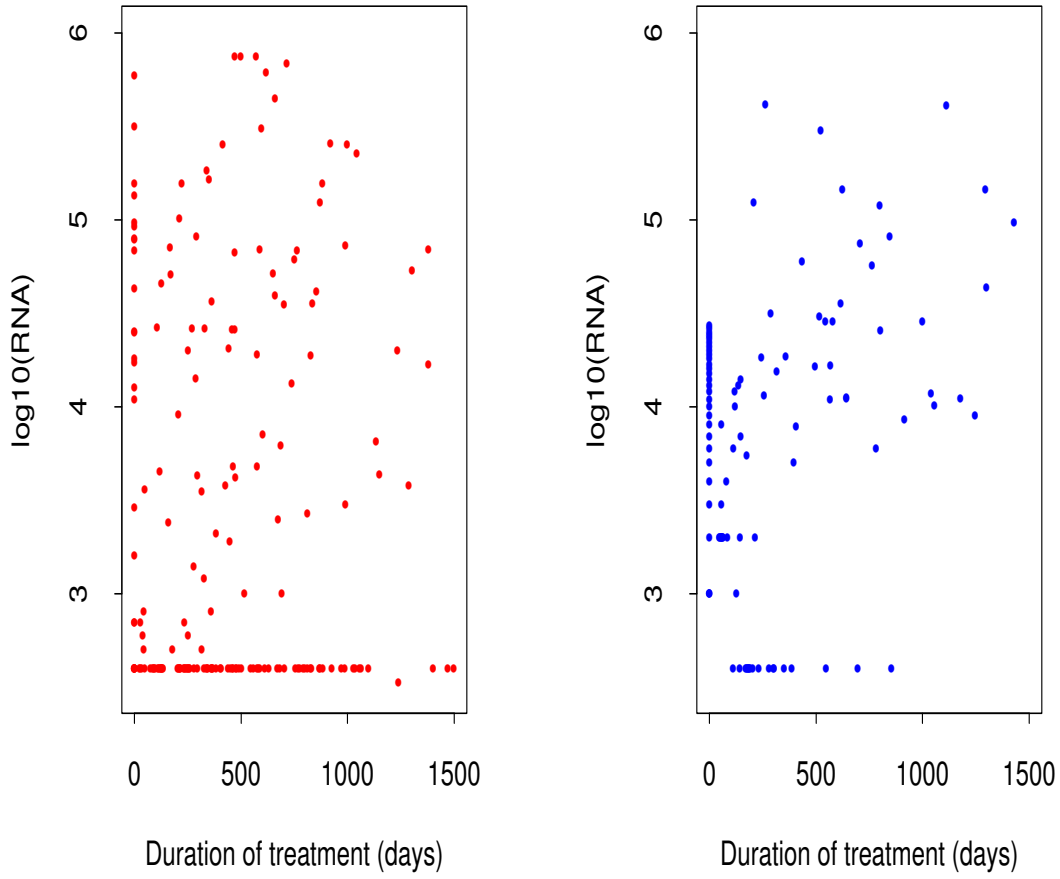

Figure 1: Scatter plot of viral load ($\log_{10}$ of copy number of HIV RNA in plasma) versus duration of treatment with HAART (left) or non-HAART (right)

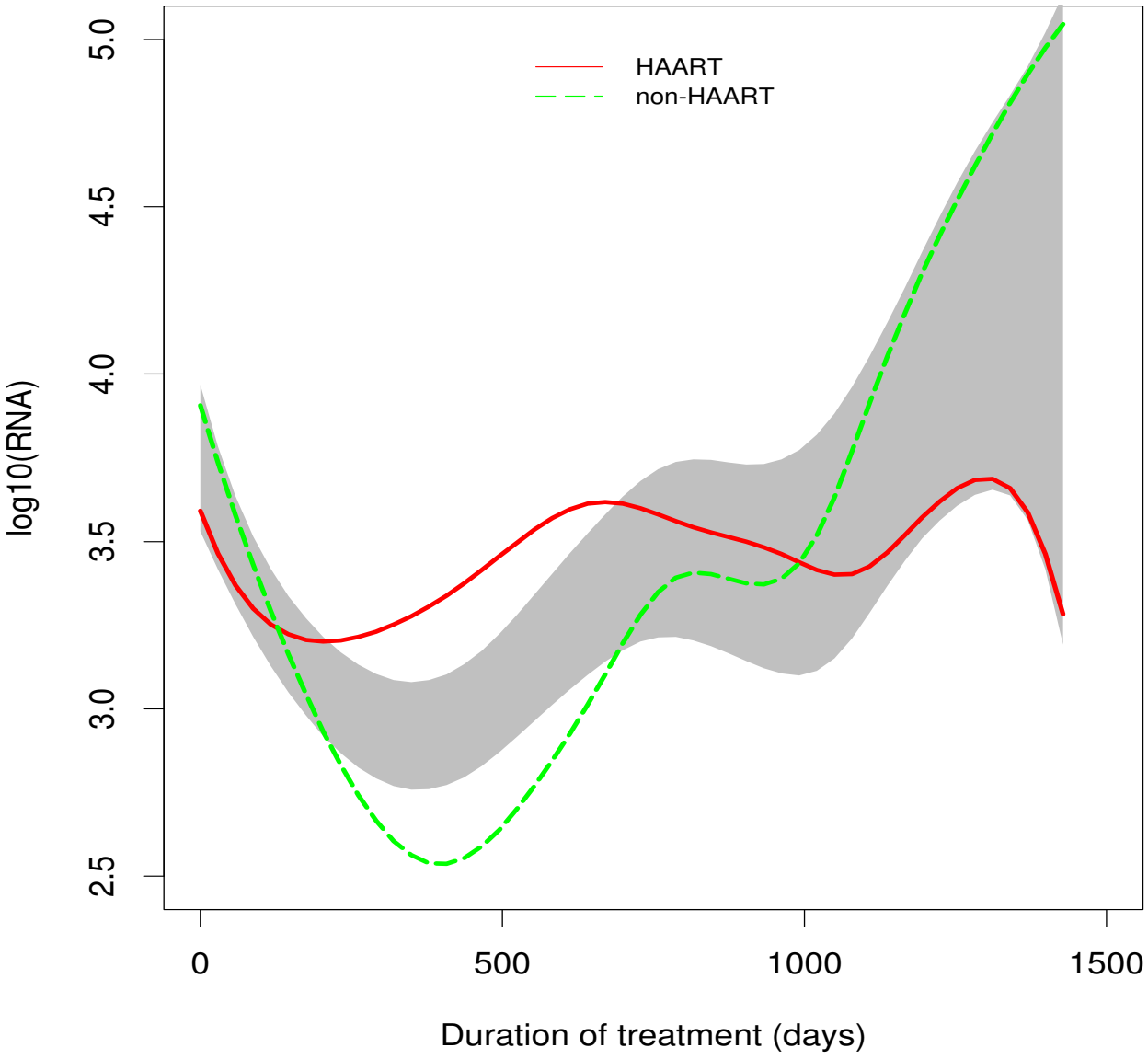

Figure 2: Estimates of the two population curves for the HAART (full line) and non-HAART (broken line) groups. The shaded area represents the reference band

3. Survival and Progression to AIDS: Analysis of the Efficacy of Highly Active Antiretroviral Therapy in Taiwan

Statistical Analysis

Cumulative probability for the events of developing AIDS and death for HIV infected individuals before and after 1997 were calculated. We compared the estimated the overall survival function during the follow-up period for these two groups. To adjust for potential confounders, multivariate analysis by the Cox proportional hazards model was conducted. Adjustments were made for gender, age of HIV diagnosis, exposure risk, and CD4 count at diagnosis.

Results

Descriptive characteristics of the study population are shown in Table 1. Among the 540 HIV infected individuals diagnosed between 1993 and 1997, the majority of them were male (93.96%) and young individuals (<35 years old, 69.26%). Forty-two percent of them were heterosexual, 44.76% were homosexual, and 21.77% were bisexual. Nearly 18.0% of them were diagnosed as AIDS by 1997. Almost 80% of them had CD4 count greater than or equal to 200 at diagnosis. Similarly, among the 1147 HIV infected individuals without AIDS diagnosis at the beginning of the combined antiretroviral therapies program set up by the government, the majority of them were male (94.35%) and young individuals (<35 years old, 65.30%). Thirty percent of them were heterosexual, 51.61% were homosexual, and 18.31% were bisexual. Nearly 7% of them were diagnosed as AIDS by 2002. Almost 80%

of them had CD4 count greater than or equal to 200 at diagnosis.

The cumulative probability decreased from 17.78% to 7.32 % for developing AIDS and from 10.93% to 3.49% for mortality overall for all HIV infected individuals before and after 1997. The differences in cumulative probability of developing AIDS before and after 1997 varied among different groups. We found greater decrease for men than women (10.00 % vs. 2.07%), for infected individuals of 35-44 age group (18.97%) in HIV diagnosis than 15-24 (7.12%), 25-34 (10.22%), 45-54 (10.51%), or ≥55 (6.28%) age groups, for infected individuals who had heterosexual behaviors (12.91%) than infected individuals who had homosexual behaviors (10.25%) or bisexual behaviors (3.86%), for infected individuals with 51-98 CD4 count (30.00%) than infected individuals with ≤50 CD4 count (27.69%), 99-199 CD4 count (23.22%) or ≥200 CD4 count (5.41%). The differences in cumulative probability of mortality before and after 1997 also varied among different groups. We found greater decrease for men than women (7.75 % vs. 2.55%), for infected individuals of 45-54 age group (16.41%) in HIV diagnosis than 15-24 (-0.71%), 25-34 (7.67%), 35-44 (15.46%), or ≥55 (4.97%) age groups, for infected individuals who had homosexual behaviors (8.05%) than infected individuals who had heterosexual behaviors (5.73%) or bisexual behaviors (7.72%), for infected individuals with ≤50 CD4 count (42.76%) than infected individuals with 51-98 CD4 count (36.43%), 99-199 CD4 count (25.28%) or ≥200 CD4 count (0.9%).

The estimated relative hazards (RHs) of developing AIDS and death are shown in Table 3. Without adjustment, we found a substantial decrease in RH of developing AIDS after 1997 (RH=0.515; 95% confidence interval [CI],

0.384-0.692). With adjustment of gender, age at entry, exposure category, and CD4 count at diagnosis effects, the RH remained significance (0.551, 95% CI, 0.41-0.74). The other significant factors associated with developing AIDS were gender, age at entry, and CD4 count at diagnosis. We found significantly increased HR of developing AIDS for female compared to male (crude HR=1.498, CI, 0.704-3.191; adjusted HR=2.640, CI, 1.208-5.769), for infected individuals of 35-44 age group (crude HR=3.046, CI, 1.703-5.448; adjusted HR=1.918, CI, 1.051-3.503) and for infected individuals of 45-54 age group (crude HR=5.044, CI, 2.646-9.614; adjusted HR=2.568, CI, 1.307-5.046) compared to 15-24 age group, but significantly decreased HR of developing AIDS for infected individuals with 51-98 CD4 count (crude HR=0.328, CI, 0.187-0.572; adjusted HR=0.310, CI, 0.175-0.549), for infected individuals with 99-199 CD4 count (crude HR=0.239, CI, 0.152-0.377; adjusted HR=0.273, CI, 0.172-0.434), and for infected individuals with ≥200 CD4 count (crude HR=0.054, CI, 0.038-0.078; adjusted HR=0.059, CI, 0.040-0.088) compared to infected individuals with CD4 count ≤50.

For RH's of death, without adjustment we found a substantial decrease in RH after 1997 (RH=0.461; 95% confidence interval [CI], 0.308-0.690). With adjustment of gender, age at entry, exposure category, and CD4 count at diagnosis effects, the RH remained significance (0.477, 95% CI, 0.317-0.716). The other significant factors associated with death were age at entry, and CD4 count at diagnosis. We found significantly increased RH of death for infected individuals of 35-44 age group (crude HR=6.739, CI, 2.364-19.213; adjusted HR=3.774, CI, 1.290-11.035), for infected individuals of 45-54 age group (crude

HR=8.858, CI, 2.857-27.464; adjusted HR=3.873, CI, 1.210-12.399), and for infected individuals of ≥55 age group (crude HR=12.895, CI, 4.364-38.102; adjusted HR=5.822, CI, 1.859-18.235) compared to 15-24 age group, but significantly decreased HR of death for infected individuals with 51-98 CD4 count (crude HR=0.308, CI, 0.195-0.740; adjusted HR=0.454, CI, 0.230-0.896), for infected individuals with 99-199 CD4 count (crude HR=0.254, CI, 0.145-0.445; adjusted HR=0.293, CI, 0.165-0.519), and for infected individuals with ≥200 CD4 count (crude HR=0.038, CI, 0.023-0.062; adjusted HR=0.050, CI, 0.030-0.084) compared to infected individuals with CD4 count ≤50.

The results reported here are being written as a manuscript to be submitted.

Table 1: Characteristics of HIV persons in Taiwan, 1993-2002.

	Period 1		Period 2	
	n	%	n	%
Sex				
Male	507	93.96	1090	94.35
Female	33	6.04	57	5.65
Age at HIV diagnosis				
15-24	120	22.22	195	17.00
25-34	254	47.04	554	48.30
35-44	99	18.33	241	21.01
45-54	31	5.74	81	7.06
≥55	36	6.67	76	6.63
Exposure category				
Homosexual	210	38.89	345	30.08
Heterosexual	222	41.11	592	51.61
Bisexual	108	20.00		
Developing AIDS				
Yes	97	17.96	84	7.32
No	443	82.04	1063	92.68
CD4 count at diagnosis				
≤50	34	7.24	41	3.57
51-98	20	4.23	35	3.05
99-199	45	10.46	103	8.98
≥200	441	78.07	968	84.39

Table 2: Cumulative probabilities of developing AIDS and Death among HIV infected persons: 1993-1997 and 1997-2002.

	Period 1			Period 2		
	# of individuals	AIDS N(%)	Death N (%)	# of individuals	AIDS N(%)	Death N (%)
Total	540	96 (17.78)	59 (10.93)	1147	84 (7.32)	40 (3.49)
Sex						
Male	507	93 (18.34)	57 (11.24)	1090	80 (7.34)	38 (3.49)
Female	33	3 (9.09)	2 (6.06)	57	4 (7.02)	2 (3.51)
Age at HIV diagnosis						
15-24	120	11 (9.17)	1 (0.83)	195	4 (2.05)	3 (1.54)
25-34	254	42 (16.54)	25 (9.84)	554	35 (6.32)	12 (2.17)
35-44	99	27 (27.27)	19 (19.19)	241	20 (8.30)	9 (3.73)
45-54	31	9 (29.03)	7 (22.58)	81	15 (18.52)	5 (6.17)
≥55	36	7 (19.44)	7 (19.44)	76	10 (13.16)	11 (14.47)
Exposure category						
Homosexual	210	46 (21.90)	23 (10.95)	345	31 (8.99)	18 (5.22)
Heterosexual	222	34 (15.32)	22 (9.91)	592	30 (5.07)	11 (1.86)
Bisexual	108	16 (14.81)	14 (12.96)	210	23 (10.95)	11 (5.24)
CD4 count at diagnosis						
≤50	34	26 (76.47)	22 (64.71)	41	20 (48.78)	9 (21.95)
51-98	20	10 (50.00)	9 (45.00)	35	7 (20.00)	3 (8.57)
99-199	45	17 (37.78)	14 (31.11)	103	15 (14.56)	6 (5.83)
≥200	441	43 (9.75)	14 (3.17)	968	42 (4.34)	22 (2.27)

Table 3: Estimated relative hazards of period and related risk factors and their 95% confidence intervals for developing AIDS and death from multivariate proportional hazard models.

	Developing AIDS				Death			
	Unadjusted		Multivariate adjusted		Unadjusted		Multivariate adjusted	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Period (period 1 as reference)								
Period 2	0.515	0.384-0.692	0.347	0.233-0.518	0.461	0.308-0.690	0.436	0.291-0.654
Sex (female as reference)								
Male	1.498	0.704-3.191	2.552	1.013-6.427	1.501	0.052-4.082	2.503	0.992-6.314
Age at HIV diagnosis (15-24 as reference)								
25-34	2.031	0.168-3.532	1.655	0.860-3.187	3.525	1.257-9.890	1.241	0.640-2.407
35-44	3.046	1.703-5.448	2.043	0.997-4.184	6.739	2.364-19.213	1.490	0.722-3.074
45-54	5.044	2.646-9.614	2.456	1.094-5.511	8.858	2.857-27.464	1.876	0.835-4.212
≥55	3.150	1.537-6.307	1.334	0.499-3.568	12.895	4.364-38.102	1.407	0.523-3.782
Exposure category (homosexual as reference group)								
Heterosexual	1.639	1.176-2.284	1.200	0.791-1.821	1.406	0.951-2.079	1.087	0.713-1.657
Bisexual	-	-	0.689	0.393-1.206	0.769	0.446-1.326	0.668	0.381-1.173
CD4 count at diagnosis (≤50 as reference)								
51-98	0.328	0.187-0.572	0.413	0.204-0.835	0.625	0.312-1.253	0.596	0.294-1.207
99-199	0.239	0.152-0.377	0.317	0.181-0.554	0.346	0.200-0.601	0.387	0.219-0.684
≥200	0.054	0.038-0.078	0.094	0.059-0.150	0.059	0.038-0.094	0.070	0.042-0.114