Current Trends and Future Projection of HIV/AIDS Epidemic in Taiwan: A Modeling Analysis

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Abstract: *Background*: In the past decade, HIV/AIDS epidemic in Taiwan experienced an outbreak of HIV-1 CRF07_BC among intravenous drug users (IDU) in 2004-2006 that led to the reported HIV/AIDS case number more than doubled in less than 3 years and subsequent changes in free anti-retroviral therapy (ART) treatment program for persons living with HIV/AIDS (PLWHA).

Methods: We investigate HIV underreporting in Taiwan by utilizing a discrete-time compartmental mathematical model for disease transmission and HIV/AIDS surveillance data during 2001-2011.

Results: The estimated underreporting ratio in 2011 is 0.45:1, down from 1:1 ratio in 2000. We also provide future projections of the numbers of reported and unreported PLWHA in Taiwan, assuming that model parameters remain unchanged in the near future.

Conclusion: N-step-ahead forecasting comparison with 2012-2014 observed data indicates lower than expected number of known PLWHA and new deaths, perhaps attributable to increased treatment, but higher number of newly reported HIV/AIDS cases, which requires further investigation.

Keywords: HIV/AIDS, Taiwan, projection, underreporting, reproduction number, mathematical model.

INTRODUCTION

Since the reporting of the first HIV/AIDS case in 1984, Taiwan has always maintained a low HIV/AIDS prevalence. However, there has been a sharp increase in reported case number in the last decade. By the end of 2013, the cumulated number of reported HIV/AIDS cases among Taiwanese had risen to 26,475, 11,176 of whom had developed full-blown AIDS with 4,171 deaths [1]. The main modes of transmission are sexual transmission (both heterosexual and homosexual) and needle- or apparatus-sharing. While maintaining a low HIV prevalence of slightly more than 0.1%, a couple of events stood out that helped to shaping the HIV/AIDS epidemic in Taiwan.

First, in 1997 comprehensive free anti-retroviral therapy (ART) was introduced in Taiwan as part of National Health Insurance Plan [2, 3]. Free access to ART was provided to all HIV-infected citizens, and early intensive treatment was encouraged, except for patients with blood HIV-RNA levels of less than 5000 copies/mL and peripheral CD4 cell counts within the normal range. Although some modifications of the program have been made through the years to be in line with changes in World Health Organization (WHO) recommended guidelines for when to start ART in people living with HIV [4], and with government budg*et al*locations, the patient outcome of this program has been shown to be effective, and provides strong evidence of the efficacy of ART [5, 6]. However, its impact on the spread of HIV is still open to debate.

Secondly, there was an explosive 2004-2006 outbreak of HIV-1 CRF07_BC among intravenous drug users (IDU) in Taiwan, which more than doubled the total number of reported HIV cases in less than 3 years, resulting in a 45-fold increase in cumulative IDU/HIV cases [3, 7-9]. As a consequence, for a short time IDUs were the major at-risk group for infection in Taiwan, overtaking men who have sex with men (MSM) and heterosexual infections. Since 2007, there had been a sharp drop in reported number of HIV-infected IDUs and sexual transmission once again is the predominant mode of infection. However, the latest data on reported HIV cases still indicate a steady increasing trend.

Benefits of ART therapy for HIV-infected patients have transformed HIV infection into a chronic disease. ART therapy policy varies significantly from country to country. In Taiwan, the national guidelines for HIV-infected persons include treatment for persons living with HIV (PLWH) if their CD4 counts fall below a certain level. In recent years, increasing numbers of PLWHs in Taiwan receive ART treatment. There are also several ongoing campaigns aiming towards prevention of disease transmission (such as the harm reduction, free syringe and methadone replacement programs implemented in 2005 and case managers programs initiated in 2007). Changes in policy for guidelines for free ART treatment also occurred during the time. A summary illustration of the timeline for HIV/AIDS epidemic and changes in guidelines for ART treatment in Taiwan during 1984-2013 is given in Fig. (**1**). As a result of the change in ART treatment guidelines, in 2006, 4,661 (35 %) of PLWHA received ART [10], while the number of treated PLWHA

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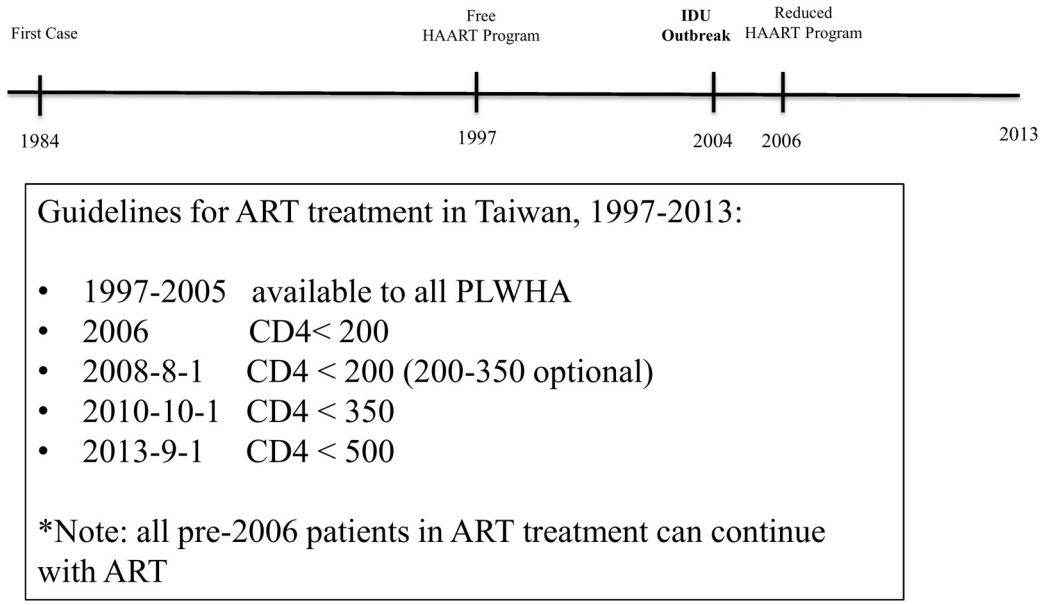

Fig. (1). Timeline for HIV/AIDS epidemic and changes in guidelines for ART treatment in Taiwan, 1984-2013.

increased to 6,427 (42.7%) in 2009 [11]. That is, more than 20% increase in treatment proportion and almost 40% increase in actual number of treated patients within two years.

Many modeling tools have been utilized to estimate HIV infections; e.g., Asian Epidemic Model (AEM) for HIV/AIDS epidemic in the Asia-Pacific region [12], the Joint United Nations Programme on AIDS (UNAIDS) Estimation and Projection Package (EPP) [13], and the UNAIDS Workbook Method for estimating HIV prevalence in low level or concentrated epidemics [14]. Each method is designed for specific purposes of estimation and projection of HIV epidemics and has been known to work well for some HIV-prevalent countries. However, each method also requires high-quality and detailed data due to its model complexity and level of details in the modeling.

In this work, we will make use of a discrete-time compartmental disease transmission model and Taiwan government HIV surveillance data to estimate the epidemiological parameters, in order to understand the recent trends of the epidemic and to provide projection based on these model estimates. The strength of this method is that the data requirement for modeling is minimal, merely routine government HIV/AIDS surveillance would suffice, provided it is accurate in its reporting of clinical progression, i.e., diagnosis time, AIDS onset time, death, etc. The discrete time model is preferred since the data we will fit to the model is given in discrete time, as all data are. Therefore, it is more natural to similarly describe the temporal changes of our model discretely. Discrete models have previously been used successfully in modeling infectious diseases such as SARS [15-17]. Our main focus is to make use of the known HIV surveillance data to infer the current and future projected numbers of undetected persons living with HIV, and to shed lights on the scope of HIV underreporting in Taiwan.

MATERIALS AND METHOD

HIV/AIDS Surveillance Data

The Taiwan Centers for Disease Control (TCDC) website contains annual reports with HIV/AIDS surveillance data from 1984 to present [1, 18]. The data include yearly reported HIV and AIDS case data, as well as online HIV/AIDS statistics including AIDS-related mortality data [1] given in Fig. (**2**). In our work, we will use the reported numbers of persons living with HIV, person living with AIDS, and deaths each year for our model fit and parameter estimation. The time series data used in our model fit are those from 2001 to 2011. To test predictive accuracy, we intentionally withhold the 2012-2014 data for the purpose of 1- to 3-step ahead forecasting comparison, a commonly used procedure for comparing predictive accuracy [19], with the model-projected numbers by assuming all model parameters remains the same in these three years.

Model Formulation

We propose a discrete-time compartmental model to describe disease transmission, in order to make use of the available surveillance data. We let I_n be the number of unreported persons living with HIV in year n; P_n is the number of reported person living with HIV in year n; A_n is the number of persons living with AIDS; and D_n is the cumulated deaths due to AIDS-related illness (ARI). The model flow diagram is given in Fig. (**3**) and the model equations are given below, the time unit is year.

$$\begin{aligned} I_{n+1} &= (1+\lambda)(1-\gamma)I_n \\ P_{n+1} &= (1-\alpha-\mu_1)[(1+\lambda)\gamma I_n + P_n] \\ A_{n+1} &= (1-\mu)\{\alpha[(1+\lambda)\gamma I_n + P_n] + A_n\} \\ D_{n+1} &= D_n + \mu\{\alpha[(1+\lambda)\gamma I_n + P_n] + A_n\} + \mu_1[(1+\lambda)\gamma I_n + P_n] \end{aligned} \quad (1)$$

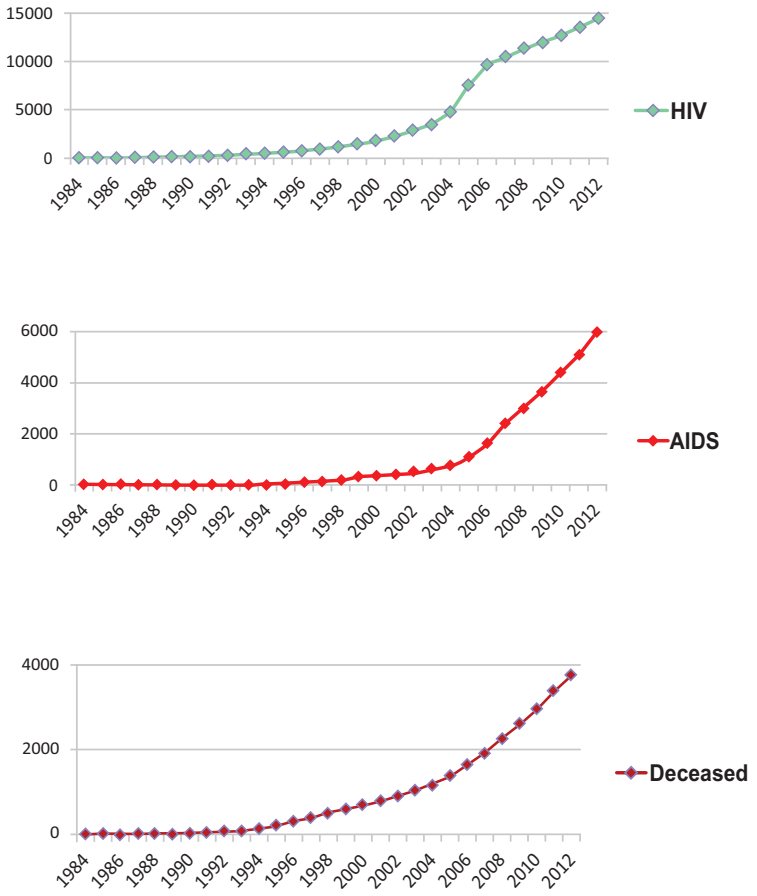

Fig. (2). HIV/AIDS surveillance data in Taiwan, 1984-2012. (source: Taiwan CDC).

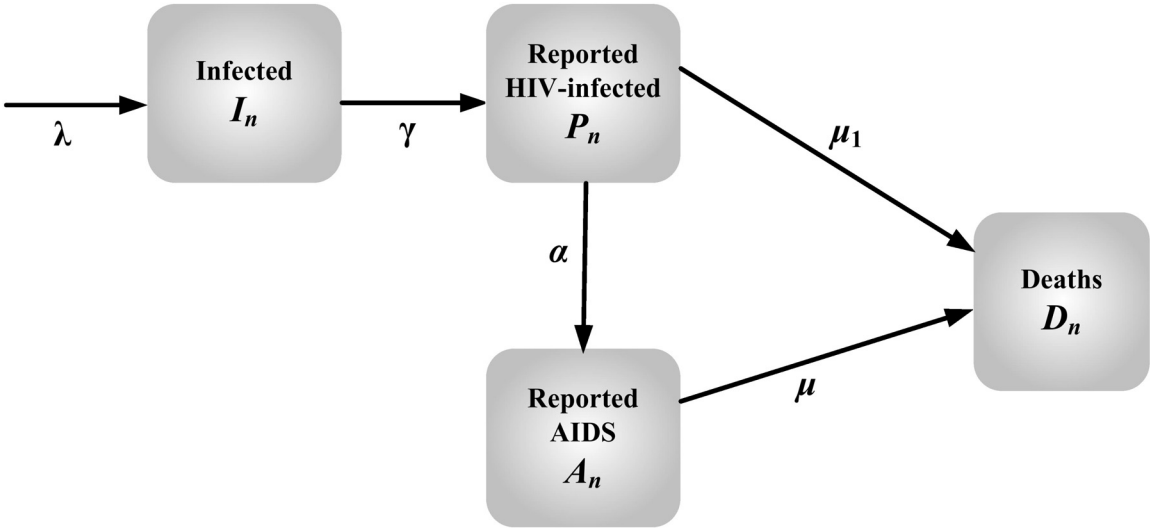

Fig. (3). Model flow diagram.

Here λ is the infection rate, γ is the reporting rate, α is the onset rate, μ is the mortality rate of the reported HIV cases who have not had onset of symptoms P_n, and μ_1 is the mortality rate of persons living with AIDS A_n. We assume that infection by a known person living with HIV or an AIDS patient is negligible, while the reporting/detection of HIV occurs either prior to or at the time of onset.

Parameter Estimation

To estimate the model parameters by fitting the model in Equation (1) with the time series of HIV/AIDS data in Fig. (**1**), we utilize the three-stage least squares method (3SLS), which combines two-stage least squares (2SLS) with seemingly unrelated regressions (SUR) [20] and is commonly used in econometrics [21]. 3SLS applies

generalized least squares estimation to a linear system of simultaneous discrete equations, which is considered a multi-equation simulation model that allows us to account for the interrelationship within the set of "endogenous" variables, I_n, P_n, and A_n. Each of the discrete equations is first been estimated using 2SLS which is, however, inefficient when a system of equations contains lagged dependent variables, as we have in our present model. We can then achieve an improvement in efficiency by applying 3SLS which yields more efficient parameter estimates than does 2SLS, since it takes into account of the cross-equation correlation between the estimated parameters. This procedure has previously been used successfully for estimation of model parameters in [15-17].

For the model fitting, we divide the times series data of HIV cases, AIDS cases, and deaths into three time periods in the ART treatment era, namely, 2001-2003, 2004-2006, and 2007-2011. We choose this partition of time periods since 2004-2006 was the time period when the HIV-1 CRF07_BC outbreak among intravenous drug users (IDU) in Taiwan occurred. Therefore, we divide the years after 2001 into 3 time periods, to highlight the temporal changes before, during, and after the 2004-2006 HIV/IDU outbreak.

The parameter estimation was performed in two stages. We first estimate the AIDS onset rate α and the mortality rates (μ and μ_1) using the time series data of P_n and A_n during each of the 3 time periods: 2001-2003, 2004-2006, and 2007-2011. We then make use of these results to further estimate the time series I_n, the infection rate λ and the reporting rate γ for each of the three time periods, as well as the time series of undetected persons living with HIV.

For the second stage of the estimation, we need to know the initial number of undetected infectives I_0. To overcome this obstacle and to further investigate more recent trends, we make use of the estimated number of undetected HIV-infected individuals in 2000 in Taiwan from Hsieh *et al.* [22], where the number of undetected HIV-infected individuals in 2000 was estimated using a compartmental model of differential equations fitted to the 1993-2000 HIV/AIDS reported case numbers, to be the initial value for I_0 in our model. We are then able to estimate I_n (for $n>1$), and subsequently the reporting rate γ as well as a point estimate of the infection rate λ from our model by fitting the model to the time series of P_n, again divided into three time periods of 2001-2003, 2004-2006, and 2007-2011.

To test the predictive accuracy of our results, We also perform N-step-ahead forecasting experiment [19] by comparing the reported 2012-2014 HIV/AIDS surveillance data with the model-predicted numbers for these three years.

RESULTS

We first note that we have found μ_1 to be statistically not significantly different from 0. Although there were some cases where deaths occur before diagnosis of ARI, the number is not sufficient large to be statistically estimable by our process. As a result, the model parameter estimates of the AIDS onset rate α, mortality rate μ, infection rate λ, and reporting rate γ resulting from the model fit with each of the three time periods are given in Table **1** with the corresponding 95% confidence intervals (CI) from the estimation. Note also that we are unable to obtain the 95% CI of λ due to the nonlinear nature of λ relative to γ in our model.

We also compute the various mean time intervals, from infection to reporting, to onset of the reported HIV cases, and to death (see Table **1**). The temporal changes in disease progression (in years) for known persons living with HIV/AIDS (PLWHA) in Taiwan through the three time periods during 2001-2011 are illustrated in Figs. (4, 5).

More importantly, we are also able to compute the reproduction number, R_0, or the number of secondary infections caused by one infective individual during given his/her duration of infectivity before onset of ARI, in the last row of Table **1**, in order to compare the above quantities before, during, and after the CRF07_BC outbreak among IDUs. Note that we do not provide an estimation range for R_0 since it is computed *via* the point estimate of λ. Illustrative comparisons of R_0 during the three time periods are also provided in Fig. (**6**). With the parameter estimates, we can

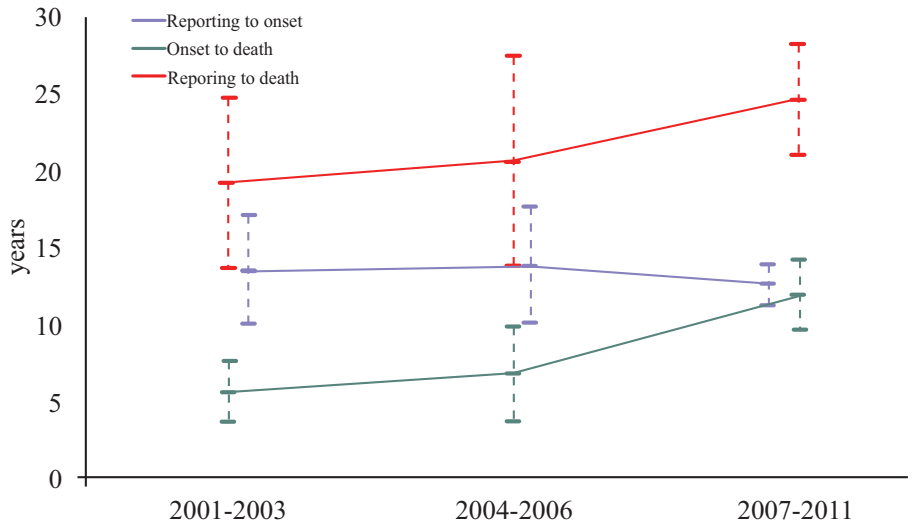

Fig. (4). Illustrative comparisons of mean time from reporting to onset/death and onset to death for 2001-2003, 2004-2006, and 2007-2011.

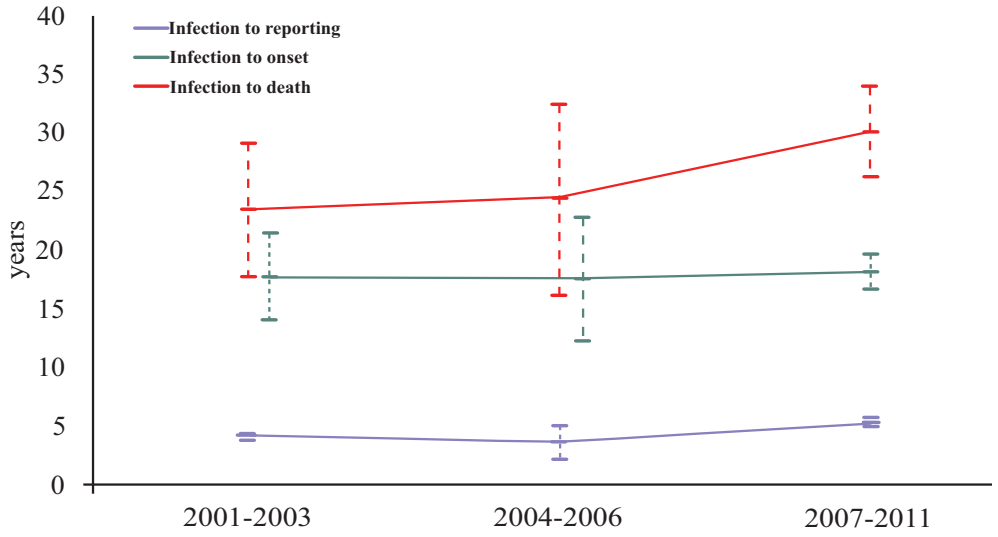

Fig. (5). Illustrative comparisons of mean time from infection to reporting/onset/death for 2001-2003, 2004-2006, and 2007-2011.

further project the epidemic in the future. In Table **2**, we compute the projected numbers of PLWHA, known PLWHA, known AIDS patients, and AIDS-related deaths from 2012-2015, by assuming that the model parameter values remain the same during these years as before, in 2007-2011. The model predicted values for these four time series are plotted against the real data during 2007-2011, along with the projected values in 2012-2015, respectively, in Figs. (**7-10**).

DISCUSSIONS

Since free ART therapy for large number of PLWHA was first introduced in Taiwan in 1997, the subsequent long mean time from detection to onset of ARI of around 13 years is most likely attributable to the effectiveness of ART treatment in Taiwan, which has been well-documented in literature (e.g., see [5]). Other studies have demonstrated longer survival of PLWHA through ART introduction as well as decreased opportunistic illness events in 200-2004 in Taiwan [23]. There is no statistically significant difference in mean time from reporting to onset of those PLWHA who had an onset of ADI during 2001-2011; in spite of the massive influx of IDU/HIV cases detected during the 2004-2006 outbreak (see Fig. **4**). However, mean time from onset to death indicates a consistent increase, with the largest jump occurring in recent years (from 6.75 years in 2004-2006 to 11.93 years during 2007-2011), thus providing strong evidence of the long-term efficacy of the extensive free ART treatment that PLWHA in Taiwan had received since 1997. Moreover, comparing the time intervals 2001-2003 and 2007-2011, the ART treatment program resulted in the yearly AIDS mortality rate declining gradually (from 0.177 to 0.084) as well as in elongated survival time from AIDS to death (5.64 to 11.93 years). The reason may be due to less toxicity and tolerability of modern antiretroviral agents introduced and to improvement of HIV patient care quality. The estimate time from disease infection to death also increased from 19.26 years to 24.62 years, although the average age of patients is similar for these two time intervals

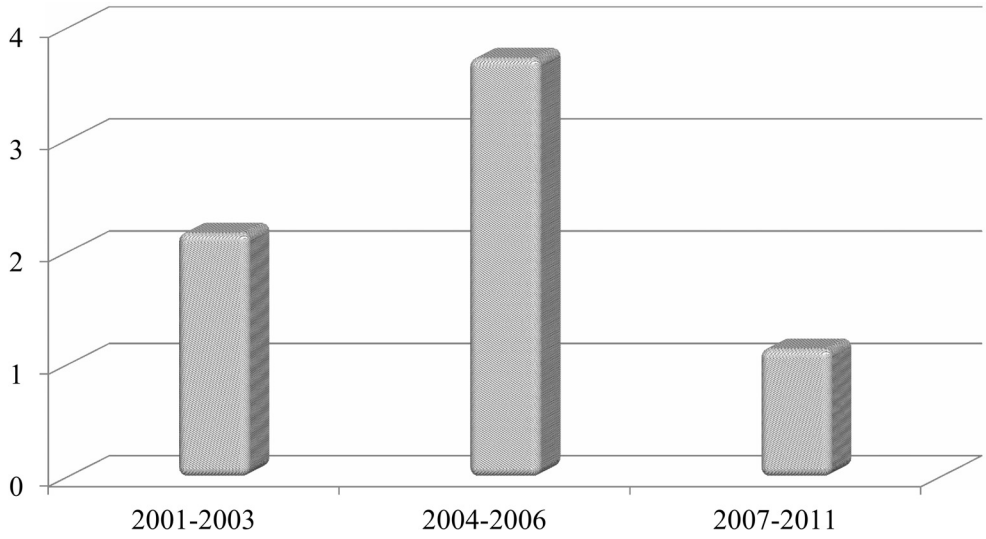

Fig. (6). Illustrative comparisons of R_0 for 2001-2003, 2004-2006, and 2007-2011.

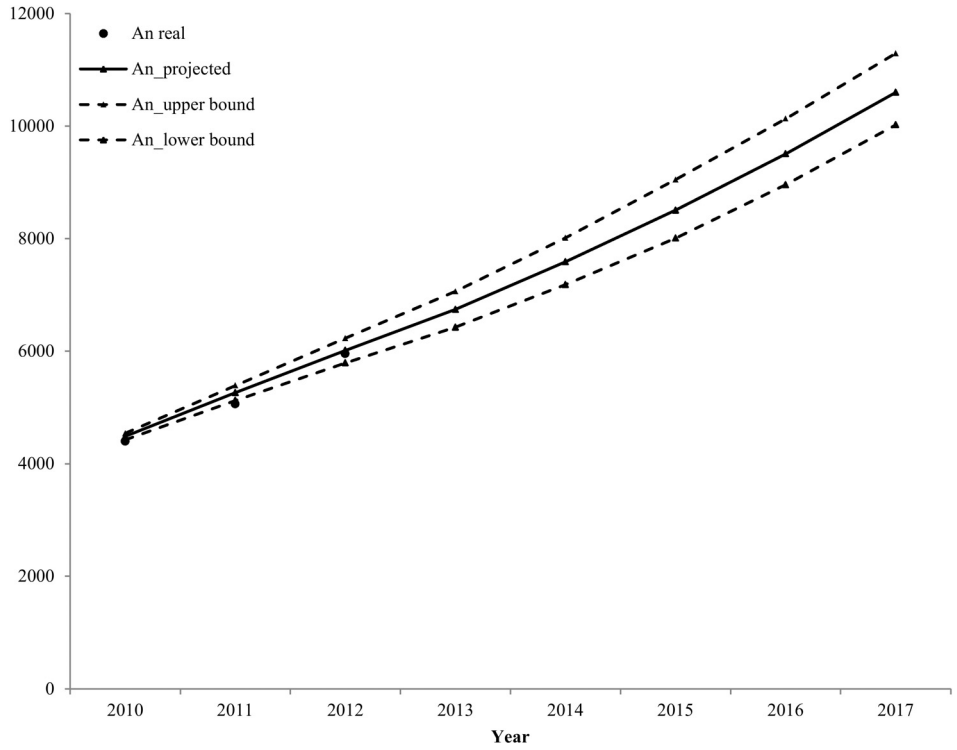

Fig. (7). Predicted number of AIDS patients, A_n, 2007-2015.

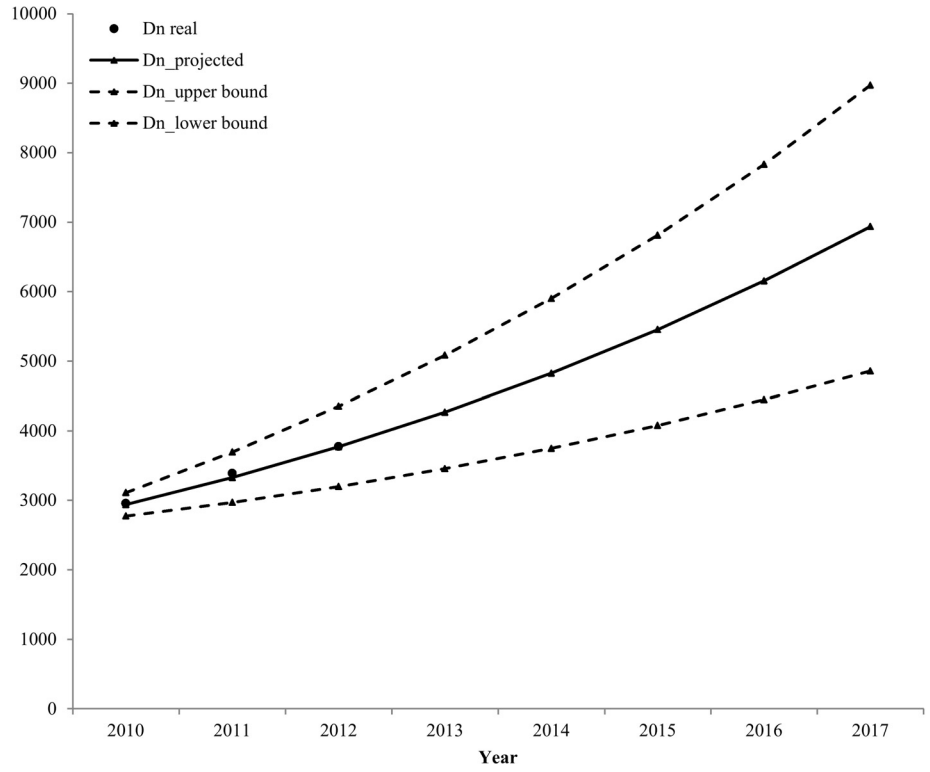

Fig. (8). Predicted number of AIDS deaths, D_n, 2007-2015.

(38.6 yrs and 37.1 yrs). The results are similar to previous studies which estimated an expected 32 more years of life for a 35-year-old patient [24].

The reporting rate γ was the highest during the 2004-2006 HIV/IDU outbreak, when compared to either before or after these three years. This is partly due to extensive testing of IDUs implemented by the government as part of the intervention measures to control the HIV/IDU outbreak [3, 8]. Larger fractions of IDUs among those being tested for HIV, who had more recent infections as determined though

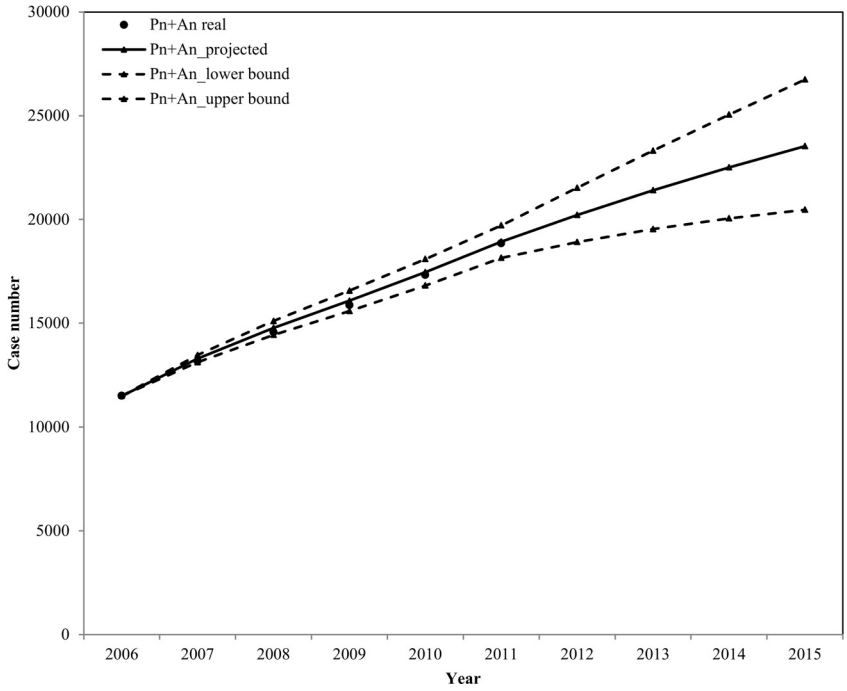

Fig. (9). Predicted number of known PLWHA, P_n+A_n, 2007-2015.

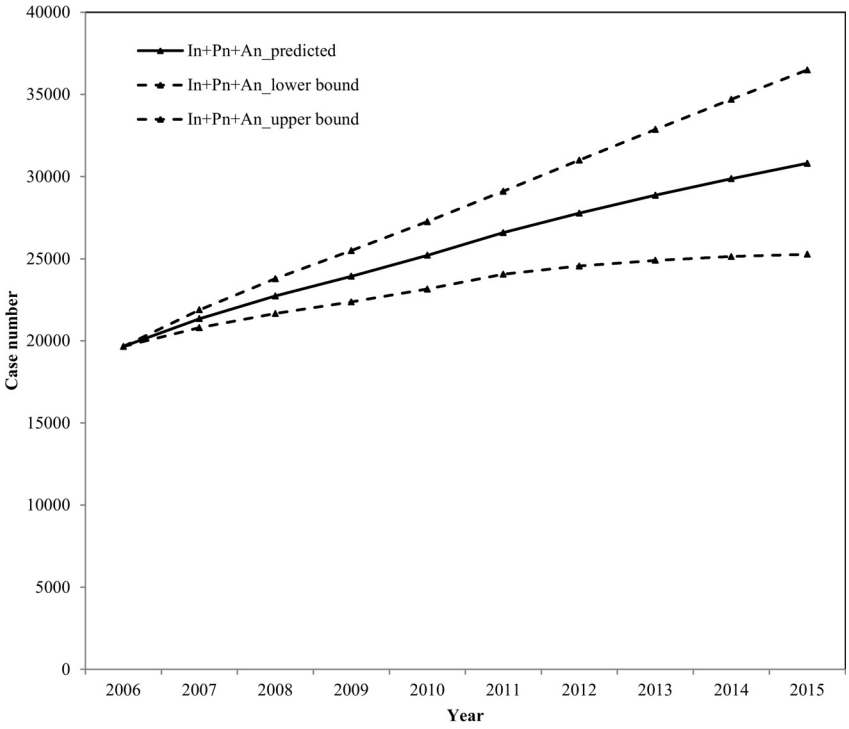

Fig. (10). Model-predicted number of PLWHA, 2007-2013.

molecular studies [7] and are more likely to be screened out through screening programs at prisons and rehabilitation centers, also contributed to the higher reporting rate. Moreover, mandatory HIV screening of persons under police custody due to violation of the Narcotics Control Act implemented since late 2004 could also have partially contributed to this sharp increase in reporting/detection [8]. As a consequence, the estimated average time from infection to reporting, or mean detection time, is the shortest during 2004-2006 at 3.67 years (also see Fig. **5**). Note that this result is the average of all new reported cases during 2004-2006. One would expect the corresponding average among new IDU/HIV cases could be much shorter. However, a similar modeling study on the IDU population in Taiwan would only be a suitable topic for future research. We also note that the reporting/detection time is significantly longer after 2007, even when compared with the pre-2004 average, which might be a cause for further investigation.

Table 1. Estimates of model parameters (with 95% CIs in parenthesis when applicable) for HIV/AIDS in Taiwan (2001-2011).

Year	2001-2003	2004-2006	2007-2011
Reporting rate γ	0.239 (0.230, 0.248)	0.272 (0.166, 0.378)	0.183 (0.175, 0.190)
Infection rate λ	0.518	1.016	0.209
Onset rate α	0.063 (0.055, 0.072)	0.072 (0.052, 0.092)	0.079 (0.071, 0.087)
AIDS mortality rate μ	0.177 (0.114, 0.240)	0.148 (0.081, 0.215)	0.084 (0.068, 0.100)
Time from infection to reporting (years)	4.18 (4.03, 4.34)	3.67 (2.24, 5.10)	5.47 (5.25, 5.69)
Time from reporting to onset	13.62 (10.07, 17.16)	13.90 (10.11, 17.70)	12.69 (11.36, 14.01)
Time from infection to onset (years)	17.80 (14.10, 21.50)	17.57 (12.35, 22.80)	18.16 (16.61,19.70)
Time from onset to death (years)	5.64 (3.64, 7.64)	6.75 (3.71, 9.79)	11.93 (9.65, 14.22)
Time from reporting to death (years)	19.26 (13.71, 24.80)	20.65 (13.82, 27.49)	24.62 (21.01, 28.23)
Time from infection to death (years)	23.44 (17.74, 29.14)	24.32 (16.06, 32.59)	30.09 (26.26, 33.92)
Reproduction number R_0	2.17	3.73	1.14

Table 2. Estimation and future projection of HIV/AIDS epidemic in Taiwan, 2007-2015. (* denotes real data during 2007-2011).

Year	PLWHA	Known PLWHA	Known AIDS	Deaths
2007	21716 (21 142,22 287)	12 951*	2 430*	1 917*
2008	23081 (21 954,24 203)	14 345*	2 978*	2 263*
2009	24280 (22 618,25 937)	15 643*	3 640*	2 608*
2010	25553 (23 371,27 730)	17 093*	4 395*	2 954*
2011	26935 (24 246,29 622)	18 627*	5 057*	3 388*
2012	28 128 (24 715,31 550)	20 006 (18 812,21 209)	5 840 (5 598,6 062)	3 912 (3 380,4 488)
2013	29 229 (25 021,33 478)	21 206 (19 432,23 020)	6 504 (6 179,6 821)	4507 (3 829,5 245)
2014	30 251 (25 215,35 372)	22 325 (19 945,24 789)	7 150 (6 718,7 588)	5 161 (4 317,6 086)
2015	31 195 (25 303,37 226)	23 365 (20 352,26 517)	7 775 (7 215,8 359)	5 872 (4 841,7 014)

To summarize, although the 2004-2006 IDU/HIV outbreak had an impact on the detection/reporting of HIV, it did not have a noticeable effect on the clinical progression of the disease from infection to onset of ARI. The increase in survival time of AIDS patients in recent years indicates the long-term benefit of ART treatment.

A previous study [20] had estimated HIV underreporting in Taiwan to be around 1:1; that is, 1 796 estimated undetected PLWHA compared to 1 840 known PLWHA in Taiwan by the end of 2000. In this work the model-estimated number of undetected PLWHA by the end of 2011 is 8 368 (Table **2**) compared with 18 627 known PLWHA, or around 0.45:1 underreporting ratio (Fig. **11**). The significant decrease in underreporting ratio is an indication of successful efforts for detection, although the 4-fold increase in actual number of undetected PLWHA indicates further need to improve detection.

The reproduction number R_0 was also significantly higher during 2004-2006, reflecting the ongoing spread of HIV infections among IDU population during that time. Again, this estimate for reproduction number is that of all new HIV cases during that time span, the corresponding reproduction number of HIV due to needle/apparatus-sharing among IDUs would undoubtedly be much higher [8]. The substantial drop in reproduction number after 2007, even when compared to pre-2004, could be an encouraging sign of an optimistic future for HIV/AIDS control and prevention in Taiwan.

For future projection of the years 2012-2015 using the estimated model parameter values, we note that the underlying assumption of this projection is that during 2012-2015, the HIV/AIDS epidemic in Taiwan remains unchanged as during 2007-2011, and hence retains the same epidemiological characteristics as quantified by the model parameter estimates for 2007-2011. In our study design, we withheld the 2012-2014 surveillance data in our estimation work, for the purpose of comparing our projections for 2012-2014 with the real data.

The n-step-ahead forecasting experiment results of the model-predicted numbers for known PLWHA, PLWHA deaths, and New HIV/AIDS cases for 2012-2014 as well as the observed data for these three years are given in Table **3**, where percentage error with "–" indicating underestimate and "+" indicating overestimate. As can be expected, the resulting percentage errors of the prediction for 2012 are better than succeeding years, due to increasingly large error

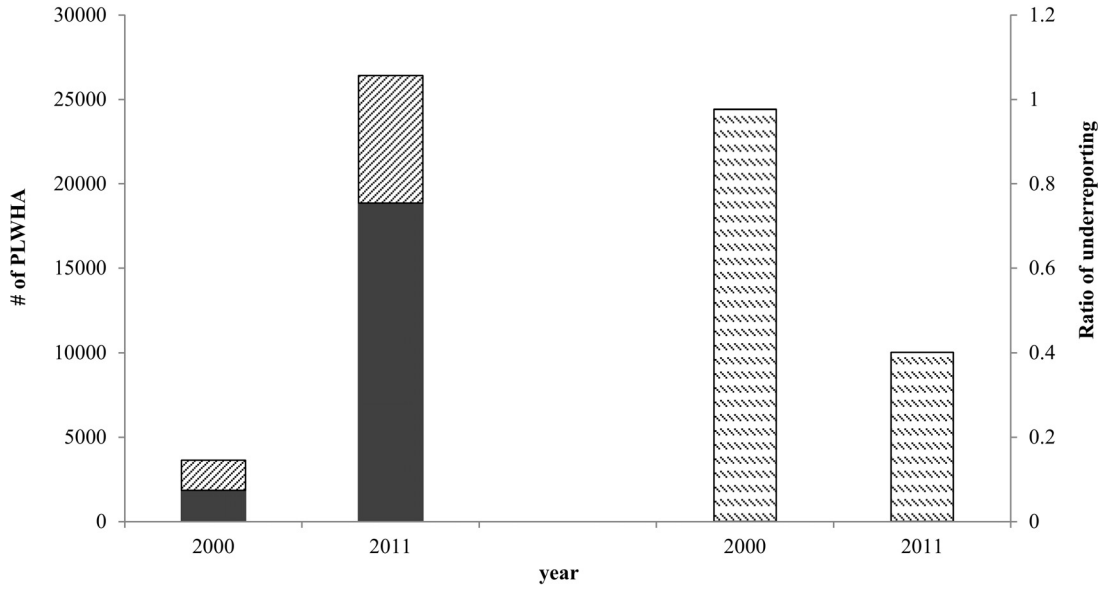

Fig. (11). Estimated number of PLWHA (bars on the left) and ratio of HIV underreporting (bars on the right) in Taiwan, 2000 and 2011. Shaded areas for number of PLWHA indicate undetected PLWHA.

Table 3. 1-step and 2-step-ahead forecasting comparison of model-predicted projections of HIV/AIDS epidemic in Taiwan for 2012-2013 (based on model estimates from 2007-2011) with observed data, with percentage error with "–" indicating underestimate and "+" indicating overestimate.

	Known PLWHA	Deaths	New HIV/AIDS cases
2012			
Observed data	20 412	3 820	2 222
Model- predicted number	20 006 (18 812, 21 209)	3 912 (3 380, 4 488)	1 828 (1 173, 2 504)
Prediction error (percentage error)	-406 (-2.25%)	+92 (+2.41%)	-394 (-17.7%)
2013			
Observed data	22 270	4 171	2 243
Model- predicted number	21 206 (19 432, 23 020)	4 507 (3 829, 5 245)	1 795 (1 069, 2 568)
Prediction error (percentage error)	-1 064 (-4.78%)	+336 (+8.06%)	-448 (-20.0%)
2014			
Observed data	24 183	4 651	2393
Model- predicted number	22 325 (19 945,24 789)	5 161 (4 317,6 086)	1773 (1001,2601)
Prediction error (percentage error)	-1 858 (-7.68%)	+510 (+10.97%)	-580 (-24.24%)

of longer-term prediction. Furthermore, for all three years there is an overestimate of number of deaths and underestimates of the other two numbers. The less-than-expected number of deaths is perhaps an encouraging sign of improved survival perhaps attributable to increased treatment in more recent years. However, higher number of new cases for all three years is perhaps a cause for alarm.

CONCLUSION

Since the prediction is made based on recent trends, i.e., model estimates for 2007-2011, the underestimates indicate that the increase in the reporting of PWLHA in 2012-2013 was higher than expected, which could either imply a worsening epidemic (assuming detection remains the same) or increased detection. On the other hand, since there had been no significant change in surveillance/detection system in Taiwan in recent years, it is a topic for further investigation.

The study demonstrates that, using an appropriate mathematical model, routine government disease surveillance data can be utilized to trace past events, investigate current situation and project future direction of a developing epidemic such as HIV/AIDS. We emphasize again, however, that predictions are based on the assumption that, in 2012-2015, all relevant epidemiological parameters

for HIV/AIDS in Taiwan remain similar to the 2007-2011 level. Since nothing remains the same for long, we expect the projections we made to be valid only for a short-term future, even if no drastic changes such as the 2004-2006 IDU outbreak occur.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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Declared none.

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