Original Article

# Risk Factors and Time-Trends of Cytomegalovirus (CMV), Syphilis, Toxoplasmosis and Viral Hepatitis Infection and Seroprevalence in Human Immunodeficiency Virus (HIV) Infected Patients

Raymond BT Lim, [1]*MBBS, MPH,* Mei Ting Tan, [1]*BSc(Hons)*, Barnaby Young, [1]*MB BChir, MRCP*, Cheng Chuan Lee, [1]*MBBS, MMed, MRCP*, Yee Sin Leo, [1]*MBBS, MMed, MRCP*, Arlene Chua, [1]*MD, ABIM, MSc*, Oon Tek Ng, [1]*MBBS, MRCP, MPH*

## Abstract

**Introduction: Chronic bacterial, viral and parasitic infections contribute to the morbidity and mortality associated with human immunodeficiency virus (HIV) infection. This study investigated risk factors and time-trends of the seroprevalence of cytomegalovirus (CMV), toxoplasmosis and hepatitis A total antibody; and co-infection with syphilis, hepatitis B and hepatitis C among newly diagnosed HIV individuals in Singapore. Materials and Methods: This was a cross-sectional study. A random sample of 50% of HIV infected patients who visited the Communicable Disease Centre (CDC), Singapore for first-time care from January 2006 to December 2011 were analysed. Results: Among the 793 study subjects, 93.4% were male; 77.9% of them were of Chinese ethnicity; mean age at HIV diagnosis was 41.4 years; and the mean baseline CD4+ T-cell count was 222 cells/mm$^3$. The prevalence of sero-reactivity for CMV was 96.8%; hepatitis A: 40.9%; and toxoplasmosis: 23.7%. Co-infection with syphilis was identified in 12.3%; hepatitis B: 8.1%; and hepatitis C: 2%. Among those co-infected with hepatitis C, 73.3% of them were intravenous drug user (IVDU). Syphilis co-infection was significantly more common among men who have sex with men (MSM) (multivariate OR: 2.53, 95% CI, 1.31 to 4.90, *P* = 0.006). Conclusion: This study described the baseline rates of HIV co-infection with syphilis, hepatitis B and C in Singapore, and sero-reactivity to CMV, toxoplasmosis and hepatitis A. The increased rates compared to the general population may have important consequences for disease progression, response to antiretroviral treatment and long-term general health.**

**Ann Acad Med Singapore 2013;42:667-73**

**Key words: HIV co-infections, Serology, Sexually Transmitted Infections**

## Introduction

For individuals infected with human immunodeficiency virus (HIV), access to effective combination antiretroviral therapy (ART) has in a short time changed the prospect of this disease to a chronic, manageable condition.[1] With virologic suppression and immune reconstitution, acquired immunodeficiency syndrome (AIDS) defining conditions now cause less morbidity and mortality and life expectancy approaches that of uninfected individuals.[2,3]

Despite these advances, 28 years after the first HIV infection was diagnosed in 1985 in Singapore, it remains an infectious disease of public health importance. Up till end of 2010, the cumulative total number of HIV/AIDS infections among residents since 1985 was 4845.[4] This is not least as the number of infections continues to increase.[5] The Singapore Burden of Disease Study 2004 estimated that HIV/AIDS contributed 26% of the disability-adjusted life years (DALYs) of infectious diseases burden.[6]

The Communicable Disease Centre (CDC) is the largest national centre for treatment of HIV patients in Singapore. Patients who present to the CDC are routinely screened at presentation for previous hepatitis A, B and C, syphilis, cytomegalovirus (CMV) and toxoplasmosis infections. This study reviewed the prevalence of sero-reactivity, transmission risk factors, and examined how the prevalence of these conditions has changed over time.

## Materials and Methods

### *Subjects*

The study population comprised a 50% random sample of HIV infected individuals who were treatment-naïve newly presenting for first-time care at the Singapore CDC from January 2006 to December 2011.

[1]Institute of Infectious Disease and Epidemiology, Communicable Disease Centre, Tan Tock Seng Hospital, Singapore
Address for Correspondence: Dr Ng Oon Tek, Institute of Infectious Disease and Epidemiology, Communicable Disease Centre, Tan Tock Seng Hospital, Singapore 308433.
Email: oon_tek_NG@ttsh.com.sg

*Study Design*

This was a cross-sectional study. Clinical data were collected from chart review (e.g. age at HIV diagnosis, ethnic group, baseline CD4+ T-cell count, HIV transmission risk factor). Baseline screening results were imported directly from the laboratory database (Table 1). It was expected that for a small number of patients, baseline results would be unavailable if screening tests were not performed at this institution.

This study was approved by the National Healthcare Group (NHG) Domain Specific Review Board (DSRB) (Reference Code: 2012/00438).

*Data Analysis*

All statistical analysis was performed using the statistical software package, STATA 11.2.

## Results

*Population Characteristics*

In total, 793 cases were analysed. The majority of subjects were men (93.4%) and of Chinese ethnicity (77.9%). The main modes of HIV transmission were heterosexual (51.1%), men who have sex with men (MSM) (33.7%), bisexual (9.2%), intravenous drug user (IVDU) (3.6%), and 2.4% of transmission routes included vertical transmission and unclear mode of transmission. The mean age at HIV diagnosis was 41.4 years and the mean baseline CD4+ T-cell count was 222 cells/mm$^3$ (Tables 2, 3 and 4).

*Overview*

The seroprevalence of CMV was 96.8%; hepatitis A: 40.9%; toxoplasmosis: 23.7%; syphilis: 12.3%; hepatitis B: 8.1%; and hepatitis C: 2%.

*Syphilis*

Of 793 subjects, 780 (98.4%) received at least a single syphilis screening test. There were 277 (35.5%) patients excluded on the basis of only one type of serological test result available, while 97 (12.4%) patients were excluded due to discordance between the initial non-treponemal and treponemal test, with no second treponemal test result available for confirmation.[7,8] Amongst these, 406 (52.1%) screening tests met our criteria and were analysed. Seroprevalence of syphilis was 12.3%. Newly diagnosed HIV individuals who were also co-infected with syphilis were most likely to be MSM (OR 2.53, 95% CI, 1.31 to 4.90, $P = 0.006$). No demographic differences were identified between those included in the analysis and those excluded, when analysed by gender ($P = 0.50$), ethnic group ($P = 0.27$), age group ($P = 0.76$), CD4+ T-cell count group ($P = 0.26$) and main mode of HIV transmission ($P = 0.13$).

Table 1. Definition of Positive Screening Test Results for Cytomegalovirus, Hepatitis A, B, C, Syphilis and Toxoplasmosis

| | Screening Tests | Definition of Positive Result |
|---|---|---|
| Cytomegalovirus (CMV) | IgG | Reactive |
| Hepatitis A (HAV) | Ig M and IgG | Reactive |
| Hepatitis B (HBV) | Core antibody (Anti-HBc), surface antigen (HBsAg), Surface antibody (Anti-HBs IgG) | Reactive HBsAg |
| Hepatitis C (HCV) | IgG, RNA PCR | Reactive IgG and detectable virus |
| Syphilis | RPR, VDRL, TPPA/ TPHA, IgG | Reactive treponemal and non-treponemal tests or 2 reactive non-treponemal tests (i.e. RPR and VDRL) |
| Toxoplasmosis | IgG | Reactive |

IgG: Immunoglobulin G; PCR: Polymerase chain reaction; RPR: Rapid plasma reagin; RNA: Ribonucleic acid; TPHA: Treponema pallidum hemagglutination assay; TPPA: Treponema pallidum particle agglutination; VDRL: Venereal disease research laboratory

Table 2. Main Demographic Characteristics of Patients in the Study

| Total | 793 (%) |
|---|---|
| Gender | |
| Female | 52 (6.6) |
| Male | 741 (93.4) |
| Ethnic group | |
| Chinese | 618 (77.9) |
| Malay | 112 (14.1) |
| Indian | 34 (4.3) |
| Others | 29 (3.7) |
| Main mode of HIV transmission | |
| Heterosexual | 405 (51.1) |
| MSM | 267 (33.7) |
| Bisexual | 73 (9.2) |
| IVDU | 29 (3.6) |
| Others* | 19 (2.4) |
| Mean Age at HIV Diagnosis (Years) | 41.4 |
| Mean CD4 Cell Count at Diagnosis/mm$^3$ | 222 |

*This includes all other modes of HIV transmission (vertical transmission and unclear mode of transmission).

HIV: Human immunodeficiency virus; IVDU: Intravenous drug users; MSM: Men who have sex with men

Table 3. Characteristics of Patients by Syphilis, Hepatitis B and Hepatitis C Status in CDC, Singapore From January 2006 to December 2011

| Category | Syphilis | | | Hepatitis B | | | Hepatitis C | | |
|---|---|---|---|---|---|---|---|---|---|
| | Non- syphilis Co-infected (%) | Syphilis Co-infected (%) | *P* Value | Non-Hep B Co-infected (%) | Hep B Co-infected (%) | *P* Value | Non-Hep C Co-infected (%) | Hep C Co-infected (%) | *P* value |
| Gender | | | | | | | | | |
| Female | 28 (96.6) | 1 (3.4) | 0.13 | 50 (98.0) | 1 (2.0) | 0.10 | 47 (95.9) | 2 (4.1) | 0.27 |
| Male | 328 (87.0) | 49 (13.0) | | 669 (91.5) | 62 (8.5) | | 706 (98.2) | 13 (1.8) | |
| Ethnicity | | | | | | | | | |
| Chinese | 280 (86.2) | 45 (13.8) | 0.19 | 552 (90.5) | 58 (9.5) | 0.04 | 592 (99.2) | 5 (0.8) | <0.001 |
| Malay | 51 (91.1) | 5 (8.9) | | 106 (96.4) | 4 (3.6) | | 100 (91.7) | 9 (8.3) | |
| Indian | 13 (100.0) | 0 (0) | | 34 (100) | 0 (0) | | 34 (100.0) | 0 (0) | |
| Others | 12 (100.0) | 0 (0) | | 27 (96.4) | 1 (3.6) | | 27 (96.4) | 1 (3.6) | |
| Age of HIV diagnosis (years) | | | | | | | | | |
| <30 | 71 (88.8) | 9 (11.2) | 0.11 | 151 (95.0) | 8 (5.0) | 0.19 | 152 (98.1) | 3 (1.9) | 0.65 |
| 30 – 39 | 88 (81.5) | 20 (18.5) | | 190 (89.2) | 23 (10.8) | | 203 (98.5) | 3 (1.5) | |
| 40 – 49 | 92 (88.5) | 12 (11.5) | | 184 (91.1) | 18 (8.9) | | 195 (97.0) | 6 (3.0) | |
| ≥50 | 105 (92.1) | 9 (7.9) | | 194 (93.3) | 14 (6.7) | | 203 (98.5) | 3 (1.5) | |
| CD4 Count (Cell/mm$^3$) | | | | | | | | | |
| ≤200 | 201 (88.2) | 27 (11.8) | 0.57 | 388 (91.7) | 35 (8.3) | 0.87 | 400 (97.6) | 10 (2.4) | 0.49 |
| 201 – 350 | 64 (84.2) | 12 (15.8) | | 150 (91.5) | 14 (8.5) | | 157 (98.1) | 3 (1.9) | |
| >350 | 91 (89.2) | 11 (10.8) | | 181 (92.8) | 14 (7.2) | | 196 (99.0) | 2 (1.0) | |
| Main Mode of HIV Transmission | | | | | | | | | |
| Heterosexual | 206 (92.0) | 18 (8.0) | 0.04 | 374 (93.7) | 25 (6.3) | 0.43 | 386 (80.0) | 3 (20.0) | <0.001 |
| MSM | 104 (81.9) | 23 (18.1) | | 237 (89.8) | 27 (10.2) | | 261 (100.0) | 0 (0) | |
| Bisexual | 27 (87.1) | 4 (12.9) | | 66 (91.7) | 6 (8.3) | | 71 (98.6) | 1 (1.4) | |
| IVDU | 11 (84.6) | 2 (15.4) | | 26 (89.7) | 3 (10.3) | | 18 (62.1) | 11 (37.9) | |
| Others* | 8 (72.7) | 3 (27.3) | | 16 (88.9) | 2 (11.1) | | 17 (100.0) | 0 (0) | |

*This includes all other modes of HIV transmission (vertical transmission and unclear mode of transmission).

HIV: Human immunodeficiency virus; IVDU: Intravenous drug users; MSM: Men who have sex with men

Table 4. Risk Predictors of Syphilis, Hepatitis B and Hepatitis C Co-infections in CDC, Singapore From January 2006 to December 2011

| Variable | Syphilis | | | | Hepatitis B | | | | Hepatitis C | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | OR, Univariable Analysis* (95% CI) | *P* Value | OR, Multivariable Analysis (95% CI) | *P* Value | OR, Univariable Analysis* (95% CI) | *P* Value | OR, Multivariable Analysis (95% CI) | *P* Value | OR, Univariable Analysis* (95% CI) | *P* Value | OR, Multivariable Analysis (95% CI) | *P* Value |
| Gender | | | | | | | | | | | | |
| Female | 1.00† | - | - | - | 1.00† | - | - | - | 1.00† | - | - | - |
| Male | 4.18 (0.56 – 31.44) | 0.16 | | | 4.63 (0.63 – 34.12) | 0.13 | | | 0.43 (0.09 – 1.97) | 0.28 | | |
| Ethnicity | | | | | | | | | | | | |
| Chinese | 1.00† | - | - | - | 1.00† | - | - | - | 1.00† | - | 1.00† | - |
| Malay | 0.61 (0.23 – 1.61) | 0.32 | | | 0.36 (0.13 – 1.01) | 0.05 | | | 10.66 (3.50 – 32.45) | <0.001 | 13.50 (2.99 – 60.95) | 0.001 |
| Indian | - | - | | | - | - | | | - | - | - | - |
| Others | - | - | | | 0.35 (0.05 – 2.64) | 0.31 | | | 4.39 (0.50 – 38.85) | 0.18 | 20.75 (1.69 – 255.22) | 0.02 |
| Age of HIV Diagnosis (Years) | | | | | | | | | | | | |
| <30 | 1.00† | - | - | - | 1.00† | - | - | - | 1.00† | - | - | - |
| 30 – 39 | 1.79 (0.77 – 4.18) | 0.18 | | | 2.28 (0.99 – 5.25) | 0.05 | | | 0.75 (0.15 – 3.76) | 0.73 | | |
| 40 – 49 | 1.03 (0.41–2.58) | 0.95 | | | 1.85 (0.78 – 4.36) | 0.16 | | | 1.56 (0.38 – 6.33) | 0.54 | | |
| ≥50 | 0.68 (0.26 – 1.79) | 0.43 | | | 1.36 (0.56 – 3.33) | 0.50 | | | 0.75 (0.15 – 3.76) | 0.73 | | |
| CD4 Count (Cell/mm$^3$) | | | | | | | | | | | | |
| ≤200 | 1.11 (0.53 – 2.34) | 0.78 | - | - | 1.17 (0.61 – 2.22) | 0.64 | - | - | 2.45 (0.53 – 11.29) | 0.25 | - | - |
| 201 – 350 | 1.55 (0.64 – 3.73) | 0.33 | | | 1.21 (0.56 – 2.61) | 0.63 | | | 1.87 (0.31 – 11.35) | 0.50 | | |
| >350 | 1.00† | - | | | 1.00† | - | | | 1.00† | - | | |
| Main Mode of HIV Transmission | | | | | | | | | | | | |
| Heterosexual | 1.00† | - | 1.00† | - | 1.00† | - | 1.00† | - | 1.00† | - | 1.00† | - |
| MSM | 2.53 (1.31 – 4.90) | 0.006 | 2.53 (1.31 – 4.90) | 0.006 | 1.70 (0.97 – 3.01) | 0.07 | | | | | | |
| Bisexual | 1.70 (0.53 – 5.38) | 0.37 | 1.70 (0.53 – 5.38) | 0.37 | 1.36 (0.54 – 3.44) | 0.52 | | | 1.81 (0.19 – 17.67) | 0.61 | 1.70 (0.17 – 17.30) | 0.65 |
| IVDU | 2.08 (0.43 – 10.12) | 0.36 | 2.08 (0.43 – 10.12) | 0.36 | 1.73 (0.49 – 6.10) | 0.40 | | | 78.63 (20.16 – 306.75) | <0.001 | 102.96 (20.04 – 529.06) | <0.001 |
| Others‡ | 4.29 (1.05 – 17.61) | 0.01 | 4.29 (1.05 – 17.61) | 0.04 | 1.87 (0.41 – 8.59) | 0.42 | | | - | - | - | - |

*Variables that are statistically significant under univariable analysis will be included in the multivariable analysis model.

†Denotes reference group.

‡This includes all other modes of HIV transmission (vertical transmission and unclear mode of transmission).

HIV: Human immunodeficiency virus; IVDU: Intravenous drug users; MSM: Men who have sex with men

*Hepatitis A*

Results were available for 679 subjects (85.6%). The seroprevalence of hepatitis A total antibody was 40.9%. This was higher than the prevalence of 25.9% in the general Singapore population reported in 2003.[9] Our seroprevalence was lower than other studies of HIV populations: 56.6% (France);[10] 60.9% (Taiwan);[11] and 74% (Spain).[12]

*Hepatitis B*

Results were available for 782 subjects (98.6%). A reactive HBsAg test was reported in 8.1%. This was higher than the prevalence of 4% in 1999 and 2.8% in 2005 reported in the general population by the National Seroepidemiological Survey of Hepatitis B.[13] Our hepatitis B co-infection rate was comparable to other studies: 6.1% (Chile),[14] 6.3% (China),[15] 8% (South Alberta, United States),[16] 15.2% (East and Northeast India), [17] and 17.3% (Tanzania, South Africa).[18] The MSM population did not have a statistically significant higher risk of hepatitis B co-infection compared to other transmission risk groups (OR 1.70, 95% CI, 0.97 to 3.01, $P = 0.07$).

*Hepatitis C*

Results were available for 768 subjects (96.8%). HCV IgG was detected in 4.6% of the patients, 43% of whom had active Hepatitis C (confirmed with HCV RNA reactivity). This was marginally higher than the prevalence of 1.7% in the local general population in 1991.[19] However, our hepatitis C co-infection rate was lower compared to other HIV infected populations: 7.4% (East and Northeast India);[17] 17.6% (South Alberta, United States);[16] 18.1% (Tanzania, South Africa);[18] and 59% (China).[15] IVDU was identified as the most important predictor of hepatitis C co-infection in our multivariable analysis model (OR 102.96, 95% CI, 20.04 to 529.06, $P < 0.001$).

*Cytomegalovirus (CMV)*

Results were available for 753 subjects (95%). The seroprevalence of CMV lgG was 96.8%. This was higher compared to 87% in our local antenatal population,[20] but similar to studies conducted in other HIV infected populations: 84.1% (South Alberta, USA);[16] 94% (Iran);[21] and 98.5% (Chile).[22]

*Toxoplasmosis*

Results were available for 771 subjects (97.2%). The seroprevalence of toxoplasmosis IgG was 23.7%, compared to 17.2% in our local antenatal population.[20] The seroprevalence for other studies conducted in HIV infected populations were: 10.6% (South Alberta, United States);[16] 26% (Chile);[14] 44.8% (Malaysia);[23] 49.8% (Iran);[24] and 54.2% (Nigeria).[25]

*Temporal Trends in Selected Conditions*

The proportion of syphilis increased from 11.8% (2006 to 2008) to 13% (2009 to 2011), but this was not statistically significant ($P = 0.72$). The prevalence of Hepatitis B decreased non-significantly from 10% (2006 to 2008) to 6.2% (2009 to 2011), ($P = 0.06$). The proportion of hepatitis C co-infection was relatively similar from 1.9% (2006 to 2008) to 2% (2009 to 2011), ($P = 0.87$) (Table 5).

Table 5. Temporal Trends in Syphilis, Hepatitis A and Hepatitis C Co-infections in CDC, Singapore

| Co-infection | Prevalence n (%) at CDC From 2006 to 2008 | Prevalence n (%) at CDC From 2009 to 2011 | *P* Value |
|---|---|---|---|
| Syphilis | 28 (11.8) | 22 (13.0) | 0.72 |
| Hepatitis B | 38 (10.0) | 25 (6.2) | 0.06 |
| Hepatitis C | 7 (1.9) | 8 (2.0) | 0.87 |

## Discussion

This study examined the seroprevalence of CMV, syphilis, viral hepatitis and toxoplasmosis in newly diagnosed HIV individuals in Singapore. Though our seroprevalence was comparable to other HIV infected populations, the prevalence of CMV (96.8%), hepatitis A (40.9%), toxoplasmosis (23.7%), hepatitis B (8.1%) and hepatitis C (2%) appeared to be higher than the general population in Singapore.[9,13,19,20] This suggests that local HIV infected patients are at a higher risk of developing complications brought about by these concomitant medical conditions.

The transmission modalities of HBV, HCV and HIV are known to be similar, but the transmission efficacy of each virus differs. HCV transmission is more efficient in certain high-risk populations, such as in IVDU.[26] Among those co-infected with hepatitis C, 73.3% of them were IVDUs. In addition, IVDU was identified as the most important risk predictor of hepatitis C co-infection in our multivariable analysis model (OR 102.96, 95% CI, 20.04 to 529.06, $P < 0.001$).

In the United States, HIV/HBV co-infection rates are highest among MSM and IVDU populations. This is in contrast to Asia and sub-Saharan Africa, where vertical and early childhood exposure are more common modes of transmission, and the overall HBV prevalence is much higher.[27] The relatively low seroprevalence rate in our newly diagnosed HIV population (8.1%) probably reflects the success of vaccination through the National Childhood

Immunisation Programme (NCIP) and improvements in living standards compared to the region.[28] Nonetheless, hepatitis B chronic infection remains the most common cause of liver cirrhosis locally,[29] and it is crucial that all HIV infected patients who are not carriers and also not immune should receive vaccination.

Similar to other studies, MSM is the population at highest risk of syphilis co-infection.[30,31] This is of particular concern given that the incidence of HIV in the local MSM population is on the rise[32,33] as it suggests that a large proportion of this group may still be engaging in high risk sexual activity. This is also despite a falling background rate of infectious syphilis in the general population: from 18 per 100,000 population in 1986 to 4 per 100,000 in 2009.[4] Hence there is an urgent need to reach out to this susceptible group of individuals to increase their awareness. To reduce the burden of syphilis co-infection, screening tests should be performed regularly for all MSM who remain sexually active. This combined with epidemiological surveillance and educational campaigns might help to reduce the burden of syphilis co-infection in our HIV infected population.

CMV infection is endemic in Singapore,[20] which reflects the high rates seen in the tropics. The high seroprevalence of CMV (96.8%) in our newly diagnosed HIV patients indicates that it might not be necessary to include CMV as part of the baseline serology workup for a newly diagnosed HIV patient in the local context.

Cerebral toxoplasmosis is a life-threatening opportunistic infection in HIV infected patients which can be prevented by appropriate chemoprophylaxis.[34] As prior exposure to toxoplasmosis is relatively common in Singapore (23.7%), routine screening should continue for all newly diagnosed patients and prophylaxis should be initiated in those who are tested sero-positive and have CD4 counts below 100 cells/mm$^3$ in accordance to international guidelines.[34] For those that are sero-negative, advice on food and water safety can be given to prevent acquisition of the parasite.

This study had certain limitations. First, the determination of CMV, syphilis, toxoplasmosis and viral hepatitis was based on cross-sectional measurement of various serologies which only reflected historical exposure to the organism. Thus, it is difficult to determine the temporal relationship between infections with HIV and these organisms, limiting our ability to draw causal inferences about the conditions. Second, other important variables such as socioeconomic status, educational level and safer sexual practices (e.g. condom usages) were not available which might pose as potential risk predictors for conditions such as syphilis and hepatitis B. Third, 52.1% of patients were evaluated for syphilis, which was comparatively lesser than other conditions. One reason for this was that we did not review the clinical and treatment history to establish co-infection for patients with discordance between the initial non-treponemal and treponemal test when the second treponemal test result was unavailable. Nonetheless we were able to show that there were no demographic differences between those included in the analysis and those excluded in terms of gender, ethnic group, age group, CD4+ T-cell count and main mode of HIV transmission. Fourth, we did not correlate patient's CD4 count with positive CMV and toxoplasmosis serology. This would have given a better picture of the number of patients who are at risk of CMV and toxoplasmosis reactivation among newly diagnosed HIV patients.

## Conclusion

This study has demonstrated that our local newly diagnosed HIV patients are living with co-infections from syphilis, hepatitis B and C in addition to positive serology from CMV, toxoplasmosis and hepatitis A that may play important roles in their disease progression, responses to antiretroviral treatment and general health. It is foreseeable that liver diseases from viral hepatitis B and C, and the disease burden from syphilis will continue to rise and we hope scientific findings could be translated into sustainable prevention programmes and improved public health policies in the near future.

REFERENCES

1. Justice AC. HIV and aging: time for a new paradigm. Curr HIV/AIDS Rep 2010;7:69-76.
2. Battegay M, Elzi L. Morbidity and mortality in HIV-infected individuals − a shift towards comorbidities. Swiss Med Wkly 2009;139:564-70.
3. Sighem A, Gras L, Reiss P, Brinkman K, Wolf F. Life expectancy of recently diagnosed symptomatic HIV-infected patients approaches that of uninfected individuals [abstract]. 17th CROI 2010;526.
4. Ministry of Health, Singapore. Communicable Diseases Surveillance in Singapore 2010. Available at: http://www.moh.gov.sg/content/moh_web/home/Publications/Reports/2011/communicable_diseasessurveillanceinsingapore2010.html. Accessed 4 September 2012.
5. Sen P, Chio MT, Tan HH, Chan RK. Rising trends of STIs and HIV Infection in Singapore − a review of epidemiology over the last 10 years. Ann Acad Med Singapore 2006;35:229-35.
6. Ministry of Health, Singapore. Singapore Burden of Disease Study 2004. Available at: http://www.moh.gov.sg/content/moh_web/home/Publications/Reports/2009/singapore_burdenofdiseasestudy2004.html. Accessed 4 September 2012.
7. Centres for Disease Control and Prevention (CDC). Morbidity and Mortality Weekly Report (MMWR): Sexually Transmitted Diseases Treatment Guidelines 2006 [Internet]. Available at: http://www.cdc.gov/std/treatment/2006/rr5511.pdf. Accessed 4 September 2012.
8. Centres for Disease Control and Prevention (CDC) Morbidity and Mortality Weekly Report (MMWR): Discordant results from reverse sequence syphilis screening - five laboratories, United Sates, 2006-2010. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6005a1.htm. Accessed 4 September 2012.

9. Lee HC, Ang LW, Chiew PK, James L, Goh KT. Changing epidemiological patterns of hepatitis A infection in Singapore. Ann Acad Med Singapore 2011;40:439-47.
10. Rey D, Frick-Michot E, Partisani M, Hess-Kempf G, Cheneau C, Priester M, et al. Hepatitis A seroprevalence in HIV-infected patients. Med Mal Infect 2005;35:402-6.
11. Sun HY, Kung HC, Ho YC, Chien YF, Chen MY, Sheng WH, et al. Seroprevalence of hepatitis A virus infection in persons with HIV infection in Taiwan: implications for hepatitis A vaccination. Int J Infect Dis 2009;13:e199-205.
12. González-García JJ, Mahillo B, Hernández S, Pacheco R, Diz S, García P, et al. Prevalences of hepatitis virus coinfection and indications for chronic hepatitis C virus treatment and liver transplantation in Spanish HIV-infected patients. Enferm Infecc Microbiol Clin 2005;23:340-8.
13. Hong WW, Ang LW, Cutter JL, James L, Chew SK, Goh KT. Changing seroprevalence of hepatitis B virus markers of adults in Singapore. Ann Acad Med Singapore 2010;39:591-8.
14. Pérez CC, Cerón AI, Fuentes LG, Zañartu SC, Balcells MME, Ajenjo HC, et al. Hepatitis B, C, Treponema pallidum and Toxoplasma gondii co-infections in HIV infected patients. Rev Med Chil 2009;137:641-8.
15. He N, Chen L, Lin HJ, Zhang M, Wei J, Yang JH, et al. Multiple viral coinfections among HIV/AIDS patients in China. Biosci Trends 2011;5:1-9.
16. Johns DG, Gill MJ. Seroprevalence of cytomegalovirus, Toxoplasma gondii, syphilis, and hepatitis B and C virus infections in a regional population seropositive for HIV infection. Can J Infect Dis 1998;9:209-14.
17. Saha K, Firdaus R, Santra P, Pal J, Roy A, Bhattacharya MK, et al. Recent pattern of Co-infection amongst HIV seropositive individuals in tertiary care hospital, Kolkata. Virol J 2011;8:116.
18. Nagu TJ, Bakari M, Matee M. Hepatitis A, B and C viral co-infections among HIV-infected adults presenting for care and treatment at Muhimbili National Hospital in Dar es Salaam, Tanzania. BMC Public Health 2008;8:416.
19. Yap I, Guan R, Kang JY, Tay HH, Lee E, Choong L, et al. Seroprevalence of antibodies to the hepatitis C virus in Singapore. Southeast Asian J Trop Med Public Health 1991;22;581-5.
20. Wong A, Tan KH, Tee CS, Yeo GS. Seroprevalence of cytomegalovirus, toxoplasma and parvovirus in pregnancy. Singapore Med J 2000;41;151-5.
21. Mehrkhani F, Jam S, Sabzvari D, Fattahi F, Kourorian Z, Seyed Alinaghi S, et al. Cytomegalovirus co-infection in patients with human immunodeficiency virus in Iran. Acta Med Iran 2011;49:551-5.
22. Luchsinger V, Luzoro A, Martínez MJ. High seroprevalence of cytomegalovirus, herpes simplex type 1 virus and Epstein Barr virus infection among human immunodeficiency virus-infected adults. Rev Med Chil 2010;138:809-14.
23. Nissapatorn V, Lee C, Quek KF, Leong CL, Mahmud R, Abdullah KA. Toxoplasmosis in HIV/AIDS patients: a current situation. Jpn J Infect Dis 2004;57:160-5.
24. Mohraz M, Mehrkhani F, Jam S, Seyed Alinaghi S, Sabzvari D, Fattahi F, et al. Seroprevalence of toxoplasmosis in HIV(+)/AIDS patients in Iran. Acta Med Iran 2011;49:213-8.
25. Osunkalu VO, Akanmu SA, Ofomah NJ, Onyiaorah IV, Adediran AA, Akinde RO, et al. Seroprevalence of Toxoplasma gondii IgG antibody in HIV-infected patients at the Lagos University Teaching Hospital. HIV AIDS (Auckl) 2011;3:101-5.
26. CDC IDU HIV Prevention. September 2002 Hepatitis C virus and HIV coinfection. Available at: http://www.cdc.gov/idu/hepatitis/hepc_and_hiv_co.pdf. Accessed 4 September 2012.
27. MI Andersson, CJ van Rensburg. Viral hepatitis and HIV co-infection: review [abstract]. South African Gastroenterol Review 2011;9:16-21.
28. Lim SG, Mohammed R, Yuen MF, Kao JH. Prevention of hepatocellular carcinoma in hepatitis B virus infection. J Gastroenterol Hepatol 2009;24:1352-7.
29. Ong SC, Lim SG, Li SC. How big is the financial burden of hepatitis B to society? A cost-of-illness study of hepatitis B infection in Singapore. J Viral Hepat 2009;16:53-63.
30. Brosh-Nissimov T, Mor Z, Avramovich E, Katchman E, Avidor B, Mor O, et al. Syphilis outbreak among men who have sex with men, Tel Aviv, Israel, 2008-2009. Isr Med Assoc J 2012;14:152-6.
31. Spielmann N, Münstermann D, Hagedorn HJ, an der Heiden M, Houareau C, Gunsenheimer-Bartmeyer B, et al. Time trends of syphilis and HSV-2 co-infection among men who have sex with men in the German HIV-1 seroconverter cohort from 1996-2007. Sex Transm Infect 2010;86:331.
32. Wong CS, Lye DC, Lee CC, Leo YS. HIV infection in Singapore: predominance of men who have sex with men. Singapore Med J 2011;52:860-3.
33. Cutter JL, Lim WY, Ang LW, Tun Y, James L, Chew SK. HIV in Singapore − past, present, and future. AIDS Educ Prev 2004;16:110-8.
34. Centers for Disease Control and Prevention. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. Available at: http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi_041009.pdf. Accessed 4 September 2012.