

Profiling advanced disease in an Asian clinical human immunodeficiency virus cohort: comparison of two definitions for acquired immunodeficiency syndrome

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Objective To compare advanced human immunodeficiency virus disease defined immunologically and clinically by evaluating the characteristics of human immunodeficiency virus patients in Hong Kong.

Design Retrospective observational study.

Setting A human immunodeficiency virus cohort database established at a university and the major human immunodeficiency virus specialist services in Hong Kong.

Patients Patients diagnosed with acquired immunodeficiency syndrome at the study centres between 1985 and 2006 were included.

Main outcome measures Comparison of advanced human immunodeficiency virus disease defined (a) clinically as World Health Organization stage IV, and (b) immunologically as a CD4 count lower than 350/ μ L.

Results Between 1985 and 2006, a total of 1317 patients, a majority of whom Chinese, were evaluated. Of these, 914 (69%) and 335 (25%) fulfilled the criteria for immunologically and clinically defined advanced disease, respectively. The mean age of the study population was 38 years and male-to-female ratio 4:1. There were two peaks in the frequency distribution of CD4 counts, one at a low count of less than 100/ μ L and the other between 200 and 400/ μ L. All except four with clinically defined advanced disease had CD4 counts lower than 350/ μ L on presentation. Of those with immunologically defined advanced disease, men having sex with men accounted for a lower proportion in the clinically advanced category, and *Pneumocystis pneumonia* was the commonest advanced disease at presentation.

Conclusions Both clinical and immunological definitions provide a consistent means for assessing advanced disease, the implications of which are different. Such profiling has been made possible through the operation of a standardised cohort database, which is useful in (1) enhancing human immunodeficiency virus epidemiology studies, and (2) evaluating the performance of public health services.

Key words

Acquired immunodeficiency syndrome; CD4-positive T-lymphocytes; HIV infections; leukocyte count; Penicillium

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Introduction

Historically, the initial description of acquired immunodeficiency syndrome (AIDS) as a clinical entity in 1981 preceded the isolation of human immunodeficiency virus (HIV), its causative agent, by more than 2 years.^{1,2} While antibody tests were soon used in research,^{3,4} it was not till 1985 that a standard antibody test (initially termed HTLV-III antibody or LAV antibody) was introduced,⁵ and the more sensitive third-generation HIV antibody test was not marketed until a decade later.⁶ Not surprisingly, advanced clinical disease was the primary focus in the first decade of the HIV pandemic. In many countries, AIDS surveillance instead of HIV surveillance was the primary tool for assessing HIV epidemiology, which is a phenomenon that continues to hold true to this day in some countries. Different definitions for AIDS have been recommended by the Centers for Disease Control and Prevention (CDC) in Atlanta, the World Health Organization (WHO), and in Europe.⁷⁻⁹ However, referring to late-stage HIV disease, the term 'AIDS' does not have a universally accepted definition. This discrepancy has resulted from the varied

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透過剖析晚期HIV感染患者的亞洲隊列來比較愛滋病的兩種定義

- 目的** 透過對香港HIV患者的特徵研究，比較晚期HIV感染於免疫缺陷和臨床症狀方面的兩種定義。
- 設計** 回顧觀察性研究。
- 安排** 由香港一所大學設立HIV隊列資料庫及香港愛滋病專科醫療服務。
- 患者** 從1985年到2006年於研究中心被確診為患有愛滋病的病人。
- 主要結果測量** 比較晚期HIV感染的兩種定義：(1) 世界衛生組織臨床分級為第四級（臨床剖析）和(2) 免疫缺陷方面CD4水平低於350/ μ L（免疫剖析）。
- 結果** 評估了1985年至2006年期間共1317名病人，其中大部份屬華籍。914人（69%）按免疫剖析被診斷為晚期HIV感染患者，另335人（25%）按臨床剖析被診斷為晚期HIV感染患者。病人平均年齡38歲，男女比例為4：1。CD4水平分佈出現兩個高峰，分別是少於100/ μ L的低水平及200/ μ L至400/ μ L的水平。被臨床剖析診斷為HIV感染的患者，除4位外，其餘的CD4水平均低於350/ μ L。至於免疫剖析的患者，男男性行為者只佔臨床剖析的少數。免疫剖析的患者病發時最普遍的病徵為肺囊蟲肺炎。
- 結論** 臨床定義或免疫缺陷定義各有不同含意，但兩者都為晚期HIV感染提供了有效的診斷。透過剖析標準的隊列資料庫，可以加強HIV流行病學研究，並對公共醫療服務水平加以評估。

geographical pattern of opportunistic infections, inequality of health services, and variation of clinical diagnosis, which makes comparison across countries extremely difficult.

In the last decade, the advent of highly active antiretroviral therapy (HAART) has changed the landscape of HIV disease. A recent study in Europe concluded that "AIDS surveillance data no longer reflects the underlying trends of HIV satisfactorily".⁹ Whereas methodological advances have improved the quality of prevalence and incidence studies, a robust marker of HIV disease for the purpose of evaluating its morbidity pattern and the impact of public health interventions was long overdue. In line with the standardisation of case definitions of almost any medical condition, there was a pressing need to characterise HIV disease specifically. In this connection, WHO's clinical staging has continued to be a useful instrument, with stage IV likened to the 'AIDS' reported in most countries. In the guidance issued by WHO in 2007, for an HIV-positive individual, the term "advanced HIV infection" was defined immunologically by a CD4 count of less than 350/ μ L.⁷ These two indicators, either alone or in combination, may be more objective markers for evaluating advanced HIV diseases. We undertook a

comparison of advanced HIV disease defined both immunologically (CD4 <350/ μ L) and clinically (WHO stage IV) by examining the characteristics of a cohort of HIV patients in Hong Kong. As a high proportion of reported HIV patients were included in this newly established cohort, the comparison allowed us to assess the performance of these two indicators as a measure of HIV-related morbidity in the population.

Methods

Data source: Hong Kong human immunodeficiency virus cohort database

The Hong Kong HIV cohort database was introduced in 2006, and began as a collaborative research project of the Chinese University of Hong Kong and the Hong Kong SAR Government Department of Health, and two major HIV specialist services. The latter consisted of (1) the Integrated Treatment Centre, and (2) the Queen Elizabeth Hospital HIV service, both of which offered HIV care as a public service, in accordance with internationally established standard guidelines. With a total caseload of about 1800, of which over 70% were in receipt of HAART, the cohort functioned as a harmonised data warehouse of clinical HIV/AIDS in complementing regular HIV reporting, a voluntary system that has been in place since 1984. The anonymised cohort database was comprised of two modules—a baseline module and a longitudinal module. The former captured characteristics of HIV-positive individuals at the time of initial HIV diagnosis, and included: demographics, diagnosis setting, essential laboratory markers (CD4 and viral load), and AIDS-defining illnesses (whenever appropriate). The longitudinal module captured the yearly updates on the development of AIDS-defining illnesses, CD4/viral load and antiretroviral therapy received. In this study, data from the baseline module were retrieved as a means of supporting the analysis of advanced HIV diseases. The ethics committees of the respective clinical services at the Department of Health and the Hospital Authority approved this project.

Defining advanced human immunodeficiency virus disease

All HIV patients registered in the cohort had been diagnosed with the infection by both a screening enzyme-linked immunosorbent assay test and a confirmatory Western blot for HIV antibody. The latter was performed at one of the three public service laboratories in collaboration with the Department of Health HIV Surveillance Unit. Enumeration of CD4 counts was by a single laboratory using standard flow cytometry. Clinical conditions related to HIV/AIDS were diagnosed by specialist HIV physicians in accordance with guidelines established by the

Scientific Committee on AIDS in Hong Kong,¹⁰ which were based on international criteria for HIV/AIDS diagnosis and reporting. This study only included patients with a baseline CD4 count on record, who had also been evaluated for the presence of advanced diseases.

Two categories of adult patients (age ≥15 years) with advanced HIV disease were defined:

1. Immunologically defined advanced HIV disease referred to a CD4 count of less than 350/μL within 3 months of the laboratory HIV diagnosis.
2. Clinically defined advanced HIV disease referred to a clinical diagnosis of advanced disease benchmarked as WHO stage IV. In Hong Kong, the CDC 1993 classification criteria were adopted for diagnosing an AIDS condition with the following modifications: (a) CD4 count per se was not used as a criterion for AIDS, (b) *Penicillium marneffei* was specifically included, and (c) pulmonary tuberculosis (TB) and/or TB lymphadenopathy was specifically excluded unless the CD4 count was below 200/μL at presentation.¹⁰ The 'AIDS' using the Hong Kong criteria was similar to WHO stage IV disease, after excluding (c) above. In this study, therefore, clinically defined advanced disease actually corresponded to a diagnosis of AIDS using the Hong Kong criteria, except for pulmonary TB, within 3 months of the laboratory HIV diagnosis.

Comparison of advanced human immunodeficiency virus disease as per the two definitions

Comparison was made at three levels. The first referred to demographics of included cases (age, gender, ethnicity, routes of transmission). The second referred to the setting of the HIV diagnosis (year of positive test, concurrent report of AIDS, in the community versus hospital). The third dealt with clinical/virological correlations (initial CD4 count, viral load, and a diagnosis of TB).

Collected data were entered into standard spreadsheets, and analysed using the Statistical Package for the Social Sciences (Windows version 13.0; SPSS Inc, Chicago [IL], US). Comparison of the two pairs of mutually exclusive groups entailed using odds ratios for: clinically defined advanced and non-advanced disease, and immunologically defined advanced and non-advanced disease. Any P value of less than 0.05 was taken to be statistically significant.

Results

Characteristics of human immunodeficiency virus patients in the cohort database

Of 1777 cases in the database with records on AIDS-

TABLE 1. Characteristics of human immunodeficiency virus (HIV) patients in the Hong Kong HIV observational cohort (n=1317)

Characteristic	No. of patients
Age (years)	
Mean (standard deviation)	38 (12)
Median (range)	36 (16-82)
Gender	
Male	1055 (80%)
Female	262 (20%)
Ethnicity	
Chinese	1078 (82%)
Asian non-Chinese	178 (14%)
Other ethnicities	61 (5%)
Route of transmission	
Sexual transmission	1239 (94%)
Injection drug users	45 (3%)
Perinatal infection	0 (0%)
Blood/blood product transfusion	6 (0.5%)
Unknown (not reported)	27 (2%)
Sexual transmission in male subjects (n=987)	
Heterosexual	555 (56%)
Men having sex with men	432 (44%)
Source of referral (n=933)	
Self-referred	6 (1%)
Sexually transmitted infection clinic	287 (31%)
Tuberculosis and chest clinic	68 (7%)
Other public clinics	65 (7%)
Other private clinics	134 (14%)
Following hospitalisation	170 (18%)
Drug rehabilitation services	18 (2%)
AIDS* counselling service/non-governmental organisations	185 (20%)
AIDS (using Hong Kong criteria)	
At HIV diagnosis	397 (30%)
CD4 counts	
Mean (standard deviation)	252 (233)
Median (range)	218 (0-1683)
<350/μL	914 (69%)
Viral load	
Undetectable (viral load ≤500/mL)	33 (3%)
Median viral load (log), range	67 000 (4.83), 530-5 700 000

* AIDS denotes acquired immunodeficiency syndrome

defining illnesses, 460 (26%) were excluded because of missing CD4 values. A total of 1317 HIV patients (diagnosed between 1985 and 2006) were therefore evaluated; the vast majority (88.9%) were reported in or after 1997 (Table 1). At presentation, the mean

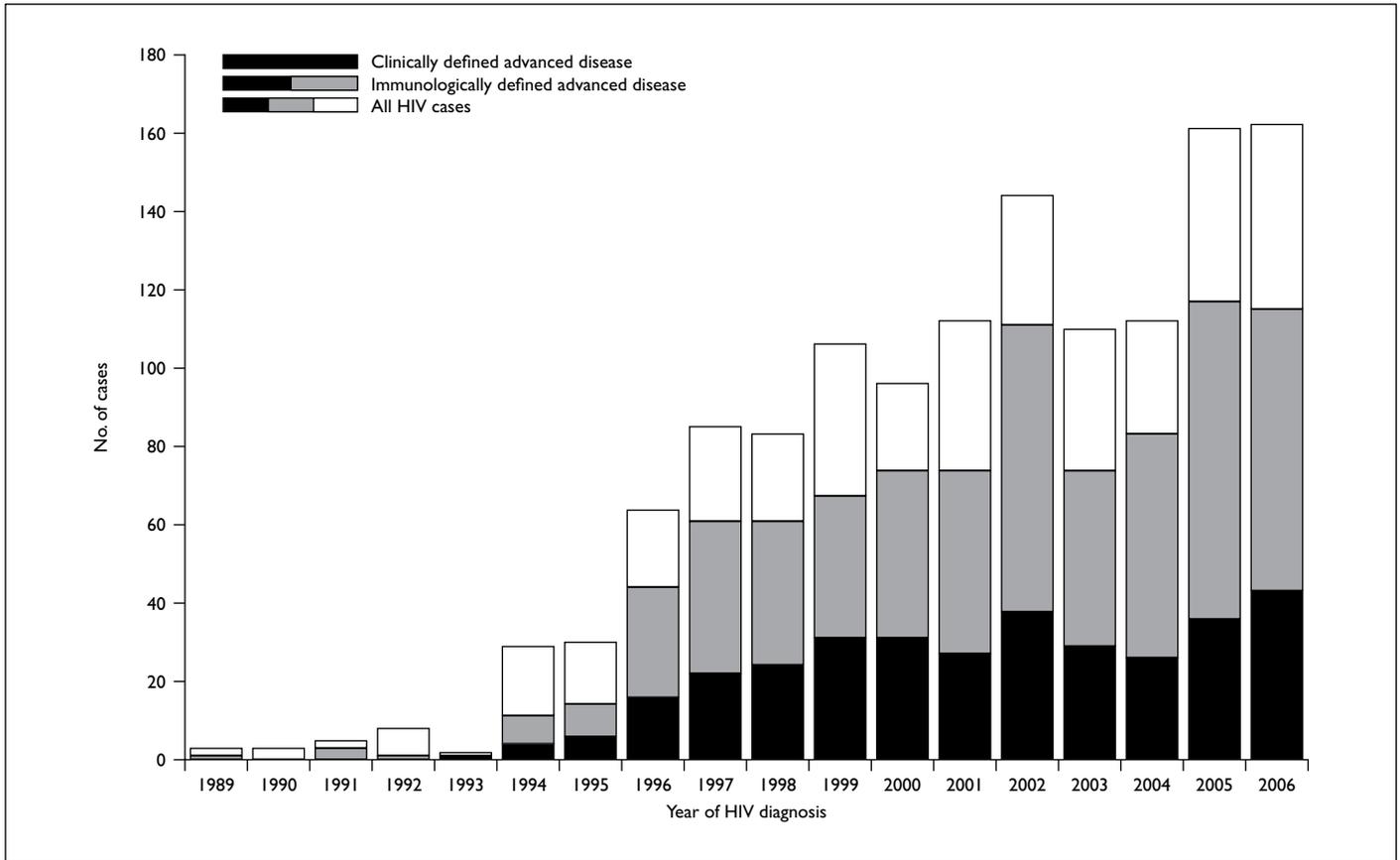


FIG 1. Yearly distribution of cases with advanced disease defined immunologically and clinically in the Hong Kong human immunodeficiency virus (HIV) observational cohort

age of these patients was 38 years and the male-to-female ratio was 4:1. Sexual transmission accounted for almost all cases (94%). For male patients, heterosexually acquired infections were more common than via men having sex with men (MSM), the ratio being 56% versus 44%. A majority (82%) were Chinese referred from other clinical services, through voluntary counselling and testing (VCT) services, or self-referred.

Overall, 914 (69%) of the patients had a CD4 count of less than 350/ μ L at presentation (ie immunologically defined advanced disease); while 335 (25%) had clinically defined advanced disease. Figure 1 shows the distribution of reported HIV infections and the proportion with advanced disease by year. Between 1997 and 2006, 63 to 77% of all HIV infections fulfilled the criteria for immunologically defined advanced disease, whereas for clinically defined advanced disease, the range was 22 to 29%; the proportion satisfying the AIDS case definition for Hong Kong was between 26 and 39%. The respective percentages remained relatively stable over years. The wide fluctuation of the proportions before 1997 was probably a reflection of the small number of cases within the dataset.

Clinically versus immunologically defined advanced disease

Of the 335 clinically defined patients with advanced disease, over half (53.1%) were diagnosed to have *Pneumocystis pneumonia* (PCP), whereas a quarter had fungal infections, namely: penicilliosis (12.8%), oesophageal candidiasis (7.2%), and cryptococcosis (5.7%) [Table 2]. All except four patients with clinically defined advanced disease had a presenting CD4 count of less than 350/ μ L. Clinically defined advanced disease accounted for 25% of all enrolled patients in the cohort. Their age was generally higher (mean age, 40.5 vs 37.5 years; $t=4.08$, $P<0.01$). More patients with clinically defined advanced than non-advanced disease were aged more than 40 years (40% vs 32%, odds ratio [OR]=1.45; 95% confidence interval [CI], 1.12-1.87). More patients with clinically defined advanced than non-advanced disease had a viral load of 5 log or more (60% vs 32%; OR=3.19; 95% CI, 2.38-4.27) [Table 3]. Regarding the four patients presenting with clinically defined advanced disease but a CD4 count of higher than 350/ μ L, one had PCP (CD4=361/ μ L), and three had extrapulmonary TB (CD4=355, 427, 546/ μ L).

The 914 immunologically defined advanced

disease subjects accounted for over two thirds of the eligible cohort. Again, those with advanced rather than non-advanced disease were older (mean age, 39.5 vs 35.4 years; $t=6.25$, $P<0.01$). Subjects with immunologically defined advanced versus non-advanced disease yielded similar patterns to that encountered according to the clinical categorisation. The immunologically defined advanced disease patients were older; a significantly higher proportion of them were aged more than 60 years compared to those with a higher CD4 count (7% vs 3%; OR=2.99; 95% CI, 1.52-5.89). Since almost all (except four) clinically defined advanced disease patients were also immunologically advanced, low CD4 count patients (CD4 <350/ μ L) with and without clinical disease were compared. A higher proportion without clinical disease were MSM than heterosexuals (48% vs 26%; OR=2.70; 95% CI, 1.93-3.79). There were more VCT referred cases in those without clinical disease.

Correlating CD4 counts and clinical disease

Figure 2 shows the variation of CD4 counts with the frequency and the occurrence of clinical disease. About a quarter (27%) of the enrolled patients had an initial CD4 count of not more than 50/ μ L. Overall there appeared to be two peaks, one at the very low CD4 count (<100/ μ L), and the other between 200 and 400/ μ L. *Pneumocystis pneumonia* was the commonest marker of advanced disease at all CD4 count values, accounting for more than 50% of all such cases. Tuberculosis (extrapulmonary), however, was more prevalent at higher CD4 counts, accounting for 2.2% for CD4 counts of 50/ μ L or below, 5.7% for counts of more than 50/ μ L to 100/ μ L, and 14.3% for counts of over 100/ μ L, the corresponding percentages being 10.3, 16.7 and 30.0, respectively (for all TB cases). Over half of the patients presenting with CD4

TABLE 2. World Health Organization stage IV disease (clinically defined advanced disease) in the cohort (n=335)

Disease	No. (%)
HIV* wasting syndrome	1 (0.3)
<i>Pneumocystis pneumonia</i>	178 (53.1)
Oesophageal candidiasis (or candidiasis of trachea, bronchi, or lungs)	24 (7.2)
Extrapulmonary tuberculosis	12 (3.6)
Kaposi's sarcoma	4 (1.2)
Cytomegalovirus infection (retinitis or infection of other organs)	12 (3.6)
Central nervous system toxoplasmosis	5 (1.5)
HIV encephalopathy	1 (0.3)
Extrapulmonary cryptococcosis including meningitis	19 (5.7)
Disseminated non-tuberculous mycobacterial infection	16 (4.8)
Progressive multifocal leukoencephalopathy	3 (0.9)
Chronic cryptosporidiosis (with diarrhoea)	2 (0.6)
Chronic isosporiasis	1 (0.3)
Disseminated mycosis (penicilliosis)	43 (12.8)
Recurrent non-typhoidal <i>Salmonella</i> bacteraemia	7 (2.1)
Lymphoma (cerebral or B-cell non-Hodgkin) or other solid HIV-associated tumours	6 (1.8)
Invasive cervical carcinoma	1 (0.3)

* HIV denotes human immunodeficiency virus

counts of 100/ μ L or less had an episode of clinically defined advanced disease. This proportion fell with increasing CD4 counts. At CD4 counts of over 350/ μ L, clinical disease was exceedingly infrequent (<2.5%).

Discussion

Through an analysis of data in the Hong Kong HIV cohort database, we have managed to compare

TABLE 3. Comparison of patients with advanced and non-advanced disease*

	Clinically defined advanced disease			Immunologically defined advanced disease		
	Yes	No	OR (95% CI)	Yes	No	OR (95% CI)
Age >40 years	135 (40%) [†]	312 (32%)	1.45 (1.12-1.87)	346 (38%) [†]	101 (25%)	1.81 (1.39-2.35)
Age >60 years	22 (7%)	53 (5%)	1.23 (0.74-2.06)	65 (7%) [†]	10 (3%)	2.99 (1.52-5.89)
Male gender	273 (81%)	778 (80%)	1.13 (0.83-1.55)	733 (80%)	318 (80%)	1.05 (0.78-1.41)
Chinese ethnicity	282 (84%)	792 (81%)	1.25 (0.90-1.75)	756 (83%)	318 (80%)	1.24 (0.92-1.67)
Sexual transmission	312 (93%)	923 (94%)	0.81 (0.49-1.34)	864 (95%)	371 (93%)	1.38 (0.86-2.22)
MSM (for male subjects only)	65 (26%) [†]	367 (50%)	0.34 (0.25-0.47)	277 (40%) [†]	155 (53%)	0.59 (0.45-0.78)
VCT referred cases (n=928)	6 (6%) [†]	185 (23%)	0.20 (0.09-0.46)	111 (20%)	80 (22%)	0.84 (0.61-1.17)
AIDS at HIV diagnosis	335 (100%) [†]	58 (6%)	16.86 (13.14-21.64)	392 (43%) [†]	1 (0.3%)	300.21 (42.00-2145.79)
CD4 <200/ μ L	325 (97%) [†]	311 (32%)	69.70 (36.63-132.65)	636 (70%) [†]	0 (0%)	0.30 (0.28-0.34)
Viral load ≥ 5 log (n=1060)	151 (60%) [†]	260 (32%)	3.19 (2.38-4.27)	361 (49%) [†]	50 (16%)	4.98 (3.57-6.96)

* OR denotes odds ratio, CI confidence interval, MSM men having sex with men, VCT voluntary counselling and testing services, AIDS acquired immunodeficiency syndrome, and HIV human immunodeficiency virus

[†] P<0.05

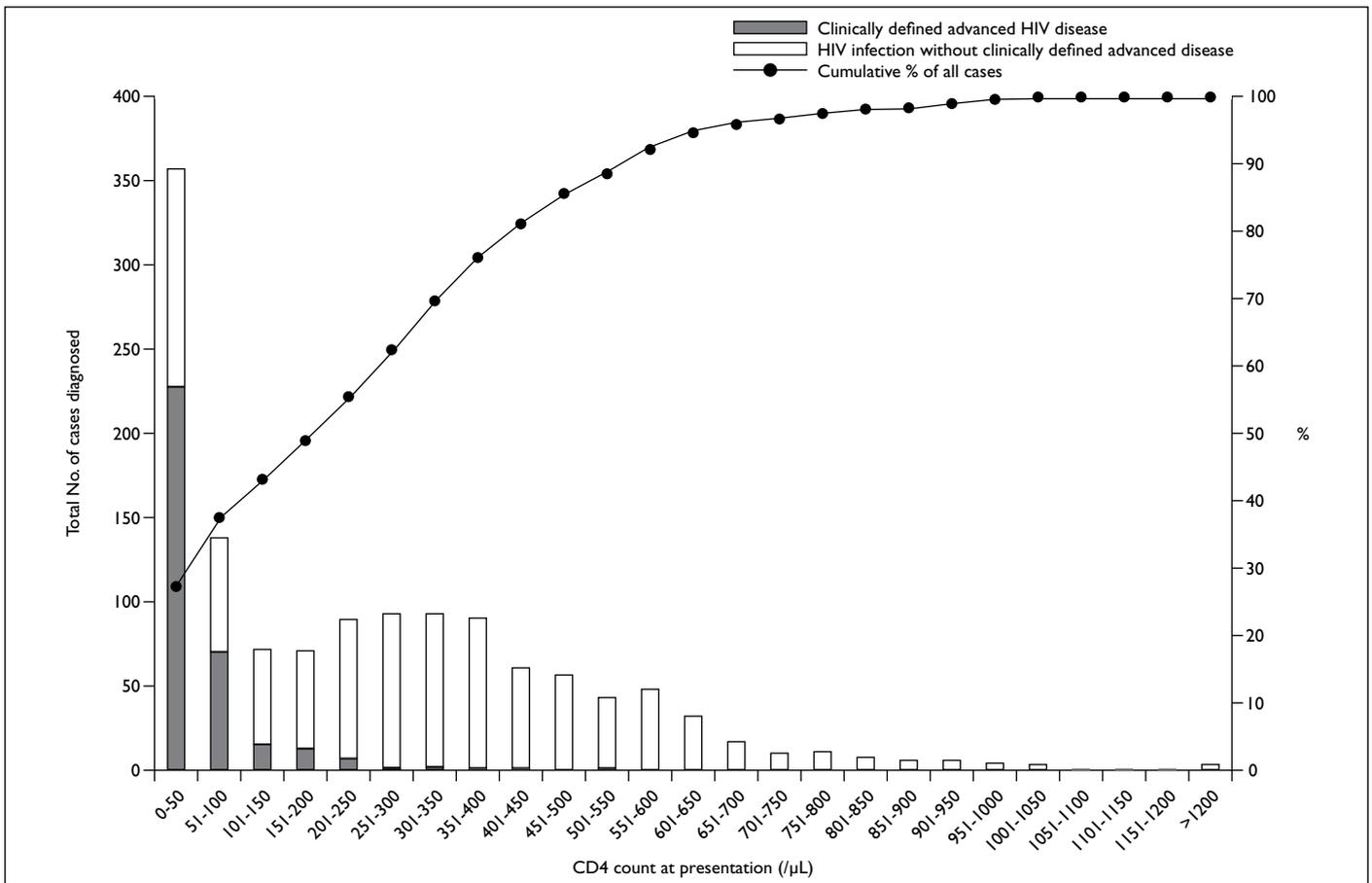


FIG 2. Relationship between CD4 count and clinically defined advanced human immunodeficiency virus (HIV) disease

the status of patients according to two definitions of advanced HIV disease. As HAART is generally unavailable outside the clinical services, this database captured practically all Hong Kong patients, none of whom had received prior antiretroviral therapy. Presentation of advanced disease could be regarded as consistent with the natural history of the condition. In this study, we used the WHO criteria to define advanced HIV disease clinically (stage IV) and immunologically (CD4 <350/µL). By tracking the yearly statistics, it became clear that consistency could be achieved by using either definition. There were two main differences between the definitions. First, the number, and therefore, proportion of patients with immunologically defined advanced disease was more than two-folds greater than that for clinically defined advanced disease. Assuming that all clinical diseases could be spotted without a delay, most of the patients were still reasonably healthy (with CD4 counts of 200-350/µL); less than 5% of all clinical diseases were actually diagnosed with such counts. Second, while the proportion defined according to the two definitions changed in parallel over time, their clinical significance differed. Unlike a low CD4 count per se, clinically defined advanced disease is a direct measure of morbidity due to HIV infection.

Caution must however be exercised, as the exact nature of the clinical disease varies considerably. In Hong Kong clinically defined advanced HIV disease included penicilliosis, a condition which is exceedingly rare outside South-East Asia.^{11,12} Separately, TB as an advanced HIV disease includes all forms of the condition in western countries. In Hong Kong and developing countries where TB infection is endemic, the definition only applied to extrapulmonary disease. On the contrary, a majority (two thirds) of immunologically defined advanced disease patients did not have overt symptomatology of severe immune deficiency. Some may have 'category B' conditions,⁸ the characterisation of which is more difficult, which also makes data comparison difficult. A diagnosis of immunologically defined advanced disease can therefore at best be used as an indicator of impending physical ill health instead of a direct measure of morbidity.

Aside from comparison according to these definitions, delineation of the pattern of advanced disease can be a means of identifying service or intervention gaps in the public health control of HIV/AIDS. Figure 2 suggests that there may be two populations of HIV patients in the cohort. There

are those who did not seek medical attention until progression to advanced disease (as exemplified by low CD4 counts and a high proportion with clinical disease on presentation). These patients may explain the positive skew on the graph. There is another superimposing population (the distribution of which is near normal) having a high proportion with CD4 counts between 200 and 400/ μ L. In our cohort composed of patients largely infected through sex, late presenters were predominantly heterosexually acquired. By contrast, MSM had a more even distribution in terms of presenting CD4 counts. The pattern, if monitored over time, may help health authorities assess service needs in community groups that tend to present late. Either a clinical or immunological definition would enable late presenters to be identified, so long as there is an effective medical system in place that sick patients can turn to.

In practical terms, an immunological marker offers a more objective means both to detect patients who may be clinically ill and identify those prone to disease progression. However, a CD4 count cut-off value of 350/ μ L (as recommended in the WHO guidelines⁷) may be too high to reflect morbidity, while 100 or 150/ μ L may be too low (having insufficient sensitivity) for detecting impending deterioration. There is also the added complexity of a variation of normal ranges of CD4 counts that may affect the choice of the cut-off values.¹³ Currently, CD4 count is one important criterion for initiating HAART in clinical practice. Whereas it is generally recommended to start HAART if the CD4 count falls to below 200/ μ L, the grounds for initiating treatment at higher counts (especially exceeding 350/ μ L) are less clear.¹⁴ In our experience, presentation of patients with CD4 counts of over 250/ μ L was usually not associated with any major opportunistic infection (Fig 2). Thus, a CD4 count of lower than 250/ μ L may be a reasonable count for considering the initiation of HAART in our Chinese population. With increasing access to HAART in developed as well as developing countries, a one-criterion-fits-all policy may need replacement by evidence-based cut-off values using data collected from local clinical cohorts.¹⁵ In many developing countries, however, the major problem is the late presentation of most patients, such that optimal timing for initiating HAART for HIV infection is often missed.¹⁶

Finally, the establishment of an observational cohort database is the key to effective evaluation of HIV morbidity. Since the beginning of the AIDS epidemic, clinical cohorts have contributed to both the unravelling of HIV epidemiology and clinical service development around the world. With a very humble annual budget, the Multicentre AIDS

Cohort Study has been described as a “modest investment of National Institutes of Health (NIH) yielding big dividends”, not just in terms of scientific publications, but more importantly the development of useful clinical guidelines.¹⁷ Increasing numbers of clinical cohorts have been set up to serve similar functions in countries in Europe and the developing world.¹⁸⁻²¹ Some of these entail multi-centre regional cooperation, including the TREAT Asia project in which 17 sites across Asia are participating (<http://www.amfar.org/cgi-bin/iowa/asia/index.html>).²² The Hong Kong HIV observational cohort is a one-city cohort comprising largely of Chinese patients with good access to diagnostic and treatment services in the public sector. With the increasing number of HIV patients in China and Chinese-speaking communities, the Hong Kong cohort is uniquely positioned to generate useful information for improving both epidemiological surveillance and treatment effectiveness. Resorting to cohort data for epidemiologic assessment is not without limitations. The Hong Kong cohort is drawn from about two thirds of all reported cases.²³ As the enrolled subjects are those that have attended a specialist clinical service, the overall pattern inevitably excluded subjects who did not seek conventional medical services, those who were not aware of their HIV status, and those who had left the territory. As a significant proportion of reported HIV infections were in persons using the services of the specialist clinics, to date such bias was likely to be small.²³ With a rising number of cases reported in Hong Kong, there is a need to ensure that the cohort remains robust, so as to reflect the true epidemiological pattern of the infection. Our assessment of advanced disease testifies to the worthiness of this endeavour.

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