

Benefits of early detection and treatment of human immunodeficiency virus infections

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Opportunistic infections are the major causes of morbidity and mortality in people living with the human immunodeficiency virus (HIV). Their occurrence and presentations hinge on the degree of immunodeficiency, as reflected by the patient's CD4 cell counts. For example, while conditions like cytomegalovirus (CMV) retinitis and fungal infections emerge in severely immunocompromised patients, say, at CD4 levels below 50/ μ L, tuberculosis (TB) may manifest at a much earlier stage. For TB/HIV co-infection, prompt treatment with anti-TB regimens is clearly indicated. However, the best timing for initiating antiretroviral therapy has been debated, ever since effective highly active antiretroviral therapy (HAART) became the gold standard in management. There was the concern of immunological rebound arising from HAART, which might lead to a pathological immune reconstitution inflammatory syndrome (IRIS) in co-infected patients.¹ In the current issue of the *Hong Kong Medical Journal*, Chan et al² reported favourable clinical outcome for initiating HAART within 2 months of starting anti-TB treatment. The findings corroborate results of overseas research, which have led to the consensus for initiating HAART at 2 weeks if the CD4 count is <50/ μ L, while deferral to 8 weeks can be considered if the count is higher.³ Taking the strategy further, a study in South Africa reported a lower mortality if concurrent treatment of HIV and TB was provided.⁴ Contrary to previous practice, recent HIV treatment guidelines are in fact advising against sequential treatment with anti-TB followed by HIV therapy.⁵ Early TB treatment is now an established strategy for managing TB/HIV co-infection, but caution should be exercised to prevent IRIS and minimise its harmful effects.

Evidently, reduction of TB-associated morbidity is important in HIV care, especially in localities with high or intermediate TB burden, such as Hong Kong. Rather than focusing on early TB treatment, clinical benefits may be more significant if TB disease can be prevented in the first place. In Chan et al's study,² all TB/HIV co-infected patients were severely immunocompromised at the time of TB diagnosis, as the median CD4 count was only 74/ μ L. In most countries around the world, a CD4 level of 350/ μ L or below is considered a conservative threshold for initiating HAART.⁶ In another study in Hong Kong, the relative hazard of progression to acquired immunodeficiency syndrome (AIDS) was 27-fold higher if the presenting CD4 count was <150/ μ L.⁷

The very low baseline CD4 counts among patients in this Hong Kong cohort, all of whom HAART-naïve, suggested that a majority of the HIV diagnoses were made no earlier than the respective TB diagnoses. Apparently, the window of opportunity for preventing TB disease has been missed as HIV patients did not present themselves early enough for clinical care. If the diagnosis of HIV were to be made earlier, the main strategy could entail baseline screening for latent TB infection (LTBI), followed by yearly screening if the initial tests prove negative. Currently there are two possible methods to screen for LTBI, either through the application of the tuberculin skin test (TST) or by interferon-gamma release assay (IGRA). The research question for Hong Kong is the specific role of these tests: whereas TST results are difficult to interpret against a background of high bacille Calmette-Guérin vaccination coverage, the sensitivity and specificity of IGRA for LTBI detection in an intermediate TB burden locality have not yet been established. Once detected, LTBI treatment can be offered, which serves the purpose of preventing progression to TB disease.³

Despite shortcomings in effectively achieving early TB detection, the epidemiological outlook of HIV is not necessarily gloomy. The question is: are we seeing an increasing burden of HIV-related complications? Let us look for clues in the HIV surveillance reports released by Department of Health.⁸ In the last 4 years, the reported number of AIDS cases has reached a plateau of about 80 per year. Against the background of a continuing rise of new HIV infections, this pattern reflects the slowing of disease progression, which can only be possible through earlier HIV diagnosis, earlier screening, and therefore prophylaxis against opportunistic infection, wider access to LTBI detection and treatment, and the expanded use of HAART. Some may be skeptical about the validity of HIV surveillance data, as HIV numbers can be influenced by changes in reporting behaviours and programmatic efficiency. This is not the case for AIDS (equivalent to the number of HIV-infected patients who develop complications suggestive of underlying immunodeficiency), which is a more robust index for HIV-associated morbidity at population level. The chance of missing an AIDS diagnosis in the public service, which presumably takes care of a majority of HIV patients in Hong Kong, is small. From the surveillance data, the proportion of AIDS cases with TB as an AIDS-defining illness

has continued to account for about one fifth of all cases. While these reflect 'late' diagnosis, they carry a more positive meaning than conditions like CMV retinitis, the occurrence of which is indicative of very bad immunodeficiency. Any HIV specialist in Hong Kong would agree that we are seeing very few CMV retinitis cases these days, thanks to HAART and early HIV diagnosis! The results from Chan et al's cohort² highlight the outcome of a proportion of HIV patients who failed to be identified at an early stage. However, this does not mean that late diagnosis is becoming more common.

While the clinical benefit of early diagnosis and treatment for HIV infection is increasingly obvious, its public health impact remains poorly appreciated. More recently, a landmark study HPTN052 concluded that prompt HAART was associated with a 96% reduction of transmission risk from HIV-positive patients to their seronegative partners.⁹ This observation illustrates the importance of both 'early diagnosis' as well as 'early treatment' in the context of public health. On top of reducing morbidity and mortality in those living with HIV, the chance of virus transmission is also minimised. Interestingly, the results have also been instrumental in encouraging epidemiologists to translate individual viral loads into population viral load measures.^{10,11} Rather than

relying on counting the number of HIV patients with complications like TB for assessing population risks, we are heading towards a new era of measuring virus at a population level in evaluating the future risk of HIV transmission. Further research is, however, needed to confirm the effectiveness of HAART in reducing transmission in different population groups, specifically men who have sex with men (MSM) who now account for a higher proportion of newly diagnosed HIV infections in Hong Kong. An earlier study at the end of 2000 suggested that MSM did not present late at diagnosis.¹² The ultimate scenario of HIV morbidity and population transmission dynamics must be derived from an integration of clinical and epidemiological observations over time, coupled with an understanding of the pattern of early versus late diagnoses among different population groups. Establishment of cohorts and studying them longitudinally are crucial.¹³

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