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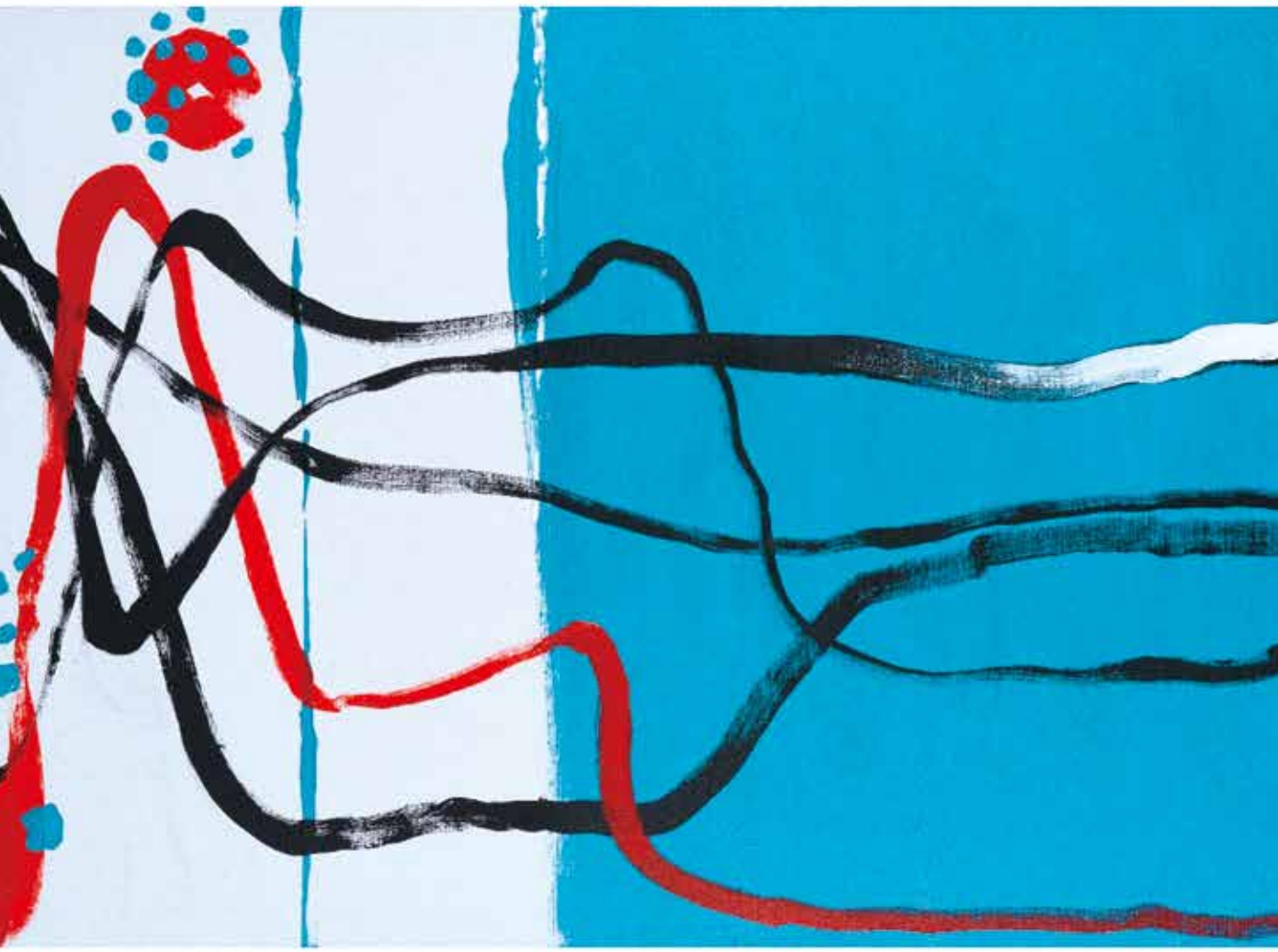
THE HONG KONG MEDICAL DIARY 香港醫訊

VOL.27 NO.3 March 2022

Infectious Diseases - HIV



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CrCl, creatinine clearance; DDIs, drug-drug interactions; DHHS, Department of Health and Human Services; EACS, European AIDS Clinical Society; FTC, emtricitabine; HBV, hepatitis B virus; HIV, human immunodeficiency virus; IAS, International AIDS Society; INSTI, integrase strand transfer inhibitor; PLHIV, people living with HIV; STR, single-tablet regimen; TAF, tenofovir alafenamide.

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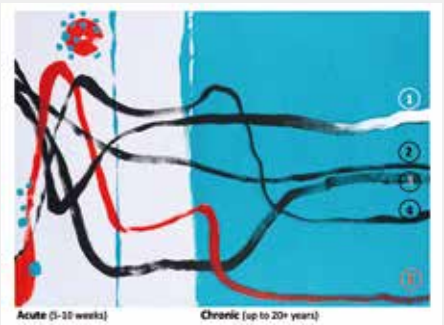

萬水千山縱橫
Oil on canvas (500 x 700 mm)

This is a painting with double meaning. The landscape is depicted in an abstract manner with the use of quick rough lines to give the impression of mountains immersed in a sunset.

Embedded in this imagery is a deeper medical meaning: having HIV does not stop someone from living a healthy life. With the right treatment and care, patients can continue to experience the beauty of nature in their life. Starting antiretroviral treatment promptly and taking it daily helps the immune system recovery and restores normalcy to life.

The zone on the right of the painting in turquoise shows the chronic phase of HIV infection after antiretroviral treatment.

Key: From the top, white-end line: Blood CD4 + T cells
Second black line: Immune resources
Middle black line: Mucosal CD4 + T cells
Fourth black line: Immune activation
Bottom red line: HIV viral load

Ms Carrie CHEUNG
MMedSc (HKU) MSSc (CUHK)

Ref: Appay V et l. HIV infection as a model of accelerated immunosenescence. Handbook of Immunosenescence, 2019 https://doi.org/10.1007/978-3-319-99375-1_50

Published by
The Federation of Medical Societies of Hong Kong

Design and Production
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Editorial

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Editor

Dr Andrew TY WONG

The HIV/AIDS pandemic has been with us for 40 years since the first cases were reported in 1981. It has infected nearly 80 million people and killed 36 million. It is lamentably still thought of as a disease of marginalised populations by the general public and even by healthcare professionals.

During my medical career in the past three decades, I have witnessed the evolution of HIV/AIDS as a disease resulting in almost certain death to a chronic and manageable condition, thanks to advances in antiretroviral therapy (ART). ART has also evolved from a heavy pill burden multiple times a day with significant adverse effects to a mostly single tablet regimen. ART is now much better tolerated and potent. Adherent patients can expect to achieve excellent virological control while on therapy. In this issue, Dr Owen T Y TSANG has written a comprehensive state-of-the-art account of ART and its future developments. ART has also been used for pre- or post-exposure prevention. Professor S S LEE has provided valuable insight into various tactics used to successfully control HIV in many countries with pre-exposure prophylaxis (PrEP).

ART, while being a huge game-changer, is far from a panacea for the global HIV/AIDS problem. At-risk persons have to come forth to get tested before ART can be initiated. The astuteness of clinicians in detecting early signs of HIV/AIDS plays an important role in early detection. Dr CK KWAN has provided a well-illustrated account of skin conditions that may make one consider HIV infection as the cause. Neuropsychiatric problems are common in HIV/AIDS patients even on ART. Dr Philip CHAN and Dr Patrick CK LI have shared an updated account of neurological conditions in the era of ART.

Whilst infectious disease specialists are at the forefront of the management of HIV/AIDS patients, HIV medicine has been and will continue to be a multidisciplinary specialty. The role of primary care physicians in providing joint care with infectious disease service cannot be over-emphasised. HIV is an inflammatory disease and there is, for example, an increased incidence of cardiovascular disease in HIV. Similarly, there is an increased incidence of HIV-related cancer and non-HIV related cancer in HIV patients; cancer screening with collaborative care between public or private HIV medical providers helps to ensure timely best care. To facilitate such collaboration, I have written an article on non-ART health concerns of HIV/AIDS patients.

The stigma issue associated with HIV/AIDS has continued to plague and to perpetuate the pandemic. This is of great importance as many potentially positive HIV patients avoid testing because they fear the stigma of a positive test. To ensure the marginalised populations, which account for the bulk of new cases nowadays, can access HIV services in safety and with dignity, social hurdles have to be overcome. Despite the recent popularised notion of 'U=U' (Undetectable viral load equals Untransmittable disease by sexual route), stigma and discrimination prevail. Dr Winston GOH's article on how medical care can be made LGBTQ+ friendly is a most timely reminder for all healthcare providers to upkeep equity of access to care.

This is the first issue in the history of the Hong Kong Medical Diary solely dedicated to HIV medicine 40 years into the HIV/AIDS pandemic. The coming decade will certainly witness further medical advances in treatment and prevention. However, only with the solidarity of the lay public and the medical community in putting the disease in proper perspective can the suffering from HIV/AIDS decrease. To end, I would like to express my sincere gratitude to all contributing authors and the editorial board and team for their unfailing support to make this memorable issue a reality.

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HKAMB0050_v1.0 4/23/2021

Pre-Exposure Prophylaxis on the Frontier of HIV Prevention

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Dr Shui-shan LEE

This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 March 2022.

BACKGROUND

The World Health Organization (WHO) estimated that there were some 37.7 million people living with human immunodeficiency virus (HIV) globally as of the end of 2020.[1] With sexual transmission as the main route of virus spread, conventional HIV prevention strategies have encompassed socio-behavioural interventions emphasising safer sex promotion. In the last decade, a paradigm shift has occurred that brought biomedical prevention to the forefront.[2] Founded on the effectiveness of antiretroviral (ARV) therapy, the two key strategies of HIV prevention today are "Treatment as Prevention" (TasP) targeting HIV-infected individuals and pre-exposure prophylaxis (PrEP) for the uninfected who are at risk respectively. TasP is siphoned from the clinical intervention of highly active antiretroviral therapy (HAART), which is covered elsewhere in this series.

PrEP involves the prescription of ARVs to people at higher risk of HIV transmission, the effectiveness of which was demonstrated in clinical trials, and the strategy has been reviewed extensively in the literature.[3] In 2012, the United States Food and Drug Administration approved the daily use of oral co-formulated tenofovir disoproxil fumarate 300 mg and emtricitabine 200 mg (TDF/FTC) for PrEP. Subsequently in 2019, co-formulated emtricitabine 200 mg and tenofovir alafenamide 25 mg (F/TAF) was approved for PrEP. While new PrEP modalities have continued to be experimented,[4] TDF/FTC has remained the most commonly prescribed regimen internationally. Epidemiologically, high uptake and adherence are the key attributes of effective PrEP, the implementation of which is expected to lead to a reduction of HIV incidence.[4]

WHO SHOULD BE ON PrEP, HOW AND WHEN

PrEP is indicated for HIV-negative individuals with high HIV risk as reflected by their engagement in condomless anal and/or vaginal sex, or the practice of sharing injection equipment among people who inject drugs (PWID). Worldwide, men who have sex with men (MSM) account for a significant proportion of all newly diagnosed HIV infections, constituting the community group that is often prioritised for PrEP access, in western countries as well as the developing world.[5,6] Algorithms on eligibility screening and monitoring have been designed by professional bodies to facilitate the implementation of PrEP in the community.[7]

Currently the two main PrEP regimens, both comprising co-formulated TDF/FTC, are the latter's prescription on a daily or on-demand basis. The most widely used on-demand regimen, also referred to as "event-based" PrEP, adapted from the IPERGAY study,[8] is composed of 2 tablets of co-formulated TDF/FTC taken 2-24 hours before sex, followed by a tablet each at 24 and 48 hours subsequently. Endorsed by WHO, both regimens are safe and have proven to be highly effective for HIV prevention. Daily oral PrEP could be almost 100% effective in preventing HIV transmission in adherent persons.[9] Potential PrEP users should have been screened negative for HIV infection and HBsAg and should have normal renal function status (eGFR >60 mL/min) before starting TDF/FTC. Subsequent monitoring includes adherence, HIV and eGFR testing (Fig. 1). Provision of sexual health advice tailored to individual needs plus screening for sexually transmitted infections (STI) including syphilis, gonorrhoea and chlamydia are done in parallel.

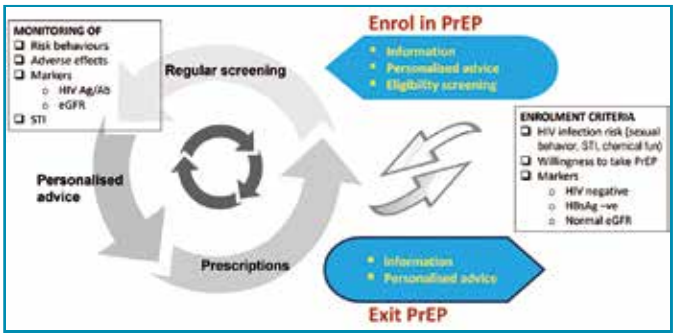

Fig. 1. Enrolment and monitoring of individuals in a pre-exposure prophylaxis(PrEP) programme for the prevention of HIV infection. (Personal collection)

THE CHALLENGES OF IMPLEMENTING PrEP PROGRAMMES

In spite of the well-established rationale and the abundant scientific evidence for PrEP, its coverage has not been optimal. The UNAIDS's target of having 3 million people on PrEP by 2020 was not achieved.[10] As of the end of December 2021, just over 1.9 million PrEP initiations have been recorded worldwide.[11] While cost is one of the major obstacles, there is also the "purview paradox" - that ARV prescription is beyond the purview of public health practice while HIV specialist services are geared towards patients, not uninfected healthy

adults in the community.[12] In the Asia Pacific, a free community setting model was most commonly adopted, which could enhance approachability, availability and acceptability of PrEP.[13] In implementing PrEP programmes, targeting MSM at high risk of infection could be a challenge, and may not be the most cost-effective strategy.[14]

Adverse effects arising from the use of PrEP are uncommon, which may include gastrointestinal upset, diarrhoea, headache, insomnia, and impairment of renal functions. These are often mild and short-lived (lasting for a few days) and are reversible even if they occur. The implementation of PrEP has given rise to debates about the emergence of "risk compensation", the phenomenon of increased STI acquisition, which may be due to increased practice of unprotected sex or due to frequent screening at PrEP consultations.[15] There is also the concern about the efficacy of PrEP, but the failure of HIV protection after PrEP has been extremely rare in the real-world setting.[16] Breakthrough infections are often associated with poor adherence rather than genuine failure. There is the new challenge of making the effective diagnosis of HIV infection while a person is on PrEP, because of the delayed appearance of immunological markers and low level of viral RNA in peripheral blood. This phenomenon has arisen from the partial viral suppression and the delayed seroconversion in the presence of ARVs.[17]

PrEP IN HONG KONG

In Hong Kong, a majority of the incident HIV infections in the last decade were reported among MSM. In 2020, they accounted for about two-thirds of all newly diagnosed HIV infections.[18] Unlike other Asian countries, HIV infection has so far been uncommon among PWID. PrEP is clearly indicated for MSM in Hong Kong but to date no PrEP service has been established in the public sector. Patented TDF/FTC is an unaffordable medicine though this can theoretically be prescribed by any medical practitioner in the private sector. Since 2017, three university-run PrEP studies have been rolled out which managed to provide PrEP to some, albeit just a few hundred, MSM who were willing to join as participants.[19] Results from these studies suggested that there was a high willingness of high-risk MSM to take PrEP if the monthly cost is HKD500 or below.[20] An on-demand mode of PrEP use was feasible with MSM demonstrating high retention in the established pilot study.[21]

In the lack of affordable PrEP services, MSM in Hong Kong are increasingly accessing TDF/FTC through informal sources such as sharing with friends, purchasing online, and taking part in "PrEP tourism" in Thailand.[22] These informal channels often involved the acquisition of generic alternatives at a fraction of the cost compared to patented TDF/FTC. There are problems for informal PrEP use, such as incorrect regimen, defective supervision, low adherence, lack of medical surveillance and health monitoring, and inattention to sexual health.[23] Currently, most private primary care doctors in Hong Kong have no or little involvement in HIV testing and prevention.[24] Engaging primary care services in filling some or all of these gaps would be one possible solution in enhancing the delivery of PrEP.

PrEP 2.0

The effectiveness of oral TDF/FTC in preventing HIV transmission has paved the way for the development of the next generation of PrEP. Following regular use of F/TAF, novel oral agents such as islatravir are in the pipeline, alongside long-acting injectables (e.g. Cabotegravir), vaginal rings, broadly neutralising antibodies, implants and transdermal forms of PrEP delivery.[25] Alternative regimens would become approved for PrEP in the years to come. The major challenges in scaling up access in the real-world setting have, however, remained unchanged.[9] For Hong Kong, there's an urgent need for an affordable PrEP regimen, a sustainable platform for effective service delivery to prioritised communities, access to parallel safety monitoring and the screening of STI/HIV.

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Pre-Exposure Prophylaxis on the Frontier of HIV Prevention" by Dr Shui-shan LEE and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 March 2022. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

1. The effectiveness of pre-exposure prophylaxis (PrEP) against HIV has been proven in clinical trials.
2. PrEP is only indicated for individuals with suspected HIV infection following unprotected sexual exposure.
3. World Health Organization has endorsed the use of daily PrEP but not on-demand PrEP for HIV prevention.
4. High uptake of PrEP by people at risk of HIV infection is important to reduce HIV incidence at the population level.
5. Oral co-formulated tenofovir disoproxil fumarate 300 mg and emtricitabine 200 mg (TDF/FTC) is the commonly used regimen for PrEP.
6. Adverse effects from taking PrEP are normally mild and short-lived.
7. "Risk compensation" refers to the enhanced adoption of safer sex in PrEP users.
8. Men who have sex with men (MSM) constitute one of the community groups that should be prioritised for implementing PrEP.
9. Formal access to patented TDF/FTC for PrEP is currently unavailable at any public health service in Hong Kong.
10. Needle-sharing in people who inject drugs is a common cause of HIV transmission in Hong Kong.

ANSWER SHEET FOR MARCH 2022

Please return the completed answer sheet to the Federation Secretariat on or before 31 March 2022 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Pre-Exposure Prophylaxis on the Frontier of HIV Prevention

Dr Shui-shan LEE

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Answers to February 2022 Issue

New Advances in Surgery for Benign Prostatic Hyperplasia

1. F 2. T 3. T 4. F 5. F 6. T 7. T 8. T 9. T 10. T

Neurological Manifestations of HIV in the Antiretroviral Therapy Era

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INTRODUCTION

HIV-1 infection involves the central nervous system (CNS). The virus invades the CNS within days after transmission. HIV-1 RNA level is measurable in over 90% of the cerebrospinal fluid (CSF) samples collected during later Fiebig stages (III-V) of acute HIV infection.[1] Neuronal damage soon follows - CSF neurofilament light (NFL), a marker of neuro-axonal damage, is elevated in 40% of untreated individuals within the first year of infection[2]. Cognitive impairment (CI) and depressive mood are common in untreated people living with HIV (PLWH). In the pre-antiretroviral therapy (ART) era, PLWH with advanced immunodeficiency frequently presented with AIDS dementia complex (ADC), characterised by cognitive, motor and behavioural abnormalities.[3]

The availability of modern ART converts HIV-1 infection into a manageable chronic illness. Sustained plasma HIV-1 suppression is now a readily achievable target for PLWH with stable access to ART. ART leads to substantial recovery of T-cell immunity, making opportunistic infections exceedingly rare nowadays. The availability of less neurotoxic antiviral agents further reduces the incidence of HIV-associated sensory neuropathy.[4] Yet, the benefit of ART may be incomplete in the CNS and HIV-associated neurocognitive disease (HAND) persists in the ART era[5]. The frequency of HIV-associated dementia (HAD), an equivalent diagnosis to ADC but employing the "Frascati" research criteria of HAND, has dropped from 15%[6] to below 5% in treated PLWH[7]. However, milder forms of HAND, namely asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND), remain common and range 30-60% in PLWH on ART.[8-10]

The prevalence of HAND is similar in Asian societies and ranges 23-26% in Singapore and South Korea.[11,12] In a cognitive screening study conducted at the Queen Elizabeth Hospital, 26% of treatment-naïve HIV-infected clinic attendees scored below the cut-off (≤ 25) of the Montreal Cognitive Assessment (MoCA).[13] Moreover, despite plasma viral suppression and substantial recovery of CD4 T-cell level 6 months after ART, their MoCA performance did not improve. While the study did not include a conventional neuropsychiatric assessment for a formal diagnosis of HAND, the finding is in line with others' observation of HAND persistence. This article aims to review the neurological aspects of HIV, including the pattern of neuropsychiatric symptoms in HAND, screening recommendations from different guidelines, potentially reversible causes of cognitive decline in PLWH and considerations of ART regimen.

NEUROPSYCHIATRIC PROFILE OF PLWH ON SUPPRESSIVE ART

Apart from depressive symptoms, untreated PLWH in the pre-ART era frequently presented with a subcortical-type of CI involving motor skills, cognitive speed and verbal fluency abnormalities. In the ART era, in addition to the aforementioned deficits, treated PLWH also demonstrate added deficits in memory (learning) and executive function.[14] Middle-aged PLWH on suppressive ART in two European cohorts demonstrated worse performance in attention, executive function, psychomotor speed and verbal learning than matched HIV-uninfected controls[15,16], suggesting the presence of a mixed pattern of subcortical and cortical CI.

The stability of cognitive function in PLWH on suppressive ART is however inconsistent among longitudinal studies, ranging from stable cognitive performance over two years, to 6-16% of cognitive decline over a period of 1.5-3 years. Particularly, declines in executive, motor and psychomotor functions are most frequently observed.[17,18] The risk factors of cognitive decline in PLWH on suppressive ART include older age, a longer duration of HIV-1 infection and pre-existing CI prior to ART initiation.[19] In contrast, PLWH without pre-existing CI or history of HAND generally demonstrated stable cognitive performance after initiation of treatment.

COGNITIVE SCREENING AND AVAILABLE TOOLS

To date, recommendations of cognitive screening in PLWH are diverse across HIV management guidelines. For instance, the World Health Organization (WHO) and the British HIV Association (BHIVA) recommend routine screening for mental health disorders in key populations of PLWH. However, the frequency of screening and the screening tool of choice are not specified. The European AIDS Clinical Society (EACS) takes a stepwise approach to tackle cognitive complaints. The EACS v10.0 guidelines[20] recommend the use of a 3-question screen that covers memory loss, mental slowing and attention difficulties for PLWH who present with cognitive complaints. Positive response in any one of the three questions warrants further evaluations. A recent study reported that the positive and negative predictive values of identifying CI through

this approach were only 0.35 and 0.7 respectively.[21] Besides, those who responded positively in all three questions showed an increased risk of depression instead of CI. Nevertheless, the approach is practical for clinical purposes as it captures a mix of neuropsychiatric symptoms in PLWH for further evaluation.

The HIV Dementia Scale (HDS) and the International HIV Dementia Scale (IHDS) are simple screening tools designed to identify more severe forms of CI in PLWH in resource-limited settings. HDS examines one's memory, attention, psychomotor speed and visuospatial function whereas IHDS examines one's memory, psychomotor and executive functions. Unfortunately, they are not sensitive to identify milder forms of HAND. Based on the recommended cut-off score, the sensitivity of HDS ranged 0.26 - 0.68 and its specificity ranged 0.67 - 0.96 in identifying HAND in treated PLWH.[22,23] In contrast, IHDS tends to overestimate the presence of CI. In two African-based studies in which two-third of the participants were on ART, 64% and 83% of the participants were screened positive by IHDS[24,25], compared to the HAD prevalence of 25-31% in Uganda and South Africa using conventional neuropsychological testing. Moreover, 77% of the HIV-uninfected controls were rated as "cognitively impaired" based on a cut-off of 10 in IHDS.[25]

Other commonly used cognitive screening tests include the Mini-Mental State Examination (MMSE) and MoCA. MMSE is used to evaluate dementia in patients with Alzheimer's disease (AD) but is not sensitive enough to detect mild cognitive impairment (MCI). MMSE is insensitive to HAND as it lacks assessments of executive function and motor skills.[26] MoCA evaluates one's visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall and orientation function, making it potentially useful for CI driven by HAND, AD, vascular cognitive impairment (VCI), or in combination. In a meta-analysis that includes eight cross-sectional studies using MoCA to identify HAND, the authors concluded that a lower threshold than the original cut-off (≤ 25/30) of MoCA would lower false positive rates and improve its diagnostic accuracy. However, the choice of cut-off always comes with a sensitivity-specificity trade-off[27]. In short, no single screening test appears to be adequate to identify HAND effectively. Combining MoCA with another screening test could be an alternative, especially if a full neuropsychiatric assessment is not readily available.

COGNITIVE IMPAIRMENT IN TREATED PLWH

While irreversible neurological damage sustained pre-ART would contribute to the persistence of HAND in the ART era, it fails to explain new-onset and progressive decline of cognitive performance in PLWH on suppressive ART. Biomarker studies suggest the likely linkage between CI and persistent systemic and intracerebral inflammation in PLWH. Indeed, apart from those who initiate ART extremely early after HIV infection, PLWH who commence ART during chronic infection frequently present with persistent T-cell dysfunction, denoted by a reversed CD4/CD8 ratio, and persistent elevation of immune activation markers in their blood and CSF. Further, PLWH with CI shows higher levels of immune activation markers in the CSF than those without. The relationship between persistent inflammation and HAND pathogenesis is thoroughly reviewed by Saylor et al.[28] While further research is needed to decipher the relationship between persistent immune activation and CI, clinicians should look out for uncommon yet reversible conditions among treated PLWH who present with new-onset or worsening neurological complaints.

NEUROSYPHILIS

Syphilis remains prevalent in PLWH, especially among men who have sex with men (MSM) with high-risk sexual behaviours. Untreated PLWH showed higher risk of treatment failure for systemic syphilis and developing neurosyphilis than HIV-uninfected individuals. Whether such correlations persist in virally-suppressed PLWH remains unclear. In clinical practice, a positive CSF VDRL remains the gold standard for diagnosing neurosyphilis. Yet, neurosyphilis should be considered if the serum VDRL titre in a virally-suppressed individual is persistently above 1:32 despite standard treatment or the CSF WBC count is > 5 cells/mm^3.

HIV-1 ESCAPE IN CEREBROSPINAL FLUID

CSF viral escape is defined as the detection of HIV-1 RNA in the CSF despite undetectable plasma HIV-1 RNA by a commercially available assay. CSF viral escape is relatively uncommon and occurs in up to 10% of PLWH on ART. CSF viral escape is usually asymptomatic and may represent an intrathecal form of the viral blip. Yet, it is associated with elevations of CSF immune activation markers and therefore potentially harmful to neuronal health. Moreover, CSF viral escape can be symptomatic and manifest with a spectrum of neurological complications, including headache, cognitive decline and confusion[29]. The onset of clinical manifestations varies from within weeks to months.[29] In symptomatic CSF escape, viral strains isolated from CSF often demonstrate different resistance profiles to the pre-ART plasma sample. The feature highlights the potential of the CNS as a discrete compartment capable of viral replication.

CNS PENETRATING EFFICACY AND ART REGIMEN MODIFICATION

Various ART modification strategies have been proposed to improve HAND, including the application of CNS Penetrating Efficacy (CPE) and ART intensification. The former is based on an antiretroviral agent's capacity to penetrate the CNS and inhibit HIV-1 replication.[30] The latter involves the addition of an integrase inhibitor and maraviroc, a CCR5 antagonist, to the standard 3-drug ART regimen. To date, the usefulness of these strategies in promoting better longitudinal cognitive outcomes in asymptomatic PLWH is inconclusive. In the case of symptomatic CSF escape, clinicians should optimise the ART regimen according to the viral resistance profile in the CSF before considering CPE and ART

intensification. There is also considerable enthusiasm towards ART simplification to reduce ART-related toxicity. This approach could be especially important to older PLWH with an increased risk of organ failure. Yet, empirical ART simplification should be avoided as certain combinations appear to be associated with the development of CSF viral escape among individuals with a longer history of untreated HIV-1 infection and multi-drug resistance.[31]

NEURO-HIV IN THE ART ERA – A SHIFTING PARADIGM

Contemporary ART has substantially improved the life expectancy and quality of life of PLWH but new challenges emerge. More recent research highlights that PLWH on suppressive ART persistently suffers from an elevated risk of non-communicable diseases (NCDs), namely metabolic dysfunctions and atherosclerosis. Compared to HIV-uninfected individuals, PLWH have about 2-fold increased relative risk (RR) of coronary arterial disease[32] and 3-fold increased RR of stroke.[33] Indeed, the focus of medical care and HIV research has gradually shifted from the management of immunodeficiency and opportunistic infections to that of NCDs, particularly age-related co-morbidities. In the context of neurology, the prevalence and incidence of CI in PLWH will likely rise with ageing, when age-related causes of CI, namely neurodegenerative diseases and cerebrovascular diseases, unfold. Given such complexity in diagnosis and management, a multi-disciplinary approach with various professionals would benefit the upcoming era of HIV care.

CONCLUSION

To reduce the frequency and severity of HAND, HIV screening should be promoted so that infection can be detected early and effective ART initiated. A convenient and well-tolerated ART regimen tailored to the patient's profile is most likely to achieve drug adherence and sustained complete viral suppression. Apart from monitoring the patient's immunological and virologic response, attention to possible metabolic complications and cardiovascular risk profile is also necessary. Routine screening for symptoms of depression and cognitive decline in the clinic setting by self-administered questionnaires or trained assistants may identify patients requiring more detailed assessment for HAND. For patients presenting with neurological symptoms, opportunistic disease should be considered if they are not on ART or have non-suppressed HIV RNA levels. Otherwise, alternative potentially treatable causes including neurosyphilis and CSF escape should be considered.

KEY MESSAGES

Stable plasma HIV-1 suppression is readily achievable by people living with HIV (PLWH) who have stable access to modern antiretroviral therapy (ART).

1. However, the benefit of ART may be incomplete in the central nervous system and HIV-associated neurocognitive disorder (HAND) persists in the ART era.
2. The cognitive deficits in HAND are diverse and may not be easily captured by a single screening tool.
3. In the setting of new-onset and progressive cognitive decline, reversible causes of cognitive impairment including neurosyphilis and cerebrospinal fluid (CSF) viral escape should be actively sought.

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viral load[2]
Significantly fewer
neuropsychiatric adverse
events vs. comparator in
three pre-specified
categories[2,#]
Convenient dosing[1]
Dizziness (P=0.001), Sleep disorders/disturbances (P<0.001) and Altered sensorium (P=0.033).
Study Design
Delstrigo Selected Safety Information
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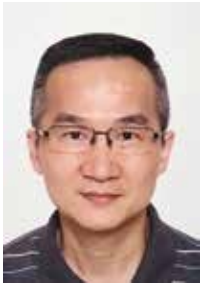
Recent Advances in HIV Treatment



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The Human Immunodeficiency Virus (HIV) epidemic has been rampaging throughout the world since its discovery by 2 French doctors at the Pasteur Institute in 1983.[1] In the 1980s, the diagnosis of HIV infection was almost proclaiming a death sentence to an individual. Drug treatment for HIV infection has come a long way since the discovery of the first antiretroviral therapy (ART), Zidovudine (AZT), a nucleoside reverse transcriptase inhibitor (NRTI), in 1987.[2] AZT showed a positive impact on disease progression and death. However, monotherapy with AZT and incomplete virological suppression resulted in the quick emergence of resistant mutations. As more and more ARTs surfaced, Dr David Ho, a leading researcher at the US Aaron Diamond AIDS Research Centre, pioneered the highly active antiretroviral therapy (HAART) treatment, based on the study of the dynamics of HIV replication. The gist of HAART is on the combination of ARTs of different mechanisms of action to achieve optimal viral suppression. The challenges of early HAART included high pill burden, multiple dosing, drug toxicities, drug-drug interaction and incomplete virological suppression. With the availability of fixed-dose tablets (FDT) that combine 2-4 ARTs from more than one class of ART, and the newer drugs with high potency and fewer side effects, patients' compliance with treatment has improved substantially. The single-tablet regimes (STR) permit one-pill-once-daily treatment for most HIV-infected patients. The Joint United Nations Programme on HIV/AIDS (UNAIDS) has proposed the 90-90-90 strategy in 2014 to expand the therapy for HIV-infected individuals to achieve the diagnosis of 90% of the HIV-infected patients, the treatment of 90% of those patients and the sustained suppression of HIV viral load (VL) of those patients being put on treatment by 2020.[3] Some countries have achieved this goal. With the advance and expansion of the use of HAART, the difference in mortality between HIV-infected population and the matched general US population has been decreased significantly from 11.1% between 1999 and 2004 to only 2.7% between 2011 and 2017.[4] Nowadays, HIV infection has become a manageable chronic illness, enabling HIV-infected individuals to live a reasonably good quality of life that is comparable to that of the general population.

WHEN AND WHAT ART SHOULD BE INITIATED IN PEOPLE LIVING WITH HIV (PLWH)

Up till now, there are seven classes of ARTs containing more than 40 medications approved [Table 1]. Some of them have been obsoleted because of the side effects

Table 1: HIV medications available in Hong Kong (Modified from Villaluz I, Grantner GR. Newly approved HIV Medications. US Pharm. 2020: 45: 17-25)

Drug Class	Generic Name (Other names and acronyms)	Brand Name	US FDA Approval Date
Nucleoside Reverse Transcriptase Inhibitors (NRTIs): block reverse transcriptase, an enzyme HIV needs for viral replication.	Abacavir (ABC)	Ziagen	Dec 17, 1998
	Lamivudine (3TC)	Epivir	Nov 17, 1995
	Tenofovir disoproxil fumarate (TDF)	Viread	Oct 26, 2001
	Zidovudine (AZT, ZDV)@	Retrovir	Mar 19, 1987
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs): bind to and later alter reverse transcriptase, an enzyme HIV needs for viral replication.	Doravirine (DOR)	Pifeltro	Aug 30, 2018
	Efavirenz (EFV)@	Stocrin	Sep 17, 1998
	Etravirine (ETR)	Intelence	Jan 18, 2008
	Rilpivirine (RPV)	Edurant	May 20, 2011
Protease Inhibitors (PIs): block HIV protease, an enzyme HIV needs for viral replication.	Darunavir (DRV)	Prezista	Jun 23, 2006
	Ritonavir (RTV), as booster for other PIs	Norvir	Mar 1, 1996
Fusion inhibitors (FI): block HIV from entering the CD4 cells	Enfuvirtide (T-20)@, subcutaneous injection	Fuzeon	Mar 13, 2003
CCR5 antagonists: block CCR5 coreceptors on the surface of certain immune cells that HIV needs to enter the cells.	Maraviroc (MVC)@	Selzentry	Aug 6, 2007
Integrase Strand Transfer Inhibitor (INSTIs): block HIV integrase, an enzyme HIV needs for viral replication.	Cabotegravir (CAB)#	Vocabria	Jan 22, 2021
	Dolutegravir (DTG)	Tivicay	Aug 13, 2013
	Bictegravir (BIC)	As FDT, see Table 2	
	Raltegravir (RAL)	Isentress	Oct 12, 2007
		Isentress HD	May 26, 2017
Attachment inhibitors: bind to the gp120 protein on the outer surface of HIV, preventing HIV from entering CD4 cells.	Fostemsavir (FTR)#	Rukobia	Jul 2, 2020

will be available in Hong Kong soon
@ drugs that are less commonly used because of side effects

and the availability of better options. There are also multiple approved FDTs, which make treatment easier and more acceptable for most PLWH [Table 2]. It has been a consensus that ART should be initiated for PLWH immediately after their diagnosis, regardless of their CD4 cell counts and clinical status.[5-7] Before selecting a specific ART regimen, it is important to review the willingness and the pregnancy status of the patients. Whether the patients have any opportunistic infections or malignancy would also dictate the ART regimen to be used as some of the ARTs may confer drug-drug interaction (DDI). Certainly, co-existing medications the patients have been taking should also be carefully reviewed to avoid DDI. Co-morbidities including cardiovascular, renal or liver problems should also be assessed. Baseline ART genotypic resistance testing (GRT) should be carried out to look for any primary resistance.

Table 2: Fixed-dose tablets (FDT) of HIV medications (Modified from Villaluz I, Grantner GR. Newly approved HIV Medications. US Pharm. 2020: 45: 17-25)

	Brand name	US FDA Approval Date
Abacavir and lamivudine (ABC / 3TC)	Kivexa	Aug 2, 2004
Abacavir, dolutegravir, and lamivudine (ABC / DTG / 3TC)	Triumeq	Aug 22, 2014
Bictegravir, emtricitabine, and tenofovir alafenamide (BIC / FTC / TAF)	Biktarvy	Feb 7, 2018
#Cabotegravir and rilpivirine (CAB / RPV), Injectable	Cabenuva	Jan 22, 2021
Darunavir and cobicistat (DRV / COBI)	Prezcobix	Jan 29, 2015
Darunavir, cobicistat, emtricitabine, and tenofovir alafenamide (DRV / COBI / FTC / TAF)	Symtuza	Jul 17, 2018
Dolutegravir and lamivudine (DTG / 3TC)	Dovato	Apr 8, 2019
Doravirine, lamivudine, and tenofovir disoproxil fumarate (DOR / 3TC / TDF)	Delstrigo	Aug 30, 2018
Elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide (EVG / COBI / FTC / TAF)@	Genvoya	Nov 5, 2015
Emtricitabine, rilpivirine, and tenofovir alafenamide (FTC / RPV / TAF)	Odefsey	Mar 1, 2016
Emtricitabine, rilpivirine, and tenofovir disoproxil fumarate (FTC / RPV / TDF)@	Complera	Aug 10, 2011
Emtricitabine and tenofovir alafenamide (FTC / TAF)	Descovy	Apr 4, 2016
Emtricitabine and tenofovir disoproxil fumarate (FTC / TDF)	Truvada	Aug 2, 2004
Lopinavir and ritonavir (LPV / RTV)@	Kaletra	Sep 15, 2000

will be available in Hong Kong soon
@ drugs that are less commonly used because of side effects

Traditionally, three or more medications are necessary to formulate an ART regimen, with 2 NRTIs as backbone (TAF/TDF + 3TC/FTC or ABC/3TC) (please refer to Table 1 for full names of the drugs for these abbreviations) plus a third agent (either an NNRTI, PI or INSTI). HLA B*5701 may need to be checked, especially in Caucasians, before the prescription of ABC to avoid the occurrence of drug-induced hypersensitivity. Moreover, ABC should also be avoided in patients with underlying cardiovascular risk, as the drug may increase the risk further. Patients with underlying renal toxicities or bone density problems (such as osteoporosis or osteopenia) should avoid TDF. TAF may be better used in these cases. However, it should also be noted that treatment with INSTIs or TAF may be associated with weight gain. The preferred third agent is usually an INSTI or DOR (an NNRTI). The alternative third agent would be DRV (the only PI recommended), but it needs to be boosted by RTV or COBI. With the increase in potency and resistance threshold of the newer HAART, dual-drug therapy (1 NRTI + INSTI, such as 3TC + DTG) is now possible. In patients with chronic hepatitis B, at least two medications active against the hepatitis B virus should be used. Therefore, TAF/TDF + FTC/3TC should be used as the NRTI backbone, while ABC/3TC or dual-drug therapy should be avoided. After starting ART, monitoring of patient's compliance and interval testing for the HIV VL and CD4 cell counts are crucial.

Switching ART

(1) In virologically suppressed patients

PLWH should be considered virologically suppressed when they have their HIV VL < 50 copies/mL for at least six months after being put on ART. Switching ART regimens may be needed whenever there are intolerable drug-related toxicities, DDI, co-existing medical conditions, pregnancy or simply just regimen simplification to improve the quality of life. The history of ART regimens, the profile of GRT, patient's compliance, and tolerability issues should be thoroughly reviewed before any modification. It is generally considered safe to switch within the same class of drug, such as TDF to TAF; EFV to DOR. The genetic barrier to resistance may need to be considered if a cross-class switching is being sought. DTG, BIC or DRV are drugs having a high genetic barrier to resistance. Switching to them should be safe if there is no resistance. In patients with the latest GRT showing no resistance and negative for hepatitis B, they can be switched to a dual-drug therapy with 3TC + DTG, DTG + RIL or 3TC + DRV/booster.

(2) In patients with virologic failure

Patients on ART with HIV VL > 50 copies/mL after a full suppression is defined as virologic failure. The patient's compliance, ART history and the GRT should be carefully reviewed. Therapeutic drug monitoring (TDM) may be required in patients whose compliance to treatment is doubtful. A new GRT is required if the VL is > 200 copies/mL to look for any underlying resistance. If compliance is the main cause for the virologic failure, emphasis should be focused on understanding the patient's difficulties. If resistance is the problem, the new regimen should preferably contain at least three active medications based on the GRT results. Treatment interruption is not recommended.

Newer and innovative therapies

Newer classes and members of HAART have been developed to overcome the problems of resistance, adding to the armamentarium for HIV treatment. Conventionally, the NRTI, NNRTI, PI & INSTI are the most commonly used ART classes. The FI

or CCR5 antagonists have limited use nowadays with the availability of more potent and convenient regimens. Attachment inhibitor is a newer ART class that binds to the gp120 protein on the outer surface of HIV, preventing HIV from binding to and entering CD4 T cells. The first-in-class member approved, Fostemsavir, is indicated for heavily treatment-experienced individuals with multidrug-resistant HIV-1 and limited treatment options. The BRIGHTE study has shown that Fostemsavir was well tolerated and demonstrated a distinct trend of increasing virological and immunological response rates through 96 weeks.[8]

Carbotegravir is another recently approved agent. This is the very first long-acting antiviral that permits much less frequent dosing intervals. This newer INSTI is combined with RPV as a long-acting injection (once every eight weeks). The initial study showed that monthly injections of carbotegravir and rilpivirine were non-inferior to standard oral therapy for maintaining HIV suppression. Injection-related adverse events were common but only infrequently led to medication withdrawal.[9] Subsequent study supported the use of this regimen to be administered every two months instead of monthly as a therapeutic option, as the efficacy and safety profiles of the two dosing intervals were similar.[10] However, the participants had to receive an initial four weeks of once-daily oral lead-in treatment of both medications to assess individual tolerability before the long-acting administration of injections.

Other products in the pipeline include long-acting maturation inhibitors, long-acting capsid inhibitors and neutralising antibodies targeting the CD4 binding site. Since these agents have novel mechanisms of action, they can potentially manage viral resistance arising from the treatment of other traditional regimens. Maturation inhibitors block a late protease cleavage event between the capsid (CA) and the spacer polypeptide (SP1). When CA-SP1 is not properly processed, an abnormal capsid is formed, and the virus is considered not infectious. However, several candidates had failed because of numerous resistance-related problems in the past. The latest agent, GSK3640254, seems to be active against previous resistant viruses and is currently undergoing clinical trials.[11]

HIV capsid inhibitors target the capsid shell of the virus to reduce the replication of HIV. Lenacapavir is an experimental first-in-class capsid inhibitor currently in phase 2/3 of clinical trials. Preliminary reports show that Lenacapavir is more potent than current HIV treatments.[12] It is formulated as a subcutaneous or oral agent with a very long half-life and thus can be administered up to every six months. However, the company announced a clinical hold on the use of injectable lenacapavir in all ongoing clinical studies on 21 December 2021 arising from concerns about the compatibility of vials made of borosilicate glass with lenacapavir solution, which could potentially lead to the formation of sub-visible glass particles in the solution of lenacapavir. However, dosing of oral formulations of lenacapavir continues.[13]

Antibody-based therapy is one of the next frontiers of HIV treatment. There are multiple epitopes such as the V2 region, V3 region, CD4 binding site, MPER, and CD20, that can be targeted by the neutralising antibodies. The first neutralising antibody being developed was ibalizumab, which is a humanised monoclonal antibody that binds CD4 extracellular domain 2, thereby preventing conformational changes in the CD4–HIV envelope glycoprotein (gp120) complex that are essential for HIV viral entry. A human study showed that it had significant antiviral activity in patients with multi-resistance HIV and limited treatment options.[14] However, the rapid emergence of resistance is a concern.

Newer modes of drug delivery systems including implantables are also found to be promising. Taking reference from the implantable contraceptives, Islatravir, the first-in-class nucleoside reverse transcriptase translocation inhibitor, has been developed as a non-degradable subcutaneous implant that slowly releases drug from a biodegradable polylactic co-glycolic acid matrix. It blocks the primer translocation and causes chain termination during viral RNA transcription. The half-life of the implant can be as long as 100 days, which makes it amenable to be administered at a dosing interval of 1 year or more.[15]

MIGRATION FROM 'TREATMENT AS PREVENTION' TO 'UNDETECTABLE EQUALS UNTRANSMITTABLE'

Not only can ART help the PLWH to restore a relatively normal physical and mental well-being, ART can also help to prevent the transmission to uninfected sexual partners. HPTN 052 is a pivotal clinical trial to demonstrate the effectiveness of ART. This study involved 1,763 serodiscordant heterosexual couples (one partner HIV +ve and one -ve), who were randomised to either starting ART or no ART. The study was stopped early (after 1.7 years) for ethical reasons as a 96% reduction in risk of transmission was observed while on ART. Several subsequent studies also confirmed the findings and supported the notion of "Treatment as prevention (TasP)". This has prompted the World Health Organization to shift the treatment strategy from "test and wait" to "test and treat" approach in 2015.[16] The UNAIDS also updated the treatment cascade strategy from 90-90-90 to 95-95-95, aiming to end the epidemic by 2030 because of the success of the TasP strategy.[17] Subsequently, a US Non-governmental organisation Prevention Access Campaign and partners launched the U=U (Undetectable equals untransmittable) campaign in 2016 to build and communicate a consensus about the fact that PLWH who are on treatment and have an undetectable viral load cannot sexually transmit HIV.[18] This campaign has been adopted by many countries.

PRE-EXPOSURE PROPHYLAXIS (PrEP)

There are multiple ways of PrEP, via either daily oral tablet, vaginal ring or gel. The oral regimens include daily TDF, TDF/FTC, TDF/3TC or TAF/FTC. PrEP is recommended to be used in adults at high risk of acquiring HIV infection. Daily oral TDF/FTC was shown to have an 86% reduction in HIV infection

among gay men.[19] Subsequent studies also found that a substantial reduction in acquiring HIV could also be achieved in people who inject drugs, and in heterosexual men and women. Daily oral TAF/FTC was also demonstrated to be non-inferior to TDF/FTC in HIV prevention and offered a better safety profile on bone density and renal function.[20] However, drug compliance is a problem. Recent efforts have been focused on strategies to enhance drug adherence. One of these approaches is long-acting PrEP. A recent study demonstrated that long-acting carbotegravir given intramuscularly every eight weeks was superior to daily oral TDF/FTC in preventing HIV infection among gay men and transgender women.[21]

CONCLUDING REMARKS

The strategies in controlling HIV viral replication by ART are optimal nowadays. However, ART treatment is essentially a lifelong therapy. The rebound of HIV VL is almost universal shortly after the cessation of ART. Newer ART classes continue to emerge, which further optimise the current armaments in the combat of the HIV epidemic and improve the quality of life of PLWH. With the extension of the use of ART and PrEP, zero HIV infection may not be an unreachable goal. One of the current research directions has been shifted to HIV cure. There is definite evidence that a cure can be achieved, as there were two individuals with HIV eradicated after haemopoietic stem cell transplantation in the United Kingdom and Germany respectively. Further research is awaited.

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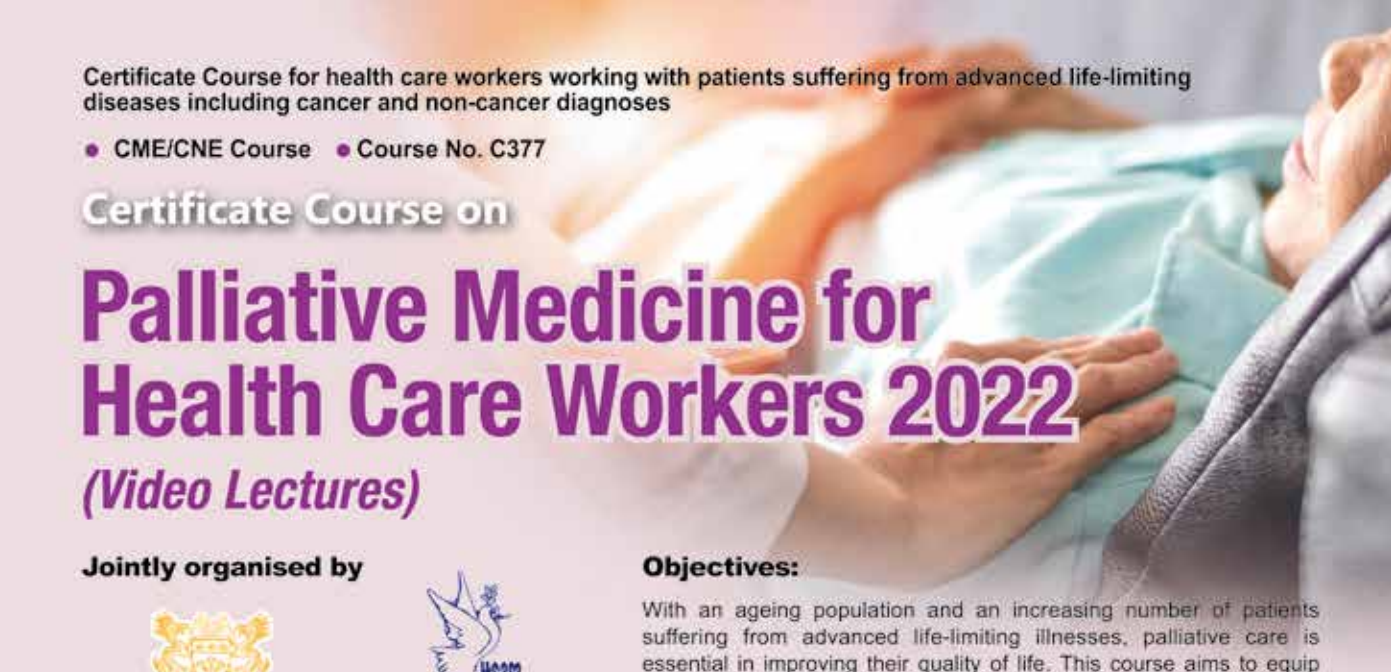

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Objectives:

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Date	Topics	Speakers
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19 Apr 2022	Pain Management in Palliative Care	Dr. Yin POON Associate Consultant Department of Medicine & Geriatrics Caritas Medical Centre
26 Apr 2022	Symptom management in palliative care (I): Nausea & vomiting, anorexia, fatigue, insomnia	Dr. Alice Ka Wai MOK Associate Consultant Department of medicine, North District Hospital
3 May 2022	Symptom management in palliative care (II): Shortness of breath, constipation, delirium	Dr. Jerry HO Associate Consultant Department of Medicine & Geriatrics Ruttonjee Hospital
10 May 2022	Palliative Radiotherapy, Chemotherapy and Targeted Therapy	Dr. Johnny LAU Associate Consultant Department of Clinical Oncology Queen Mary Hospital
17 May 2022	Advance care planning & advance directive	Dr. Benjamin CHENG Consultant Department of Medicine & Geriatrics Tuen Mun Hospital

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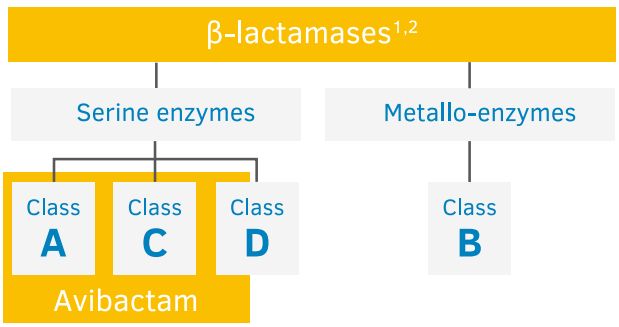

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PP-ZVA-HKG-0032 01/2021

Life Course Management of HIV-infected Adults : Special Considerations for Collaboration of Care with Primary Care Physicians

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INTRODUCTION: HIV AS A CHRONIC DISEASE

The use of increasingly sophisticated antiretroviral therapy (ART) has allowed HIV/AIDS to take a dramatic shift from an almost universally deadly disease 30 years ago to a manageable chronic medical condition.[1,2] Globally, about 50% of HIV-infected persons are over 50 years of age.[3] There is heightened concern about increased age-related comorbidities in this population.[4] The number of non-AIDS related comorbidities (NARC) was found to be over 90%, with each person having two or more.[5,6] In addition, the persistent activation of immune cells by HIV will likely increase the susceptibility to chronic inflammation and to reduced capacity to fight certain diseases.[7] The extended exposure to antiretroviral drugs appears to increase certain HIV-associated non-AIDS conditions (HANA) such as cardiovascular, bone, kidney, liver, and lung diseases, as well as many cancers not associated directly with HIV infection.[8] The well-maintained HIV-infected persons will also have other needs as for non-HIV infected persons, such as childbearing issues or the need to avert travel-related diseases. As a result of the much better prognosis of HIV-infected persons on ART, there are greater number of issues that need to be taken care of during the life course of these patients.

ROLES OF PRIMARY CARE IN HIV MANAGEMENT

HIV care is getting more complex requiring an integrated care model comprising medical, nursing, mental and other related specialties. Infectious Disease physician-led HIV service usually acts as a central hub. At the same time, patients are encouraged to be supported by primary care services to enhance management of non-HIV related conditions and to enhance preventive care as part of a multidisciplinary model of care. This model will facilitate the development of trusting long-term patient-clinician relationships in a stigma-free and welcoming care environment. In addition, primary care will often be the first contact point of patients for timely access to routine and urgent medical care. Last but not least, primary care physicians can help stress the importance of adherence to antiretroviral treatment and care. Low adherence to treatment has been found to predict approximately 50% higher mortality among HIV-infected persons.[9]

The major objective of this article is to delineate the various health needs of HIV-infected adults at different stages of life and to formulate a framework for wellness maintenance within which the primary care sector can work hand in hand with HIV service providers for optimal outcomes.

ROUTINE HEALTH MAINTENANCE OF HIV-INFECTED ADULTS AFTER INITIAL ASSESSMENT

In addition to antiretroviral therapy and HIV viral monitoring, regular health maintenance plays an important role in the care of HIV-infected persons. As a matter of fact, the common causes of illness and death in people living with HIV are similar to those in the general population. They include heart disease, diabetes mellitus, liver and kidney diseases, depression and cancers. The purpose of health maintenance is to identify modifiable risk factors early so that treatment and/or preventive measures can be instituted as soon as possible. Table 1 lists the major areas that need attention and the test/tools to be used.

METABOLIC AND NON-COMMUNICABLE DISEASES

In HIV-infected persons, traditional risk factors, antiretroviral therapy (ART) and HIV infection itself have respectively been associated with dyslipidaemia. HIV is now a recognised independent risk factor for atherosclerotic cardiovascular disease. Therefore, all HIV-infected persons should be assessed for cardiovascular risk.

Patients with elevated low-density lipoprotein (LDL) cholesterol should be managed according to established guidelines. A caveat to watch out for is the potential for drug interactions between anti-lipid medications, especially statins, with ART. Most protease inhibitors (PIs) and cobicistat inhibit the metabolism of statins, and this may predispose the patient to statin toxicity. Atorvastatin and rosuvastatin may be used but should be started at low doses and titrated to tolerability and treatment response. It is prudent to check the relevant database for potential drug interactions whenever HIV-infected patients on ART are started on medications. One such free resource is the Liverpool drug interaction website accessible at https://www.hiv-druginteractions.org/.

Prior to starting ART, fasting serum glucose and HbA1c should be taken to screen for diabetes mellitus. HbA1c levels may be affected by ART and hence should not be used to diagnose diabetes.[12] Using a cut-off value of 6.5%, HbA1c has a sensitivity of 40.9% and specificity of 97.5% for identification of incident diabetes. At a HbA1c level of 5.8%, the product of sensitivity and specificity was maximised, with values of 88.8% and 77.5% respectively.[13] The combined use of fasting glucose and HbA1c may be the best modality to screen for diabetes in HIV-infected persons on ART. When there is discordance of the two tests, the tests should be repeated.[12]

Table 1. Routine Health Maintenance for HIV-infected adults after initial assessment. (Adapted from references 10 and 11)

(A) METABOLIC	Tool	Frequency
1. Body weight	Measurement	Every visit
2. Blood pressure	Measurement	Every visit
3. Lipid profile	Blood test	Every 6-12 months
4. Glucose	Fasting glucose	Every 6-12 months
	HbA1c (for patient on ART, please see text for details)	Every 6-12 months
5. Bone mineral density	Bone densitometry	Baseline for ≥ 50 years old
(B) INFECTIOUS DISEASE	**Tool**	**Frequency**
1. Syphilis	Treponemal & nontreponemal blood test	At least annually every 3-6 months if risk of acquisition is high
2. Gonorrhoea	Urine or swab (urethral / throat / rectal) (where applicable) Nucleic Acid Amplification Test (NAAT)	
3. Chlamydia		
4. Trichomonas	NAAT	Annually for persons having vaginal sex
5. Tuberculosis	Interferon - gamma release assay or Tuberculin skin test	Annually
6. Hepatitis A/B/C	HBsAg: if non-immune or non-carrier	Annually (see below for recommendation for vaccination)
	Hepatitis C: check for anti-HCV antibody	Annually
7. Other vaccine preventable diseases:		
(a) Influenza	Vaccination	Annually
	* avoid live influenza vaccine if CD4 cell count < 200/μL	
(b) Pneumococcal infection	All patients with HIV should receive PCV13 (1 dose)	N/A
	* if not vaccinated previously, this should be the first dose	
	* if given PCV23, give PCV13 at least one year after PCV23	
	* repeat PCV23 once every 5 years after first vaccination.	Give a third and final dose of PPV23 after age 65
(c) Varicella zoster	Vaccination with recombinant zoster vaccine (RZV,Shingrix) (2 doses)	No booster is needed
	* if age > 50 years and CD4 cell count > 200/μL	
(d) Human papilloma virus	Vaccination with HPV vaccines for person up to age 45 years	No booster is needed
(e) Tetanus diphtheria pertussis	Vaccination with Tdap (1 dose)	Booster every 10 years Tetanus toxoid as indicated for wound management
(f) Meningococcal	Vaccination with ACWY meningococcal vaccine (2 doses)	Booster every 5 years Depends on risk
(g) Hepatitis A & B	Vaccination with Hepatitis A & B vaccine if non-immune	Check anti-HBs 1-2 months after completion of HBV series
(C) MENTAL HEALTH & SUBSTANCE USE	**Tool**	**Frequency**
1. Depression	Standard depression screening tool	At least annually and when clinically appropriate
	* personal health questionnaire (PHQ-9)	
2. Substance use	General messages on risk reduction	Every visit
(D) CANCER	**Tool**	**Frequency**
1. Smoking related	Smoking cessation resources	Every visit
2. Lung	Low dose CT thorax	Annually for patients aged 55-80 who have 30 pack-year of smoking and are current smokers or have quitted in the last 15 years (until smoking has been discontinued for 15 years)
3. Colon	Stool based screening	Annually for patients aged 45-75
	Colonoscopy	Every 10 years if normal
		(more frequent screening if polyps are found)
4. Liver	Alpha fetoprotein and liver ultrasound	Every 6 months (for patients with cirrhosis for any cause, or with chronic Hepatitis B)
5. Anus	Digital anorectal exam	At least annually if asymptomatic
	Anal cytology	If only high resolution anoscopy is available
6. Prostate	Digital rectal exam	For men aged 55-69
	Blood test for PSA	According to prevailing guidelines on screening
7. Breast	Mammography	Every 2 years for aged 50-75
8. Cervix	Pap smear / Pap smear + HPV testing	For age <21: Pap within 1 year of sexual activity, no later than 21
		For age 21-29: Pap at diagnosis of HIV, repeat yearly for 3 years (if all are normal in 3 years, Pap every 3 years)
		For age >=30: Pap at diagnosis of HIV, repeat yearly for 3 years (if all are normal in 3 years, Pap every 3 years)
		[OR] Pap + HPV testing (if both are negative, Pap + HPV every 3 years)

In all postmenopausal women and men aged over 50, baseline bone densitometry by dual-energy x-ray absorptiometry (DEXA) should be performed and a vitamin D level should be measured if the DEXA reveals osteopenia or osteoporosis.[14] Osteomalacia can be caused by tenofovir-induced phosphate wasting and vitamin D deficiency.

INFECTIOUS DISEASES

Screening for sexually transmitted infections (STIs) in asymptomatic HIV-infected persons should be done at least yearly. Diseases to be screened include syphilis, gonorrhoea, chlamydia (for all persons) and trichomonas (for persons with vaginal sex). Screening recommendations should follow the latest guidelines.[15] More frequent screening, for example at 3- or 6-monthly intervals, may be indicated for persons who have multiple or anonymous partners, who have had recent past STIs or who have sex in conjunction with drug use. All persons who have vaginal sex should be screened for trichomonas annually.

For screening for latent TB infection, an annual test using tuberculin skin test (TST) or interferon-gamma release assay (IGRA) should be performed. If the initial TST or IGRA was negative when CD4 cell count was less than 200 cells/uL, the patient should be retested when CD4 cell count rises to over 200 cells/uL after being put on ART when sufficient immunocompetence to mount a positive reaction happens. As for vaccination, the response to any vaccine is greater with higher CD4 cell counts while on ART. Vaccination history should be reviewed for the following vaccine-preventable diseases: pneumococcus, influenza, tetanus, diphtheria, pertussis, meningococcal disease, hepatitis A, hepatitis B, human papillomavirus and varicella zoster. Apart from these vaccines, there may be vaccines which may be required for international travel, for example, the yellow fever vaccine. It should be noted that, in general, asymptomatic persons with CD4 cell counts over 200 cells/uL are suitable to receive vaccines including live vaccines safely.[16]

MENTAL HEALTH AND SUBSTANCE ABUSE

Depression affects around 40% of HIV-infected adults and is the most common mental health condition among HIV-infected persons.[17] Alcohol use and substance abuse should be screened at every visit using the following questions: "How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?" and "How many times in the past year have you had y or more drinks in a day?" (y is 5 for men and 4 for women) 18 Depression and substance abuse negatively impact the quality of life and adherence to antiretroviral therapy. Depression and substance abuse have also been linked to sexual transmission risk behaviour. Each clinical encounter presents a good opportunity for exploring the mental health issue of the patient. When discussing substance use with patients, healthcare providers should be non-judgmental, which in turn will enhance trust and improve health outcomes.[19] In most HIV centres, there are integrated psychological or psychiatric services offering professional advice related to substance abuse and mental health issues. Short of that, brief intervention including the use of motivational interviewing can be used by trained personnel at primary care setting.[18]

CANCERS

Smoking, as one of the most important carcinogenic causes, should be strongly advised against during clinical visits. Current smoking status of patients and health advice or referral for smoking cessation at least annually should be documented.[21]

As for screening of common cancers in general populations (liver, prostate, breast, colon and lung), the same principles apply to HIV-infected persons. In patients with chronic hepatitis B or cirrhosis of any cause, ultrasound examination together with serum alpha-fetoprotein test is recommended every six months. Breast cancers may behave more aggressively in HIV-infected women (manifested as bilateral disease, early metastasis and/or poorly differentiated cell types), but there is no increase in prevalence in HIV-infected women.[22] There are overseas recommendations on screening current smokers or recently quitted persons with history of heavy smoking (> 30 pack-years) with low-dose computer tomography (LDCT).[23] HIV-infected persons who are drug-adherent with CD4 count > 500 cells/uL may receive the same benefit from LDCT screening as non HIV-infected population.[24] For transgender individuals, cancer screening practice should be based on the sex-specific organs present currently in the patients.

The incidence of anal cancer in the general population, though uncommon, has been increasing steadily over the last three decades.[25] More females are affected than males. HIV-infected persons carry 80 times higher the risk of having anal dysplasia and cancer compared to the general population.[26] Persons with a low nadir CD4 count are especially at risk.[27] Other risk groups include women with history of cervical, vaginal or vulval cancers or precancers, people who are on immunosuppressants, smokers, and men who have sex with men (MSM). 90% of HIV-infected MSM have anal HPV, often with multiple types detected.[28] High grade squamous intraepithelial lesions (HSILs) can be found in 29.1% of HIV-infected MSM from a meta-analysis.[29] The progression rate of anal HSILs to squamous cell carcinoma was estimated to be around one in 377 HIV-positive MSM per year.[27]

The Anal Cancer/HSIL Outcome Research (ANCHOR) trial aimed to assess whether periodic anal Pap tests and appropriate referral for follow up and treatment of HSILs with high resolution anoscopy (HRA) is of benefit to patients. This was a randomised clinical trial with 4,446 participants performed at 21 clinical sites around the United States. The study was terminated early because it was found that the chances of progression to anal cancer were significantly reduced.[30] With this exciting finding, we shall wait eagerly for the day when screening and treatment for anal dysplasia will become the standard of care as recommended by some guidelines.[31,32] By then, one would expect the bottleneck will become HRA which requires specialised training. Colonoscopy is not the gold standard for identifying anal precancerous lesions and cannot substitute for HRA.[33,34] Primary care physicians and all carers, as a minimum, have to do an annual digital anorectal examination and refer the patient for further investigation when anal symptoms occur so as to promote early cancer detection.

OTHER HEALTH MAINTENANCE

All HIV-infected persons should be asked about their desires for reproduction. Persons capable of bearing children (cisgender women and transgender men) should be routinely asked about their pregnancy and contraception plans. Plans for conception may influence the choice of ART. Oral health examination should be performed every six months to look for oral cancers. Patients should be regularly educated on sexual practices facilitating risk reduction to prevent sexually transmitted infections.

CONCLUDING REMARKS

A person living with HIV has a similar life expectancy to an HIV-negative person – provided they are diagnosed in good time, are able to adhere to their HIV treatment and

have good access to medical and preventive care, either related or unrelated to HIV itself. Primary care physicians have an important and complementary role to play in working with HIV care providers to optimise patient care in a seamless way.

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Dovato
dolutegravir/lamivudine

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AN INNOVATIVE NEW TREATMENT FOR YOUR PATIENTS LIVING WITH HIV

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DURABLE, NON-INFERIOR EFFICACY WITH 0 RESISTANCE
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TDF, TAF AND **ABC FREE**[2]

GEMINI-1 and GEMINI-2 96-week data in treatment-naïve patients:
DOVATO 86.0% (n=716) vs DTG + TDF/FTC 89.5% (n=717)
(Proportion of patients with HIV-1 RNA <50 copies/mL)

DTG 50 mg + 3TC 300 mg used in the GEMINI studies.

Dovato indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults with no antiretroviral treatment history and with no known substitutions associated with resistance to the individual components of Dovato[2].

Abbreviated prescribing information

Dovato Each film-coated tablet contains 50 mg dolutegravir, 300 mg lamivudine. **Therapeutic indication:** Indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults with no antiretroviral treatment history and with no known substitutions associated with resistance to the individual components of Dovato. **Posology and method of administration:** Therapy should be prescribed by a physician experienced in the management of HIV infection. Oral use. Can be taken with or without food. *Adults:* Dovato one 50 mg/300 mg tablet once daily. A separate preparation of dolutegravir is available where a dose adjustment is indicated due to drug-drug interactions (e.g. rifampicin, carbamazepine, oxcarbazepine, phenytoin, phenobarbital, St. John's wort, etravirine (without boosted protease inhibitors), efavirenz, nevirapine, or tipranavir/ritonavir). In these cases the physician should refer to the individual product information for dolutegravir. *Women of childbearing potential (WOCBP)* should undergo pregnancy testing before initiation of Dovato. WOCBP who are taking Dovato should use effective contraception throughout treatment. *Missed doses:* Take Dovato as soon as possible, providing the next dose is not due within 4 hours. If the next dose is due within 4 hours, the patient should not take the missed dose and simply resume the usual dosing schedule. *Elderly:* There are limited data available on the use of Dovato in patients aged 65 years and over. No dose adjustment is necessary. *Renal impairment:* Dovato is not recommended for use in patients with a creatinine clearance < 50 mL/min. No dose adjustment is required in patients with mild renal impairment. *Hepatic impairment:* No dosage adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh grade A or B). No data are available in patients with severe hepatic impairment (Child-Pugh grade C); therefore Dovato should be used with caution in these patients. *Paediatric population:* The safety and efficacy of Dovato in paediatric patients have not been established. **Contraindications:** Hypersensitivity to the active substances or to any of the excipients. **Warnings & precautions:** *Transmission of HIV:* Precautions to prevent transmission should be taken in accordance with national guidelines. *Hypersensitivity reactions:* Discontinue Dovato and other suspect medicinal products immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by raised liver enzymes, fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, eosinophilia, angioedema). Monitor clinical status including liver aminotransferases and bilirubin. Delay in stopping treatment with Dovato or other suspect active substances after the onset of hypersensitivity may result in a life-threatening allergic reaction. *Weight and metabolic parameters:* An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Monitor blood lipids and glucose reference according to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate. *Liver disease:* If Dovato is used in patients co-infected with hepatitis B an additional antiviral is therefore generally needed. If Dovato is discontinued in patients co-infected with hepatitis B virus, periodic monitoring of both liver function tests and markers of HBV replication is recommended, as withdrawal of lamivudine may result in an acute exacerbation of hepatitis. Patients with preexisting liver dysfunction should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered. *Immune Reactivation Syndrome:* Any inflammatory symptoms should be evaluated and treatment instituted when necessary. *Mitochondrial dysfunction following exposure in utero:* There have been reports of mitochondrial dysfunction in HIV-negative infants exposed in utero and/or post-natally to nucleoside analogues. Some late-onset neurological disorders have been reported rarely. These findings should be considered for any child exposed in utero to nucleoside and nucleotide analogues, who presents with severe clinical findings of unknown aetiology. *Osteonecrosis:* Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement. *Opportunistic infections:* Patients remain under close clinical observation of these associated HIV diseases by physicians. *Drug interactions:* The recommended dose of dolutegravir is 50 mg twice daily when co-administered with rifampicin, carbamazepine, oxcarbazepine, phenytoin, phenobarbital, St. John's wort, etravirine (without boosted protease inhibitors), efavirenz, nevirapine, or tipranavir/ritonavir. Dovato should not be co-administered with polyvalent cation-containing antacids. Polyvalent cation-containing antacids are recommended to be taken 2 hours after or 6 hours before Dovato. When taken with food, Dovato and supplements or multivitamins containing calcium, iron or magnesium can be taken at the same time. If Dovato is administered under fasting conditions, supplements or multivitamins containing calcium, iron or magnesium are recommended to be taken 2 hours after or 6 hours before Dovato. A dose adjustment of metformin should be considered when starting and stopping coadministration of Dovato with metformin, to maintain glycaemic control. The combination of Dovato with cladribine is not recommended. Dovato should not be taken with any other medicinal product containing dolutegravir or lamivudine, except where a dose adjustment of dolutegravir is indicated due to drug-drug interactions. **Interactions:** Dolutegravir is eliminated mainly through metabolism by uridine diphosphate glucuronosyl transferase (UGT) 1A1. Dolutegravir is also a substrate of UGT1A3, UGT1A9, CYP3A4, P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP). Co-administration of Dovato and other medicinal products that inhibit UGT1A1, UGT1A3, UGT1A9, CYP3A4, and/or P-gp may, therefore, increase dolutegravir plasma concentration. Medicinal products that induce those enzymes or transporters may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir. Lamivudine is cleared renally. Active renal secretion of lamivudine in the urine is mediated through the organic cation transporter (OCT) 2 and multidrug and toxin extrusion transporters (MATE1 and MATE2-K). **Pregnancy & lactation:** The safety and efficacy of a dual regimen has not been studied in pregnancy. Dovato use during pregnancy only if the expected benefit justifies the potential risk to the foetus. Not recommend HIV infected women to breast-feed their infants under any circumstances in order to avoid transmission of HIV. No data on effects on human fertility. **Adverse reactions:** Very common: headache, nausea, diarrhoea; Common: depression, anxiety, insomnia, abnormal dreams, dizziness, somnolence, vomiting, flatulence, abdominal pain/discomfort, rash, pruritus, alopecia, arthralgia, muscle disorders (including myalgia), fatigue, creatine phosphokinase (CPK) elevations, alanine aminotransferace (ALT) and/or aspartate aminotransferace (AST) elevations. **Overdose:** No specific treatment for overdose. Patient should be treated supportively with appropriate monitoring as necessary.

Safety information: Overall AE profiles were similar. There was a lower risk of drug-related AEs in the Dovato arm at week 96.

Please read the full prescribing information prior to administration. Full prescribing information is available on request from GlaxoSmithKline Ltd, 23/F, Tower 6, The Gateway, 9 Canton Road, Tsimshatsui, Kowloon, Hong Kong. Abbreviated Prescribing Information based on PI version HK122019 GDS01/EU20190701 For adverse events reporting, please call GlaxoSmithKline Limited at (852) 3189 8989 (Hong Kong) or (853) 2871 5569 (Macau) or email to HK Adverse Event mailbox: HKAdverseEvent@gsk.com

Reference: 1. Cahn P et al. Presented at: International AIDS Conference; July 21-24, 2019; Mexico City, Mexico. Slides WEAB0404LB. **2.** Dovato Full Prescribing Information, HK122019.

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Date of preparation: 13/04/2021 (04/23)

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HELP SHORTEN TIME TO RECOVERY BY 29%

IN PATIENTS HOSPITALIZED WITH **COVID-19**, VS PLACEBO*†[1]

Indication: SARS-CoV-2 Infection[‡§2]

- VEKLURY® (n=541) significantly reduced time to recovery[#] by a median of 5 days compared with placebo (n=521) in the overall study population*†[1]
- Sped up recovery[#] by a median of 1 week vs placebo in patients who received oxygen support at baseline (11 days vs 18 days; RR: 1.31; 95% CI: 1.12—1.52)†[1]
- Shortened the period to receive oxygen by a median of 8 days (13 days vs 21 days) in patients who received oxygen support at baseline*†[1]

* The median time to recovery[#] was 10 days for VEKLURY® but 15 days for placebo (RR for recovery: 1.29; 95% CI: 1.12–1.49; p < 0.001).[1]

† ACTT-1 was a double-blind, multicenter, randomized, placebo-controlled trial that compared the efficacy and safety of VEKLURY® and placebo in adult patients hospitalized with COVID-19 and lower respiratory tract infection. Of total 1,062 patients, they were randomly assigned in a 1:1 ratio to VEKLURY® or placebo. All received supportive care according to the standard of care for the trial site hospital. The primary outcome was the time to recovery.[#] The key secondary outcome was clinical status at Day 15, as assessed on the ordinal scale. Other outcomes included period with supplemental oxygen up to day 29 if it was being used at baseline.[1]

‡ Since available information on the efficacy and safety of this drug in connection with the SARS-CoV-2 infection is extremely limited, careful determination should be made as to need for administration considering the latest information.[2]

§ In line with the majority of use in clinical trials to date, in principle VEKLURY® should be used for SARS-CoV-2 infections in severe patients whose oxygen saturation of ≤ 94% (room air), requiring supplemental oxygen, under ECMO introduction, or under invasive mechanical ventilation.[2]

[#] The primary outcome was the time to recovery, defined by either discharge from the hospital or hospitalization for infection control or other non-medical reasons. Recovery RR > 1 indicate a benefit for VEKLURY®.[1]

CI=confidence interval; COVID-19=coronavirus disease 2019; ECMO=extracorporeal membrane oxygenation; RR=rate ratio; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

References: 1. Beigel JH, et al. N Engl J Med. 2020;383:1813–1826. **2.** VEKLURY® Hong Kong Prescribing Information. [RDV-MAY20 (v1.0)]

VEKLURY® Abbreviated Prescribing Information (Version: RDV-MAY20 v1.0)
Presentation: Veklury concentrate for solution for infusion 100 mg/20 mL: Each vial contains 100 mg of remdesivir. Colourless to clear yellow solution. Veklury powder for concentrate for solution for infusion 100 mg: Each vial contains 100 mg of remdesivir. White to off-white to yellow solid. **Indications:** SARS-CoV-2 Infection. In principle remdesivir should be used for SARS-CoV-2 infections in severe patients whose oxygen saturation of ≤ 94% (room air), requiring supplemental oxygen, under ECMO introduction, or under invasive mechanical ventilation. **Dosage:** Adults and pediatrics with body weight ≥40 kg: Single dose of remdesivir 200 mg IV injection on Day 1 followed by once-daily doses of remdesivir 100 mg IV injection from Day 2. Pediatrics with body weight between 3.5 kg and <40 kg: One dose of remdesivir 5 mg/kg IV injection on Day 1 followed by remdesivir 2.5 mg/kg IV injection from Day 2. Solution for concentrate for infusion is not recommended for pediatric between 3.5kg and <40kg. Treatment duration: While the optimal duration of treatment has not been established, as a guide, for patients who are on ECMO or invasive mechanical ventilation, the duration of treatment is up to 10 days. For patients who are not on ECMO or invasive mechanical ventilation, duration of treatment is up to 5 days or until Day 10 if no symptomatic improvement is observed. Renal impairment: Not recommended for adults, infants, children and adolescents with eGFR <30 mL/min/1.73m^2 and term newborns (7 to 28 days) with serum creatinine levels of ≥1 mg/dL. Hepatic impairment: Not recommended for patients with ALT levels ≥5 times the Upper Limit of Normal Range. Should be administered only if the therapeutic benefits outweigh the risks for patients with ALT levels are <5 times the Upper Limit of Normal Range. **Contraindications:** Hypersensitivity to the active substances or to any of the excipients. **Warnings and Precautions:** Patients should be closely monitored by appropriate clinical and laboratory monitoring during treatment with remdesivir. Laboratory values should be monitored on a daily basis. If any adverse drug reactions are observed, administration should be continued only if it is determined that the therapeutic benefits outweighs the risks. Kidney and liver function tests should be performed daily before and during administration and the patient's condition should be carefully monitored. The patient's condition should be carefully monitored for infusion reactions and administration should be immediately discontinued and appropriate measures should be taken if any abnormalities are observed. **Adverse reactions:** Information on the safety of remdesivir is extremely limited, and such information is still being collected. Clinically significant adverse reactions include acute renal impairment, hepatic impairment and infusion reactions (hypotension, nausea, vomiting, sweating and tremor). **Drug interactions:** *In vitro* studies have shown that remdesivir is a substrate for CYP2C8, CYP2D6 and CYP3A4, as well as OATP1B1 and P-gp, and, in addition, is an inhibitor of CYP3A4, OATP1B1, OATP1B3, BSEP, MRP4 and NTCP. No clinical drug-drug interaction studies have been conducted.

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HKVEK0008_v10 4/9/2021

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What Skin Manifestations Make Me Consider HIV Infection?

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INTRODUCTION

Skin disorders are commonly encountered in Human Immunodeficiency Virus (HIV)-infected patients and may be the first clinical manifestation of HIV infection. After HIV enters the target CD4 T lymphocytes, the virus gradually impairs the host immunity. The virus also attacks the skin Langerhans cells and dermal dendritic cells. One study suggested that around 86-96% of HIV-infected patients had mucocutaneous manifestation and there were approximately 2.4 skin problems for each patient.[1] There is wide diversity in the prevalence and clinical presentation of dermatologic diseases in HIV-infected people. This is possibly secondary to the different stages of HIV disease and the related CD4 counts, the pattern of prevailing infections and the use of medications, especially the Highly Active Anti-Retroviral Therapy (HAART).

CD4 COUNT-RELATED SKIN DISEASES

In general, declining immunity is associated with increased number and severity of skin disorders.[2,3] Compared with non-infected people, the clinical manifestations of skin lesions in people living with HIV infection (PLHIV) are more unusual and recalcitrant to standard treatments. Table 1 shows the association of rough CD4 count and skin diseases.

Table 1: The association of rough CD4 count with skin diseases (Adapted from Ho KM, Kwan CK (2019). Dermatologic Manifestation in HIV Disease. In Lee SS, HIV Manual (4th Edition), Hong Kong. Stanley Ho Centre for Emerging Infectious Diseases CUHK.)

Rough CD4 Count (cell/uL)	Skin Diseases
Early Infection >500	Acute viral syndrome Kaposi's sarcoma Viral wart Vaginal thrush
Mild Immunosuppression 200-500	Oral thrush Recurrent herpes simplex and zoster Recalcitrant seborrhoeic dermatitis Oral hairy leukoplakia Hyperkeratotic warts
Significant Immunosuppression 100-200	Disseminated herpes infection Eosinophilic folliculitis Widespread molluscum Extensive Kaposi's sarcoma Recalcitrant psoriasis
Advanced Immunosuppression <100	Cutaneous talaromycosis infection Non-healing and large herpes Cutaneous cryptococcal infection Disseminated CMV infection

INFLAMMATORY DERMATOSES

Basically, HIV-related skin diseases can be classified into three categories: (1) Inflammatory dermatoses; (2) Infectious diseases and infestations; (3) Neoplastic conditions and others.

Inflammatory dermatoses are commonly encountered in both PLHIV and those not infected. However, PLHIV may have more severe manifestations of the skin diseases, may be recalcitrant to the standard treatments or may manifest sudden onset of common inflammatory dermatoses without obvious precipitating factors. Reactive arthritis which is previously referred to Reiter's disease and inflammatory dermatoses such as seborrhoeic dermatitis and psoriasis vulgaris are common occurrence in PLHIV. On the other hand, some dermatoses are more specific for HIV infection though not pathognomonic. The classical examples are eosinophilic folliculitis, nodulocystic and pustular acne, acne conglobate in middle middle-aged adults rather than teenagers and type VI pityriasis ruba pilaris (PRP) presented as erythematous scaly elongated follicular plugs. HIV infection should be suspected if these dermatoses arise alone; HIV test should be considered in these patients.

In general, the severity of inflammatory dermatosis carries a direct proportional relationship with the CD4 count. In other words, the lower the CD4 count, the less severe the inflammatory dermatosis. In contrast, psoriasis vulgaris demonstrates paradoxical behaviour in HIV infection. The CD4 count is inversely proportional to the severity of the psoriasis. A review paper on HIV-associated psoriasis published by the Imperial College School of Medicine stated that pre-existing psoriasis may undergo severe exacerbation in HIV-infected patients and may become more severe upon progression to AIDS.[4] Another review article published in 2010 also stated that psoriasis manifests paradoxical behaviour in HIV-infected people and biologics may be considered after failure of first-line treatment.[5] Figure 1 shows an AIDS patient with a single-digit CD4 count who presented with severe psoriasis manifested as multiple generalised severe and thick hyperkeratotic plaques.

Fig. 1a and 1b: Severe psoriasis in AIDS patients with generalised hyperkeratotic plaque (Clinical photos from personal collection)

Eosinophilic folliculitis is due to the infiltration of eosinophils around the hair follicles. Clinically, it presents as inflamed papules, sometimes pustules around the hair follicles on face, scalp and upper trunk. The presentation is similar to acne especially on the face except itchiness. It commonly happens in a PLHIV who has a lower CD4 count. Although it is not pathognomonic, it is still characteristic of HIV infection. Therefore, when we encounter patients with extremely itchy acneiform papules, eosinophilic folliculitis will be flashed out and HIV screening should be arranged.

INFECTIOUS DISEASES AND INFESTATIONS

PLHIV is well known to be associated with various kinds of infections and infestations especially in those with low CD4 counts. Opportunistic infection is commonly encountered. Talaromycosis, cryptococcosis, histoplasmosis and bacillary angiomatosis are opportunistic infections with skin manifestations that alert us about HIV infection.[6] Talaromycosis, formerly penicilliosis, is commonly found in Southeast Asia in HIV infection. It presents with systemic symptoms of fever, cough, malaise, hepatosplenomegaly and lymphadenopathy together with characteristic central necrotic and umbilicated molluscum or doughnut-like skin papules over the face, chest wall and upper back. Some common infections such as crusted scabies, oropharyngeal candidiasis (thrush), disseminated herpes simplex virus and multi-dermatomal zoster infection (VZV), presenting in the severe or recalcitrant situation, would push the clinician to consider HIV infection, especially in a previously healthy adult. Extensive viral warts (Fig. 2), epidermodysplasia verruciformis (Fig. 3) and anal dysplasia are caused by human papillomavirus (HPV), and suggest a decline in immune system and possible HIV infection.

Fig. 2: Extensive viral warts on the hand (Clinical photo from personal collection)

Fig. 3: Epidermodysplasia verruciformis on neck (Clinical photo from personal collection)

Onychomycosis is commonly seen in the clinics of primary care physicians or dermatologists. The most common form is distal and lateral subungual onychomycosis (DLSO) (Fig. 4a) that involves the distal and lateral parts of the nail. It is also commonly seen in HIV-infected people.[8,9] However, proximal subungual onychomycosis (PSO) (Fig. 4b) is a rare form of onychomycosis affecting the proximal part of the nail and is more specific in HIV or AIDS patients[8,9]; such findings would alert us to order a HIV test.

Fig. 4a: Distal & Lateral Subungual Onychomycosis
Fig. 4b: Proximal Subungual Onychomycosis
(Clinical photos from personal collection)

SYPHILIS AND OTHER SEXUALLY TRANSMITTED INFECTIONS

HIV infection is well known to be acquired through sexual intercourse. Therefore, patients having sexually transmitted infections (STIs) should have HIV screening. Syphilis, which is of both individual and public health importance, increases the risk of HIV infection. Both infections share the same route of transmission. The incidence of syphilis has increased

dramatically in the past decade among men who have sex with men (MSM), particularly those with coexistent HIV infection.[10] Although syphilis is an ancient disease and the principles of recommended management have been established for decades, clinical manifestations and difficulty in interpretation of serological tests still cause frustration. Primary syphilis often presents as a painless genital ulcer (chancre) and secondary syphilis has papulosquamous rash and sometimes involves palm and sole (Fig. 5).

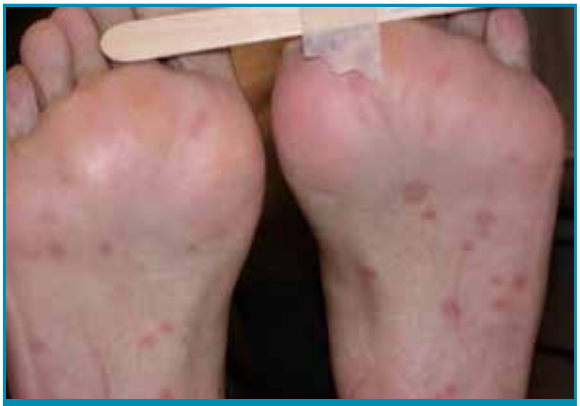

Fig. 5: Papulosquamous rash of secondary syphilis involving the soles (Clinical photo from personal collection)

NEOPLASMS

Kaposi's sarcoma is due to Human Herpes Virus 8 (HHV 8), also known as Kaposi's sarcoma-associated herpesvirus, which is a gammaherpesvirus and is well known to be associated with HIV infection. In the early 80s, a group of patients suffering from Kaposi's sarcoma, an extremely rare disease in immunocompromised patients, in whom HIV infection was subsequently discovered. This discovery becomes one of the landmarks in the history of HIV infection in humans. Kaposi's sarcoma (KS) is characterised by the proliferation of spindle cells of endothelial origin.[11] The clinical course of KS is highly variable ranging from minimal mucocutaneous lesions to multiple extensive internal organs involvement. KS causes gastrointestinal tract bleeding, intestinal obstruction, coughing, dyspnoea, haemoptysis or pleural effusions depending on different sites of involvement. KS tends to be more extensive in AIDS patients. Cutaneous lesions can be found in any location. However, it is typically concentrated on lower limbs (Fig. 6a) and head and neck regions, including oral mucosa (Fig. 6b). It presents as violaceous nodules or plaque. No one will miss the HIV test once Kaposi's sarcoma is diagnosed.

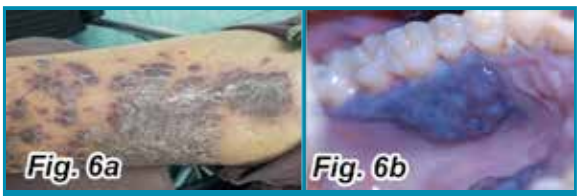

Fig. 6a: Kaposi's sarcoma on lower limbs
Fig. 6b: Kaposi's sarcoma in oral mucosa
(Clinical photos from personal collection)

Other skin cancers occur with increased frequency or altered course in PLHIV. Malignant melanoma, although not common in our locality, is more aggressive in HIV patients. Squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) are more frequent in HIV patients.[12] If these cutaneous cancers happen in relatively young and fit adults instead of the elderly, it rings a bell for HIV infection.

CONCLUSION

A wide variety of skin problems can be found in PLHIV. Although skin lesions such as Kaposi's sarcoma, proximal subungual onychomycosis, eosinophilic folliculitis or talaromycosis are not pathognomonic of HIV, they are highly illustrative and help us flash out the possibility of HIV infection. On the other hand, even though some dermatoses such as a viral wart, psoriasis or herpes zoster are common in the general population, these skin problems, if very severe and/or recalcitrant to standard treatment, should also alert us to the possibility of HIV infection. When skin cancer appears in a relatively young adult, it may also be HIV infection. Last but not least, do not forget HIV infection in those patients with sexually transmitted infections or high-risk sexual behaviours.

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How to Provide an LGBTQ+ friendly Medical Service?

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INTRODUCTION

Our patients all desire to have their problems heard and their concerns acknowledged. During consultation with a doctor, the last thing the patient wants is to have issues unresolved or symptoms ignored. However, for many in the Lesbian, Gay, Bisexual, Transgender and Questioning etc (LGBTQ+) community, there are often barriers that prevent them from seeking proper medical attention. Data from a large observational study in the U.S. suggest that 24% of transgender patients reported unequal treatment in healthcare settings, 19% were refused care altogether, and 33% did not seek preventative services.[1] Many LGBTQ+ patients avoid or delay seeking care because of negative attitudes, discrimination, or even hostile behaviour towards them by healthcare providers and institutions. Doctors, nurses, and healthcare workers should examine their existing policies and practices and work on certain key elements to improve the quality of health care for this marginalised community of our society.[2]

CREATING A WELCOMING ENVIRONMENT

LGBTQ+ patients often "scan" an office for clues to help them decide what information they feel comfortable sharing with their medical practitioners. Posting LGBTQ+ friendly symbols or stickers in the front office or displaying brochures about LGBTQ+ health concerns such as hormone therapy for transgender patients will enable clients to feel more welcome in the doctor's office.[3]

Intake forms should be updated to include gender-neutral language and use the two-step method to help identify transgender patients (Questions: What is your gender identity? Does it align with the gender you were assigned at birth?). Instead of putting "marital status", consider using the term "relationship status" or options like "partnered" in addition to "spouse" or "husband/wife."[4]

PATIENT-PROVIDER DISCUSSIONS

It is vital to discuss sexual health issues openly with your patients. Sexual orientation cannot be determined simply by looking at someone.[5] One clinician's approach is to ask about sexual orientation, behaviour, and attraction in an open and nonjudgmental way, leaving room for a patient's uncertainty. For example, "Do you know if you're attracted to men, women, both, or neither?"[5] Many patients do not self-identify through a sexual orientation label, yet may have sex with persons of their same-sex or gender, or with more than one sex.[2]

When talking with transgender people, ask questions necessary to assess the issue, but avoid unrelated probing. Explaining why you need information can help avoid the feeling of intrusion. For example, "To help your health risks, can you tell me about any history you have had with hormone use?"[1]

SPECIFIC ISSUES TO DISCUSS WITH LGBTQ+ PATIENTS

Due to the prevalence of various mental health issues, when treating LGBTQ+ patients, clinicians should routinely screen for anxiety, depression, substance abuse, post-traumatic stress disorder (PTSD), self-harm, and eating disorders.[6] Explore the degree to which your LGBTQ+ patients are open about their sexual identity and/or sexual orientation to their employers, family, and friends. Additionally, attempt to determine the extent of their social support or participation in the community. In many cases, one's level of identification within the community strongly correlates with decreased risk of sexually transmitted infections (including HIV) and improved mental health.[7]

STAFF SENSITIVITY AND TRAINING

Clinic employees should be educated in health issues unique to LGBTQ+ communities. It is essential to train all staff to be sensitive to each patient's gender identity, using the correct chosen names and referring to patients using their chosen pronouns. The importance of maintaining confidentiality about sexual orientation and identity should be emphasised. Educating clinic employees will enable clients to feel safe and open when discussing sensitive topics about their sexual history.[5]

CONCLUSION

LGBTQ+ clients face many health challenges when they present themselves to the doctor. Clinicians need to be open-minded and sensitive to the vulnerability of these patients. By spending more time with this particularly marginalised group of patients to understand their healthcare needs, the doctor-patient relationship will be strengthened.

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Dermatology Quiz

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Fig 1: Multiple purpuric rash on bilateral lower limbs

This 52-year-old lady complained to have multiple skin rash on bilateral lower limbs for a few months. The onset was insidious. Although it was not itching, there was some burning or tingling sensation. Physical examination revealed there were multiple palpable purpuric papules with some petechiae and ecchymoses on bilateral lower limbs (Fig 1).

Questions

1. What are the differential diagnoses of her skin lesion?
2. What investigation are you going to order?
3. How do you treat this patient?

(See P.33 for answers)

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
		★Zoom Live HKMA-HKSH CME Programme 2021-2022 (Online) Topic: Management of Stomach Cancer **1**	**2**	★Zoom Live HKMA-HKSTP CME Lecture - Application Of AI In Autism Risk Assessment: Combining Genomic And Behavioral Analysis - Online **3**	★Zoom Live Update on the Management of Dermatitis with Oxidative Stress (Online) **4**	**5**
6	★Zoom Live Comparing Biologic Therapies In Psoriasis - Online **7**	**8**	★Zoom Live Optimal Medical Therapy after PCI (Online) ★The Hong Kong Neurosurgical Society Monthly Academic Meeting –Review and Update of Management of Intracerebral Hemorrhage **9**	★Zoom Live A Primer to Neuro-Linguistic Programming (NLP) - The Clinical Link (Online) **10**	★Zoom Live Evolving Antidepressant Therapy Strategies for Major Depressive Disorder (MDD) **11**	**12**
13	**14**	★Zoom Live Optimizing T2DM Treatment with SGLT2 Inhibitors - Benefits Beyond Glycemic Control -(Online) **15**	★Zoom Live Updates On Personalized Treatment On BPH - Alpha-Blockers With High Uro-Selectivity Shall Be The First Line Treatment For BPH - Online **16**	★Zoom Live Attention-Deficit / Hyperactivity Disorder (ADHD) in Children and Teens: What We Need to Know for Adapting to "NEW NORM" - (Online) **17**	★Zoom Live Children's Functional Constipation and Intestinal Microbiome - Online **18**	**19**
20	★Webinar Management of Diabetic Kidney Disease: What's Hot? **21**	★Zoom Live HKMA-GHK CME Programme 2021 - 2022 - Updated In Obesity Management (Online) **22**	**23**	**24**	★Zoom Live Management of IBS in Pandemic Time - Online **25**	**26**
27	**28**	★Zoom Live Improving Long-term Allergic Rhinitis Control with Patients' Preferred Treatment(Online) **29**	**30**	**31**		

Date / Time	Function	Enquiry / Remarks
1 TUE 2:00 PM	**Zoom Live** **HKMA-HKSH CME Programme 2021-2022 (Online)** **Topic: Management of Stomach Cancer** Organiser: Hong Kong Medical Association & Hong Kong Sanatorium & Hospital Speaker: Dr KWONG Wing-hang	HKMA CME Dept. 3108 2507 1 CME Point
3 THU 2:00 PM	**Zoom Live** **HKMA-HKSTP CME Lecture - Application Of AI In Autism Risk Assessment: Combining Genomic And Behavioral Analysis - Online** Organiser: Hong Kong Medical Association & Hong Kong Science Park Speaker: Prof TSUI Kwok-wing, Stephen	HKMA CME Dept. 3108 2507 1 CME Point
4 FRI 2:00 PM	**Zoom Live** **Update on the Management of Dermatitis with Oxidative Stress (Online)** Organiser: HKMA-Shatin Community Network Speaker: Dr CHAN Yung	Ms Candice Tong 3108 2513 1 CME Point
7 MON 2:00 PM	**Zoom Live** **Comparing Biologic Therapies In Psoriasis - Online** Organiser: Hong Kong Medical Association Speaker: Dr CHAN Yung, Davis	HKMA CME Dept. 3108 2507 1CME Point
9 WED 2:00 PM	**Zoom Live** **Optimal Medical Therapy after PCI (Online)** Organiser: HKMA-Central, Western & Southern Community Network Speaker: Dr CHEONG Yan-yue, Adrian	Mr Jeffrey Cheung 3108 2514 1CME Point
7:30 PM	**The Hong Kong Neurosurgical Society Monthly Academic Meeting –Review and Update of Management of Intracerebral Hemorrhage** Organiser:Hong Kong Neurosurgical Society Speaker: Dr Carmen YIM	Dr Calvin MAK 2595 6456
10 THU 2:00 PM	**Zoom Live** **A Primer to Neuro-Linguistic Programming (NLP) - The Clinical Link (Online)** Organiser: HKMA-KLN East Community Network Speaker: Dr CHAN Kwok-hei, Paul	Mr Jeffrey Cheung 3108 2514 1CME Point
11 FRI 2:00 PM	**Zoom Live** **Evolving Antidepressant Therapy Strategies for Major Depressive Disorder (MDD)** Organiser: HKMA-KLN City Community Network Speaker: Dr CHAN Wah-fat	Ms Candice Tong 3108 2513 1CME Point
15 TUE 2:00 PM	**Zoom Live** **Optimizing T2DM Treatment with SGLT2 Inhibitors - Benefits Beyond Glycemic Control -(Online)** Organiser: HKMA-KLN West Community Network Speaker: Dr WONG Cheuk-lik	Mr Jeffrey Cheung 3108 2514 1CME Point
16 WED 2:00 PM	**Zoom Live** **Updates On Personalized Treatment On BPH - Alpha-Blockers With High Uro-Selectivity Shall Be The First Line Treatment For BPH - Online** Organiser: Hong Kong Medical Association Speaker: Dr CHENG Kwun-chung, Bryan	HKMA CME Dept. 3108 2507 1CME Point
17 THU 2:00 PM	**Zoom Live** **Attention-Deficit / Hyperactivity Disorder (ADHD) in Children and Teens: What We Need to Know for Adapting to "NEW NORM" - (Online)** Organiser: HKMA-New Territories West Community Network Speaker: Dr WONG Wing-kun, Charlotte	Mr Jeffrey Cheung 3108 2514 1CME Point
18 FRI 2:00 PM	**Zoom Live** **Children's Functional Constipation and Intestinal Microbiome - Online** Organiser: Hong Kong Medical Association Speaker: Dr LAM Ka-yi, Catherine	HKMA CME Dept. 3108 2507 1CME Point
21 MON	**Webinar** **Management of Diabetic Kidney Disease: What's Hot?** Organiser: Hong Kong Chinese Medical Association Ltd Speaker: Prof Sydney Chi-wai TANG	HKCMA Ms Candy Lam 2821 3519 1CME Point
22 TUE 2:00 PM	**Zoom Live** **HKMA-GHK CME Programme 2021 - 2022 - Updated In Obesity Management (Online)** Organiser: Hong Kong Medical Association & Gleneagles Hong Kong Hospital Speaker: Dr LAM King-yun, Joanne	HKMA CME Dept 3108 2507 1CME Point
25 FRI 2:00 PM	**Zoom Live** **Management of IBS in Pandemic Time - Online** Organiser: Hong Kong Medical Association Speaker: Dr FONG Ka-leuk	HKMA CME Dept 3108 2507 1CME Point
29 TUE 2:00 PM	**Zoom Live** **Improving Long-term Allergic Rhinitis Control with Patients' Preferred Treatment(Online)** Organiser: HKMA-Yau Tsim Mong Community Network Speaker: Dr NGAI Chi-man	Ms Candice Tong 3108 2513 1CME Point

Answers to Dermatology Quiz

Answers:

1. The clinical picture of multiple palpable purpuric papules with some petechiae and ecchymoses on bilateral lower limbs is pointing to cutaneous small vessel vasculitis. The differential diagnoses include Henoch-Schonlein purpura, polyarteritis nodosa and ANCA-associated vasculitis such as microscopic polyangiitis or Churg-Strauss syndrome. Rarely, scurvy due to vitamin C deficiency may be considered.

2. It is difficult to differentiate these diagnoses solely based on the clinical examination. Hence a skin biopsy is needed. The histology reveals the presence of vascular and peri-vascular infiltration of polymorphonuclear leukocytes with the formation of nuclear dust (leukocytoclastic), extravasation of erythrocytes and fibrinoid necrosis of the small vessel wall. Urinalysis and basic blood tests including complete blood picture, liver and renal function tests, autoimmune markers such ANA, ds-DNA, complements, and ANCA may also be needed. Moreover, cutaneous small vessel vasculitis may be secondary to certain infections, especially viral infections including hepatitis B and C, and HIV. Therefore, investigation for such infections is also necessary. Nevertheless, the aetiology of most cases is unidentifiable.

3. Medications such as thiazide diuretics, allopurinol, NSAIDs, phenytoin and certain antibiotics are related to the cutaneous small vessel vasculitis, and the culpritable medication will need to be stopped. Other general measures such as rest, applying compression, dressing for ulcers if present, emollient and treating the related infections are essential. Systemic treatments include corticosteroid, colchicine or dapsone. Other treatments reported to be helpful are hydroxychloroquine, rituximab, IVIG and immunosuppressants such as methotrexate, azathioprine, mycophenolate or cyclosporin.

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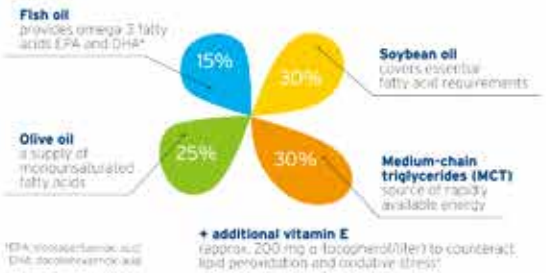

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