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Viral Diseases of Global Importance

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^ **Significantly fewer all grade treatment-related AEs compared to DTG plus ABC/3TC or FTC/TAF (secondary endpoint)#.**

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†BIKTARVY® was assessed in four Phase 3, double-blind, randomised clinical trials: two in treatment-naïve adults (Study 1489 [BIKTARVY® vs ABC/3TC/DTG, n=629] and Study 1490 [BIKTARVY® vs DTG + FTC/TAF, n=645]) and two in virologically suppressed adults (Study 1844 [switching from DTG + ABC/3TC or ABC/3TC/DTG to BIKTARVY®, n=563] and Study 1878 [switching from ABC/3TC or FTC/TDF plus boosted ATV or DRV to BIKTARVY®, n=577]) through to Week 48.

§0 cases of treatment-emergent resistance in registrational trials at week 48[3-5,7].

#Study 1489 (vs ABC/3TC/DTG): 26% (82/314) vs 40% (127/315), p<0.001; Study 1490 (vs FTC/TAF + DTG): 18% (57/320) vs 26% (83/325), p=0.022; Study 1844 (vs ABC/3TC/DTG): 8% (23/282) vs 16% (44/281), p=0.006[1-6].

¶Each BIKTARVY® tablet is approximately 15 mm x 8 mm[1].

3TC, lamivudine; ABC, abacavir; AEs, adverse events; ATV, atazanavir; CI, confidence interval; DRV, darunavir; DTG, dolutegravir; FTC, emtricitabine; INSTI, integrase strand transfer inhibitor; STR, single-tablet regimen; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

References: 1. BIKTARVY® Hong Kong Prescribing Information (version: HK-JUL18-EU-JUN18). **2.** Tsiang M, Jones GS, Goldsmith J, et al. Antiviral activity of bictegravir (GS-9883), a novel potent HIV-1 integrase strand transfer inhibitor with an improved resistance profile. Antimicrob Agents Chemother. 2016;60(12):7086-97. **3.** Gallant J, Lazzarin A, Mills A, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. Lancet. 2017;390(10107):2063-72. **4.** Sax PE, Pozniak A, Montes ML, et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. The Lancet. 2017;390(10107):2073-82. **5.** Molina JM, Ward D, Brar I, et al. Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed adults with HIV-1: 48 week results of a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. Lancet HIV. 2018;5(7):e357–e365. **6.** Gilead. Data on file BVY002. June 2018. **7.** Daar E, DeJesus E, Ruane P, et al. Efficacy and safety of switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from boosted protease inhibitor-based regimens in virologically suppressed adults with HIV-1: 48 week results of a randomised, open-label, multicentre, phase 3, non-inferiority trial. Lancet HIV. 2018;5(7):e347–e356.

BIKTARVY® Abbreviated Prescribing Information (Version: HK-JUL18-EU-JUN18)

Presentation: Each film-coated tablet contains bictegravir sodium equivalent to 50 mg of bictegravir, 200 mg of emtricitabine, and tenofovir alafenamide fumarate equivalent to 25 mg of tenofovir alafenamide. Purplish-brown, capsule-shaped, film-coated tablet debossed with "GSI" on one side and "9883" on the other side of the tablet. Each tablet is approximately 15 mm x 8 mm. **Indications:** Biktarvy is indicated for the treatment of adults infected with human immunodeficiency virus-1 (HIV-1) without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir. **Dosage:** Adults: One tablet to be taken once daily with or without food. Elderly: No dose adjustment is required. Renal impairment: No dose adjustment for patients with estimated creatinine clearance (CrCl) ≥ 30 mL/min. Not recommended in patients with estimated CrCl below 30 mL/min. Hepatic impairment: No dose adjustment for patients with mild or moderate hepatic impairment (Child-Pugh-Turcotte [CPT] Class A or B). Not recommended in patients with severe hepatic impairment (CPT Class C). Paediatric population: The safety and efficacy in children and adolescents aged less than 18 years have not yet been established. **Contraindications:** Hypersensitivity to the active substances or to any of the excipients. Co-administration with rifampicin and St John's Wort (*Hypericum perforatum*).**Warnings and Precautions:** Patients co-infected with HIV and hepatitis B or C virus: Patients with chronic hepatitis B or C treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. Discontinuation of Biktarvy therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis. Patients co-infected with HIV and HBV who discontinue Biktarvy should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. Liver disease: Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy (CART) and 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. Weight and metabolic parameters: An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Lipid disorders should be managed as clinically appropriate. Mitochondrial dysfunction following exposure in utero: Nucleos(t)ide analogues may impact mitochondrial function to a variable degree. The findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV. Immune Reactivation Syndrome: In HIV infected patients with severe immune deficiency at the time of institution of CART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders have also been reported. Opportunistic infections: Patients should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases. Osteonecrosis: Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement. Nephrotoxicity: A potential risk of nephrotoxicity resulting from chronic exposure to low levels of tenofovir due to dosing with tenofovir alafenamide cannot be excluded. Co-administration of other medicinal products: Biktarvy should be administered at least 2 hoursbefore, or with food 2 hours after antacids containing magnesium and/or aluminium. Biktarvy should be administered at least 2 hours before iron supplements, or taken together with food. Biktarvy should not be co-administered with other antiretroviral medicinal products. **Adverse reactions:** Most frequently reported adverse reactions were headache, diarrhoea and nausea. Please refer to full prescribing information for full list of adverse reactions. **Drug interactions:** Interactions between Biktarvy and other medicinal products: St. John's wort, rifampicin, rifabutin, rifapentine, atazanavir ± cobicistat, boceprevir, azithromycin, clarithromycin, carbamazepine, oxcarbazepine, phenobarbital, phenytoin, magnesium/ aluminium-containing antacid suspension, ferrous fumarate, sucralfate, ciclosporin, methadone and metformin. **Before prescribing, please consult full prescribing information which is available upon request**. Biktarvy and Descovy are registered trademarks of Gilead Sciences, Inc., or its related companies.

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Room 2603, 26th Floor, Hysan Place
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Contents

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The Cover Shot

Bench

This photo was taken in Stanley Park in Vancouver, Canada. By the breezy sea, there sits a bench with a plaque that reads, 'Look to the sea, and thy heart shall soar.' – remembering a loving husband and father who loved the sea. Now that he has passed away, he can be with the sea forever.

When we look back, there are always regrets: we could have appreciated the happy times we spent with our loved ones longer; we could have worked harder; we could have been to more amazing places. When we look forward, there are always goals, plans and dreams we want to achieve. Few people appreciate the present and take the time to feel the very moment. Carpe diem – It is important that we seize the day and cherish every present moment, to feel, to appreciate, to soar.

Mr Kai-man HO

Advance Practice Nurse, Princess Margaret Hospital
Fellow of the HK Academy of Nursing in Infectious Disease

Truvada®
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CAN HELP PREVENT HIV.

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- Do not initiate TRUVADA for a PrEP indication if signs or symptoms of acute HIV-1 infection are present unless negative infection status is confirmed[1].

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in TRUVADA users with detectable drug levels in plasma or peripheral-blood mononuclear cells vs those without detectable drug.

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- World Health Organization
- International Antiviral Society–USA
- The American College of Obstetricians and Gynecologists

TRUVADA for PrEP: One tablet, once daily[1] With or without food[1]

TRUVADA® Abbreviated Prescribing Information (Version: HK-MAR19-EU-DEC18)

Presentation: Blue, capsule-shaped, film-coated tablet, debossed with "GILEAD" on one side and with "701" on the other side. Each film-coated tablet contains 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate. **Indications:** In antiretroviral combination therapy for the treatment of HIV-1 infected adults. For the treatment of HIV-1 infected adolescents, with NRTI resistance or toxicities precluding the use of first line agents. In combination with safer sex practices for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in adults and adolescents at high risk. **Dosage:** Treatment and prevention of HIV in adults and adolescents aged 12 years and older, weighing at least 35 kg: One tablet once daily taken orally preferable with food. Renal impairment: Not recommended in adults with creatinine clearance <30 mL/min. The dosing interval should be adjusted in adults with baseline creatinine clearance 30-49 mL/min as every 48 hours. Pre-exposure Prophylaxis: Use in HIV-1 uninfected adults with estimated creatinine clearance below 60 mL/min is not recommended. Not recommended for use in individuals under the age of 18 years with renal impairment for treatment and prophylaxis. Hepatic impairment: No dose adjustment is required in patients with hepatic impairment. **Contraindications:** Hypersensitivity. Use for pre-exposure prophylaxis in individuals with unknown or positive HIV-1 status. **Warnings and Precautions:** Patients with HIV-1 harbouring mutations: Truvada should be avoided in antiretroviral experienced patients with HIV-1 harbouring the K65R mutation. Overall HIV-1 infection prevention strategy: Truvada should only be used for pre-exposure prophylaxis as part of an overall HIV-1 infection prevention strategy including the use of other HIV-1 prevention measures. Truvada should only be used to reduce the risk of acquiring HIV-1 in individuals confirmed to be HIV negative. HIV-1 uninfected individuals should be counselled at frequent intervals to strictly adhere to the recommended Truvada daily dosing schedule. Patients with hepatitis B or C virus infection: The safety and efficacy of Truvada for pre-exposure prophylaxis in patients with HBV or HCV infection has not been established. Discontinuation of Truvada therapy in patients infected with HBV may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue Truvada should be closely monitored with both clinical and laboratory follow up for at least several months after stopping treatment. If appropriate, resumption of hepatitis B therapy may be warranted. Liver disease: Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy (CART) and 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. Renal and bone effects in adults: Prior to initiating Truvada for the treatment of HIV-1 infection or for use in pre-exposure prophylaxis, it is recommended that creatinine clearance is calculated in all individuals. In individuals without risk factors for renal disease, it is recommended that renal function is monitored after two to four weeks of use, after three months of use and every three to six months thereafter. In individuals at risk for renal disease more frequent monitoring of renal function is required. Bone abnormalities may be associated with proximal renal tubulopathy. If bone abnormalities are suspected then appropriate consultation should be obtained. Renal and bone effects in the paediatric population: Truvada for treatment of HIV-1 or for pre-exposure prophylaxis, and should be monitored during use as in adults. If bone abnormalities are detected or suspected during use of Truvada in any paediatric patient, consultation with an endocrinologist and/or nephrologist should be obtained. Weight and metabolic parameters: An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Lipid disorders should be managed as clinically appropriate. Mitochondrial dysfunction following exposure in utero: Nucleos(t)ide analogues may impact mitochondrial function to a variable degree. The findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV. Immune Reactivation Syndrome: In HIV infected patients with severe immune deficiency at the time of institution of CART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders have also been reported. Opportunistic infections: Patients should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases. Osteonecrosis: Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement. Elderly: Truvada has not been studied in individuals over the age of 65 years. Excipients: Truvada contains lactose monohydrate. **Adverse reactions:** HIV-1 infection: The most frequently reported adverse reactions considered possibly or probably related to emtricitabine and/or tenofovir disoproxil were nausea and diarrhea. Pre-exposure prophylaxis: No new adverse reactions to Truvada were identified. The most frequent adverse reaction reported in the Truvada group in the iPrEx study was headache. Please refer to full prescribing information for full list of adverse reactions. **Drug interactions:** Other medicinal products containing emtricitabine, tenofovir disoproxil, tenofovir alafenamide or other cytidine analogues, such as lamivudine, nephrotoxic medicinal product (include but are not limited to: aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin 2), didanosine, adefovir dipivoxil, ledipasvir and sofosbuvir, sofosbuvir and velpatasvir or sofosbuvir, velpatasvir and voxilaprevir.

Before prescribing, please consult full prescribing information which is available upon request.

References:
1. TRUVADA Hong Kong prescribing information (HK-MAR19-EU-DEC18). 2. Baeten JM, et al. N Eng J Med 2012;367:399-410. 3. Grant RM, et al. N Eng J Med 2010;363:2587-2599. 4. Centers for Disease Control and Prevention. Preexposure prophylaxis for the prevention of HIV infection in the United States–2014: a clinical practice guideline. http://www.cdc.gov/hiv/pdf/prepguidelines2014.pdf. Published 2014. Accessed May8, 2017. 5. World Health Organization. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach. 2nd ed. http://www.who.int/hiv/pub/arv/arc-2016/en/. Published June 2016. Accessed May 8 2017. 6. Marrazzo JM, et al. JAMA 2014;312:390-409. 7. Günthard HF, et al. JAMA 2016;316:191-210. 8. The American College of Obstetricians and Gynecologists Committee on Gynecologic Practice. Obstet Gynecol 2014;123:1133-1136.

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Editorial

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Editor

Dr Andrew Tin-yau WONG

When I got invited to be the guest editor for this issue last year, I decided to focus on viral diseases as this is an area where there are ever-changing developments in diagnosis and management and also vast public health implications. It was last year that I chose to dedicate the theme for this issue to be on 'Viral diseases of global importance' and started to approach authors. Little did I know that the COVID-19 would emerge as a pandemic with unprecedented devastation globally just a few months later!

In this issue, we are excited that Dr Jacky Chan and Dr Owen Tsang have kindly shared their precious experience and perspectives on COVID-19 therapeutics amid their extremely busy schedule while fighting with COVID-19 at the most frontline position. They have put in huge efforts in summarising the state-of-the-art management options for COVID-19.

Viral hepatitis B and C are two other viruses associated with significant morbidity and mortality. To this end, the World Health Assembly in 2016 adopted Global health sector strategy on viral hepatitis, 2016-2021, which outlined a global goal of eliminating viral hepatitis as a major public health threat by 2030. The Centre for Health Protection has set up a Viral Hepatitis Control Office to formulate local strategies and an action plan. A Steering Committee on Prevention and Control of Viral Hepatitis was set up. Dr Rebecca Lam, the Consultant in charge of the Office, details the comprehensive local action plan and its implementation in the article 'Elimination of Hepatitis B and C in Hong Kong'. Focusing on mother-to-child-transmission of hepatitis B, an antiviral Tenofovir has been recommended to be added to existing hepatitis B vaccine and immunoglobulin program to further reduce the transmission rate from hepatitis B carrier mothers to their babies. Dr Wing-cheong Leung will explain the rationale behind and its implementation in Hong Kong in the article entitled 'Use of Tenofovir in further prevention of mother-to-child-transmission (MTCT) of hepatitis B virus (HBV)'.

Apart from hepatitis B and C viruses, human papillomavirus (HPV) infection is another important yet largely ignored virus with high cancer-causing potential at various anogenital and oropharyngeal sites. It is the commonest sexually transmitted diseases and is acquired very soon after sexual debut. Although HPV vaccine is useful in preventing the infection, the exposed and unvaccinated population are prone to the carcinogenic sequelae of HPV infection. Anal cancer is on the increasing trend worldwide in the past three decades. It is actually more common in women than men, especially in women with previous genital HPV infection or precancer/ cancer. In people who are infected with HIV, another important pandemic virus of the last century, HPV behaves more aggressively, and the risk of AIN is at least 30 times more than the general population! In the article 'High Resolution Anoscopy for the management of HPV-associated Anal Intraepithelial Neoplasia ', I shall explain the rationale for screening in high-risk populations and on the use of HRA.

For the lifestyle section, originally I have invited my friend from the UK, who is a doctor, to share his wisdom on ways to enhance resilience among healthcare workers in the context of high work stress and burnout rate. Unfortunately, my friend came down with COVID-19 and had to take time for rest for a full recovery. He would be pleased to share with us in another issue when the opportunity arises. In the urge of time, I have decided to share one of my hobbies, sound therapy, and written an article in collaboration with one of my teachers and friends, Anthony Nec from the UK.

I would like to express my sincere appreciation to all the contributing authors for their time and great effort. I would like to thank Mr KM Ho, who has contributed a fabulous cover photo with a meaningful caption. I would also like to acknowledge my clinical partner, Dr John Simon, for providing useful feedback on selected articles. Last but not least, I would like to thank the editorial team of FMSHK for assembling this memorable issue on infectious diseases for us. I hope you enjoy reading this issue and any feedback is welcome!

Elimination of Hepatitis B and C in Hong Kong

Dr Rebecca Kit-yi LAM

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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 August 2020.

INTRODUCTION

In recognition of the growing burden of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections and the advances in the prevention and treatment of chronic hepatitis, the World Health Assembly in 2016 adopted Global health sector strategy on viral hepatitis, 2016-2021, which outlined a global goal of eliminating viral hepatitis as a major public health threat by 2030[1]. The strategy provides a set of global targets, covering both impact (incidence and mortality) and service coverage. The impact targets refer to achieving a reduction of 90% in incidence and 65% in mortality by 2030, as compared with the baseline figures in 2015. Service coverage targets cover key interventions on (i) hepatitis B vaccination, (ii) prevention of mother-to-child transmission of HBV, (iii) harm reduction, (iv) blood safety, (v) injection safety, (vi) diagnosis of viral hepatitis B and C, and (vii) treatment of viral hepatitis B and C.

The Government of Hong Kong Special Administrative Region is determined to meet the World Health Organization (WHO) targets. It announced in the 2017 Policy Address the setting up of a steering committee to formulate strategies to prevent and control viral hepatitis effectively. Co-chaired by the Director of Health and the Chief Executive of the Hospital Authority, the Steering Committee on Prevention and Control of Viral Hepatitis (SCVH) was established in July 2018. The SCVH has been tasked to review local and international trends and developments in the prevention and control of viral hepatitis; advise the Government on policies and cost-effective targeted strategies for prevention and control of viral hepatitis; as well as conduct and coordinate the surveillance and evaluation of viral hepatitis control and recommend an appropriate response.

Against this background, this article discusses viral hepatitis elimination strategies for progressing towards the 2030 WHO targets in our local context in Hong Kong. As there are considerable differences in the epidemiology and interventions, strategies for eliminating new cases and deaths attributable to HBV and HCV infections would be elaborated respectively.

OVERALL STRATEGIES

Seroprevalence of hepatitis B surface antigen (HBsAg) has been decreasing in many populations without apparent risk of infection, such as new blood donors, antenatal women and pre-marital/pre-pregnancy screening clients, suggesting a shift from a region of high-intermediate to intermediate-low hepatitis B endemicity in the past decades[2]. However, the age- and sex-adjusted prevalence of HBsAg in the latest territory-wide epidemiological study remained high at 7.2%, implying that over 500,000 people were having chronic hepatitis B in Hong Kong[3]. The major burden of HBV infections lies in the adult population (aged 30 or above) who did not benefit from the universal neonatal hepatitis B immunisation programme which started in 1988. Given a large size of the local general population affected by hepatitis B, the strategy shall focus on enhanced prevention of mother-to-child transmission (MTCT) and expansion of services for appropriate medical management to reduce risk of chronic liver disease.

In contrast, the prevalence of chronic HCV infection was low at 0.3% in the general population in Hong Kong, but it prevails in some specific populations[3]. The complexity of HCV epidemiology would be best addressed by applying targeted interventions towards "micro-elimination" in the populations most affected by and at risk of hepatitis C. Micro-elimination is considered a pragmatic approach for achieving HCV elimination by breaking down national elimination goals into smaller goals for individual population segments and delivering treatment and prevention interventions using targeted methods for the sub-population segments[4]. Pursuing the micro-elimination of HCV means working to achieve the WHO targets in specific sub-populations.

ELIMINATION OF INCIDENT CHRONIC HBV INFECTION

The risk of chronicity following acute HBV infection can be as high as 80% - 90% in infected neonates and around 30% in infected children before six years of age, in contrast to ≤ 5% in healthy adults[5]. Knowingly, the incidence of chronic HBV infection in Hong Kong is largely driven by the infections acquired in infancy through perinatal or early childhood exposure to HBV. The primary intervention for preventing HBV infection is vaccination, which is able to induce protective antibody titres in more than 95% of healthy vaccinees[6].

In Hong Kong, universal hepatitis B immunisation for newborn infants and administration of hepatitis B immunoglobulin (HBIG) to those born to HBsAg-

positive mothers have been in place since 1988, in addition to routine HBsAg screening for pregnant women. A series of immunisation coverage surveys since 2001 showed that the coverage of the third dose of hepatitis B vaccine among children aged 3 - 5 was consistently reaching 99% or more, far above the 2030 WHO target at 90%[7]. With those efforts, a significant achievement in the prevention of HBV vertical transmission was made. Hong Kong was verified by Western Pacific Regional Office of the WHO as having successfully achieved the goal of HBV control in July 2011, and was also verified as of June 2013 as having met the goal of achieving a seroprevalence of less than 1%. Despite the success, there is a residual risk of HBV transmission to the newborns. A recent local study found that MTCT has continued to occur at a rate of 1.1% (7 out of 641) and babies born to women with high viral load were particularly vulnerable[8].

Greater efforts should be made to further prevent MTCT given the advent of potent antiviral drugs in pregnancy category B. In fact, antiviral treatment is recommended for women with HBV DNA levels exceeding 200,000 IU per millilitre in the latest international guidelines[9,10]. An initiative of providing HBsAg-positive mothers with high viral load with a treatment option to use tenofovir has been implemented in Hong Kong in a phased approach. The pilot phase commenced in two hospitals at the beginning of 2020, before rolling out in all birthing hospitals in Hospital Authority (HA).

In addition, WHO Western Pacific Region emphasises that post-vaccination serologic testing (PVST) of infants born to HBsAg-positive mothers is important to determine the effectiveness of prevention of MTCT of HBV when antenatal HBV screening is in place[11]. The PVST shall consist of tests for both HBsAg and hepatitis B surface antibody (anti-HBs) and the result can identify infants who do not have an adequate immune response to an initial hepatitis B vaccine series as well as those infected with HBV. From experience in some provinces in China, PVST programme was demonstrated to be feasible and considered an essential strategy to ensure full protection for vaccine non-responders and appropriate medical care for those infected[12]. Notably, various barriers, such as lost to follow up, parents' refusal to venous blood draws and highly skilled procedure for paediatric blood sampling, have to be tackled for successful implementation of PVST[13].

ELIMINATION OF HBV-RELATED DEATHS

Testing and treatment are the primary means of reducing HBV-related deaths for the WHO 2030 targets. In spite of widely available and accessible serological and molecular tests for hepatitis B and effective antiviral treatments, the diagnosis and treatment coverage rate in Hong Kong were still far below the WHO 2030 targets at 90% and 80% respectively. Nearly 50% of the HBsAg-positive participants in a population-based study in 2015-16 were not aware of their infection status[3]. A modelling study gave a much lower diagnosis rate for HBV infection at 27% in 2016, while an estimated 22% of those eligible for HBV treatment were being treated[14].

The complexities and healthcare resources required for maintaining HBV treatment for a huge number of cases in Hong Kong pose a major challenge in improving the coverage of diagnosis and treatment. Although the incidence of cirrhosis, hepatocellular carcinoma (HCC) and even death can be effectively reduced with antiviral treatments, the infection can rarely be cured, and most cases would require lifelong treatment once initiated. Regular assessments of the liver function, testing for various HBV biomarkers and surveillance for HCC are also recommended for those on antiviral treatment. Understandably, there would be substantial resource implications on drug, laboratory capacity, clinical equipment and workforce, calling for the development of alternative service model and stepwise capacity building for hepatitis B medical care.

ELIMINATION OF INCIDENT HCV INFECTION

As percutaneous exposure to contaminated blood is the primary cause of most HCV infection, protection of injection and blood safety are key interventions in the healthcare setting. In Hong Kong, there are guidelines and training on standard infection control practices to prevent blood-borne infections in the healthcare setting. Standard management regarding the most important blood-borne infections, including HCV, is also in place. The facility-level injection safety is protected by the standard practice of using single-use of disposable injection equipment for all therapeutic injections in healthcare facilities.

The transmission of HCV to hemodialysis patients has declined over the years due to better screening of blood products, improved dialysis procedures, and less need for blood transfusion with the availability of erythropoiesis-stimulating agents. Still, HCV prevalence remains far higher in people receiving hemodialysis than in the general population. In the HA, the prevalence of HCV infection in hemodialysis patients is around 1 - 2%. Therefore, there is an ongoing plan to treat all HCV infection of patients with end-stage renal failure undergoing dialysis (both haemodialysis and peritoneal dialysis) in the HA, irrespective of their liver fibrosis stage or candidacy for a kidney transplant.

Similar to the situation in other high-income regions of the world, injecting drug use is the major source of incidental HCV infection in the community. Recent studies gave a high prevalence of anti-HCV in people who inject drugs (PWID) and ex-PWID at 76.4% and 73.4% respectively[15,16]. A Cochrane review and meta-analysis found that a lower risk of hepatitis C acquisition was associated with opioid substitution therapy (OST), which could further be strengthened with safer injection practices[17]. It is anticipated that the methadone treatment programme, as an OST for harm reduction in Hong Kong since the 1970s, would play a role in the elimination of HCV infections among PWID. The importance of coordinated, multi-disciplinary care teams in increasing linkage of HCV care and uptake of treatment in PWID can never be overemphasised. The plan is to start engaging different stakeholders and conducting needs assessments to design the focus of effort.

In the past decade, sexually transmitted HCV infections among men who have sex with men (MSM), especially those who were HIV-positive, was increasingly reported worldwide and in Hong Kong[18, 19]. As a well-defined population in linkage to healthcare, people living with HIV are suitable for HCV micro-elimination. Empirical studies showed that scale-up of HCV testing and treatment would be followed by a decrease in the incidence of HCV infections in this key population, signifying the effect of "treatment as prevention"[20, 21].

ELIMINATION OF HCV-RELATED DEATHS

The mortality reduction target is now justified with the excellent diagnostic and therapeutic interventions for HCV infection. Direct-acting antiviral (DAA) treatment regimens for 8-12 weeks are effective for all HCV genotypes, with a cure rate generally exceeding 90%[22]. In Hong Kong, the estimated diagnosis and treatment rates were just 50.9% and 12.4% respectively, while interferon-based regimens were the first-line therapy and DAA reimbursement was restricted to patients with advanced liver diseases only[23]. Clearly, a generalised use of DAA in HCV treatment is needed for achieving a larger reduction in the disease burden. Since 2019, the HA has started to further extend the use of DAA to milder stages of the disease with a view to cover more patients who are clinically eligible for treatment until HCV is eliminated.

Removing fibrosis restrictions makes it possible to treat more people, but even countries with unrestricted access to DAAs have reported a decline in treatment rates after an initial expansion[24]. To eliminate HCV, it will be essential to find people living with HCV, many of whom have been disenfranchised from the healthcare system, and engage them in care that is adapted to their needs[25].

HONG KONG VIRAL HEPATITIS ACTION PLAN

Noting all these opportunities and challenges in the elimination of HBV and HCV, the SCVH has been working with different stakeholders to develop an Action Plan for Hong Kong. The Action Plan will set out the direction and strategies to work towards the WHO goals, thereby realising the vision "Hong Kong will be a place where new viral hepatitis infections have ceased, and where everyone with chronic viral hepatitis has access to effective and affordable care and treatment."

References

1. Global health sector strategy on viral hepatitis 2016-2021. Geneva: World Health Organization; 2016 (https://www.who.int/hepatitis/strategy2016-2021/ghss-hep/en/, accessed 11 February 2020).
2. Lin AW, Wong KH. Surveillance and response of hepatitis B virus in Hong Kong Special Administrative Region, 1988-2014. Western Pac Surveill Response J 2016; 7(1):24-8.
3. Liu KS, Seto WK, Lau EH, et al. A territorywide prevalence study on blood-borne and enteric viral hepatitis in Hong Kong. J Infect Dis 2019; 219(12):1924-33.
4. Lazarus JV, Wiktor S, Colombo M, et al. Micro-elimination - A path to global elimination of hepatitis C. J Hepatol 2017; 67(4):665-6.
5. Hyams KC. Risks of chronicity following acute hepatitis B virus infection: a review. Clin Infect Dis 1995; 20(4):992-1000.
6. World Health Organization. Hepatitis B vaccines: WHO position paper – July 2017. Wkly Epidemiol Rec 2017; 92(27):369-92.
7. Surveillance of Viral Hepatitis in Hong Kong – 2018 Report. Hong Kong: Department of Health, 2019.
8. Cheung KW, Seto MT, Kan AS, et al. Immunoprophylaxis Failure of Infants Born to Hepatitis B Carrier Mothers Following Routine Vaccination. Clin Gastroenterol Hepatol 2018; 16(1):144-5.
9. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017; 67(2):370-98.
10. Terrault NA, Lok AS, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018; 67(4):1560-99.
11. Hepatitis B control through immunization: a reference guide. Manila: World Health Organization Regional Office for the Western Pacific; 2014 (https://apps.who.int/iris/handle/10665/208163 , accessed 18 March 2020).
12. Wang F, Zhang G, Zheng H, et al. Post-vaccination serologic testing of infants born to hepatitis B surface antigen positive mothers in 4 provinces of China. Vaccine 2017; 35(33):4229-35.
13. Zheng H, Zhang GM, Chan PL, et al. Compliance among infants exposed to hepatitis B virus in a post-vaccination serological testing program in four provinces in China. Infect Dis Poverty 2019; 8(1):57.
14. Polaris Observatory Collaborators. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. Lancet Gastroenterol Hepatol 2018; 3(6):383-403.
15. Chan DP, Lee KC, Lee SS, et al. Community-based molecular epidemiology study of hepatitis C virus infection in injection drug users. Hong Kong Med J 2017; 23 Suppl 5(4):27-30.
16. Wong GL, Chan HL, Loo CK, et al. Change in treatment paradigm in people who previously injected drugs with chronic hepatitis C in the era of direct-acting antiviral therapy. J Gastroenterol Hepatol 2019; 34(9):1641-7.
17. Platt L, Minozzi S, Reed J, et al. Needle and syringe programmes and opioid substitution therapy for preventing HCV transmission among people who inject drugs: findings from a Cochrane Review and meta-analysis. Addiction 2018; 113(3):545-63.
18. Nijmeijer BM, Koopsen J, Schinkel J, et al. Sexually transmitted hepatitis C virus infections: current trends, and recent advances in understanding the spread in men who have sex with men. J Int AIDS Soc 2019;22 Suppl 6:e25348.
19. Sun HY, Uemura H, Wong NS, et al. Molecular epidemiology of acute HCV infection in HIV-positive patients from Hong Kong, Taipei, Tokyo. Liver Int 2019;39(6):1044-51.
20. Boerekamps A, van den Berk GE, Lauw FN, et al. Declining hepatitis C virus (HCV) incidence in Dutch human immunodeficiency virus-positive men who have sex with men after unrestricted access to HCV therapy. Clin Infect Dis 2018;66(9):1360-5.
21. Braun DL, Hampel BH, Nguyen H, et al. A treatment as prevention trial to eliminate HCV in HIV+ MSM: the Swiss HCVree trial. Abstract number: 81LB. Conference on Retroviruses and Opportunistic Infections. Boston, Massachusetts; March 4–7. 2018.
22. Falade-Nwulia O, Suarez-Cuervo C, Nelson DR, et al. Oral direct-acting agent therapy for hepatitis C virus infection: a systematic review. Ann Intern Med 2017;166(9):637-48.
23. Hui YT, Wong GL, Fung JY, et al. Territory-wide population-based study of chronic hepatitis C infection and implications for hepatitis elimination in Hong Kong. Liver Int 2018; 38(11):1911-9.
24. Monitoring hepatitis C treatment uptake in Australia (Issue 9). Sydney: The Kirby Institute; 2018 (https://kirby.unsw.edu.au/report/monitoring-hepatitis-c-treatment-uptake-australia-issue-9-july-2018 , accessed 18 March 2020).
25. The Canadian Network on Hepatitis C Blueprint Writing Committee and Working Groups. Blueprint to inform hepatitis C elimination efforts in Canada. Montreal, QC: Available at: canhepc.ca/sites/default/files/media/documents/blueprint_hcv_2019_05.pdf(accessed 30 June 2020).


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9-valent Vaccine (Recombinant)
TAKE
ACTION
with
「HIM」
ROLL UP
For HPV Prevention!
YOU & 「HIM」
must know!
HPV-Related Diseases
also affect Males[1]
Infection Rate in
Male>Female[2]
Males have no routine
screening program[1]
hpv.com.hk
Reference:
Selected Safety Information
Indications:
Contraindications:
Precautions:
Adverse events:
Before prescribing, please consult the full prescribing information.

MCHK CME Programme Self-assessment Questions

Please read the article entitled "Elimination of Hepatitis B and C in Hong Kong" by Dr Rebecca Kit-yi LAM 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 August 2020 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 World Health Organization has set targets to eliminate viral hepatitis as public health threats by 2030.**
2. **In Hong Kong, the seroprevalence of hepatitis B surface antigen (HBsAg) has been increasing in new blood donors and antenatal women in recent decades.**
3. **The prevalence of chronic HCV infection is >1% in the general population in Hong Kong.**
4. **Hepatitis B infection acquired in infancy is less likely to become a chronic infection than that acquired in adults.**
5. **HBV vaccination can induce protective antibody titres in more than 95% of healthy vaccines.**
6. **International guidelines recommend the use of tenofovir for women with HBV DNA levels exceeding 200,000 IU per millilitre to prevent mother-to-child transmission of hepatitis B.**
7. **Chronic hepatitis B can be treated with antiviral agents which can reduce the incidence of liver cancer and improve long-term survival.**
8. **Sexually transmitted HCV infections among men who have sex with men (MSM), especially those who were HIV-positive, have not been reported.**
9. **Direct-acting antiviral (DAA) treatment regimens for 8-12 weeks are effective for all HCV genotypes, with a cure rate generally exceeding 90%.**
10. **Injecting drug use is the major source of incidental HCV infection in Hong Kong.**

ANSWER SHEET FOR AUGUST 2020

Please return the completed answer sheet to the Federation Secretariat on or before 31 August 2020 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Elimination of Hepatitis B and C in Hong Kong

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1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

Name (block letters):_____ HKMA No.: _____ CDSHK No.: _____

HKID No.: __ __ - __ __ __ __ X X (X) HKDU No.: _____ HKAM No.: _____

Contact Tel No.:_____ MCHK No. / DCHK No.: _____(must fill in)

Answers to July 2020 Issue

Management of Advanced Airway and Lung Diseases

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

Radiology Quiz

Dr Yan-lin LI
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Dr Yan-lin LI

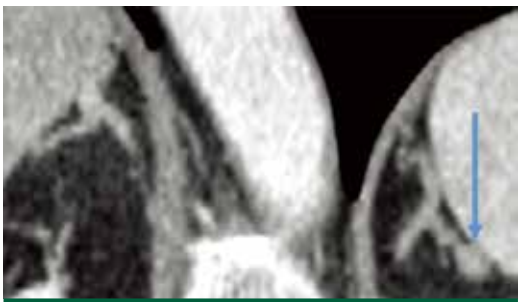

Fig.1: Multiple erythematous papules on scalp.

Fig. A healthy 50-year-old man undergoes CT scan of the abdomen as part of a health check. A selected coronal image of the scan is shown above.

Questions

1. What organ is shown?
2. What is the risk of malignancy of the lesion indicated by the blue arrow?
3. On non-contrast CT scan, the Hounsfield Unit of the lesion measured -42. What is the diagnosis?
4. The patient received a follow-up scan two years later, and a new nodule is shown in the right gland. The patient was subsequently diagnosed with primary hyperaldosteronism (Conn's syndrome) by an endocrinologist. Which lesion is the culprit, left or right?

(See P.40 for answers)

Use of Tenofovir in Further Prevention of Mother-to-child-transmission of Hepatitis B Virus

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Dr Wing-cheong LEUNG

INTRODUCTION

I was trained in Obstetrics & Gynaecology in Hong Kong in the 1990s. Over the many years of my practice, I have always assumed that the universal HBV immunisation programme for newborns in Hong Kong since 1988 after Prof Vivian Wong's landmark research in the 1980s[1] is already good enough to prevent the mother-to-child-transmission (MTCT) of hepatitis B virus (HBV).

All expectant mothers having antenatal care in the public (Hospital Authority, HA) & private sectors will undergo a routine antenatal blood test to identify their HBsAg (Hepatitis B surface antigen) status. The universal HBV immunisation programme consists of Hepatitis B immunoglobulins (HBIg) to be administered to babies born to HBsAg-positive mothers together with the first dose of HBV vaccine upon delivery (either in labour wards within hours or in postnatal wards within 24 hours after birth). The second and third doses of HBV vaccines will be given mainly in the Maternal & Child Health Centres (MCHC) at 1 and 6 months, respectively. Notably, there is no post-vaccination serological testing performed on infants after completion of the three doses of HBV vaccines to document their HBV immune status.

The World Health Organization (WHO) has the vision to eliminate viral hepatitis as a public health threat by 2030[2]. WHO has estimated that in 2015, 257 million people (> 3% of the global population) are affected by chronic HBV infection, resulting in 900,000 deaths[3]. Mother-to-child-transmission is the most important route of HBV infection, and the infection will usually remain asymptomatic for decades before the life-threatening complications of liver cirrhosis and hepatocellular carcinoma surface.

It so happened that I had the opportunity of representing our College (HKCOG) to attend the Green Ribbon World Hepatitis Day dinner held on 28 July 2018 in Kuala Lumpur. Coincidentally, several months later in 2018, I was recruited to be one of the members of the multidisciplinary Steering Committee on Prevention and Control of Viral Hepatitis co-chaired by the Director of Health, Dr Constance Chan and the Chief Executive of the HA, Dr Leung Pak-yin followed by Dr Tony Ko.

A Clinical Working Group was formed. One of its major tasks is to review the current practice on the prevention of MTCT of HBV in Hong Kong and to explore if the use of antiviral agents in pregnancy could further reduce the MTCT of HBV.

CURRENT SITUATION OF MTCT OF HBV IN HONG KONG[4]

In 2016, the overall prevalence of HBsAg carriers in Hong Kong was 7.8%. By 2016, local women aged 28 years or below should have been covered by the universal HBV immunisation programme (which had been started in 1988), and their prevalence rate of HBsAg positivity was 1.8% while the rate was 3.0% when new immigrants from Mainland China were included. However, in the same year of 2016, 5.2% of pregnant women were HBsAg-positive (dropping to 5.0% in 2017; 4.5% in 2018; and 4.0% in 2019). Despite a 99.8% HBsAg screening coverage for antenatal women, and despite a 99.5% coverage with HBIg and HBV vaccination for live births born to HBsAg-positive mothers (with 98.8% having completed all three doses of HBV vaccination), the overall MTCT rate was still 1.1% from a local study of 641 HBsAg–positive pregnant women by Cheung et al.[5]. This MTCT rate of 1.1% is consistent with the data from a U.S. study on 9,252 infants born to HBsAg-positive mothers[6]. In that study, 95% of infants received HBIg and HBV vaccine within 12 hours of birth, and almost all completed ≥ 3 doses of HBV vaccine series. Hence local data and U.S. data look pale in comparison to the WHO target of <0.1% prevalence of HBsAg-positivity among 5-year-old children by 2030.

In the absence of HBIg and HBV vaccination, about 20% to 40% of infants born to HBsAg-positive mothers are found to be infected by one year of age, with large variations, depending on maternal risk factors such as Hepatitis B 'e' antigen (HBeAg) and HBV viral load[7]. The administration of HBIg to newborns at birth together with a complete course of three doses of HBV vaccination has contributed to 75 to 90% reduction in MTCT rate. This reduction of MTCT of HBV could be further reduced by minimising the risk of Immunoprophylaxis Failure (IF). The mechanisms of IF include (i) germline infection at conception; (ii) maternal blood contamination by invasive prenatal tests; (iii) placental infection during pregnancy; (iv) maternal secretion contact during pregnancy; (v) delayed birth dose vaccination; (vi) horizontal transmission in a newborn before the infant could develop a sufficient hepatitis B surface antibody (anti-HBs) response after vaccination; & (vii) mutations in the 'a' determinant region of HBV resulting in an immune escape. A high maternal HBV DNA level during pregnancy is the strongest risk factor leading to IF and the IF rate for high maternal viral load (> 8 $\log_{10}$ copies/mL or 2 x 10^7 IU/mL) at 28-30 weeks of gestation is 5.8%[5]. (Remark: 1 IU = 5.82 copies)

THE USE OF ANTIVIRALS IN PREGNANCY TO FURTHER REDUCE THE MTCT OF HBV

Tenofovir is one of the antivirals indicated for the treatment of chronic HBV infection. Resistance to Tenofovir is rare among other antivirals. Tenofovir is a category B drug in the U.S. Food and Drug Administration (FDA) pregnancy categories, which is regarded as safe to be used in pregnancy. Breastfeeding is not contraindicated (although low quality, weaker recommendation). Cessation of antiviral therapy is usually associated with a rebound of viral load, which may be associated with a rise in liver enzymes (such as alanine aminotransferase, ALT). However, a clinically significant flare-up of hepatitis B is uncommon after stopping antiviral therapy and is considered safe in patients with no underlying liver cirrhosis or poor liver reserve. Nevertheless, adequate monitoring after cessation of antiviral therapy is necessary to ensure early identification of cases of hepatitis flare-ups as recommended by international guidelines[8].

The use of antivirals in HBsAg-positive pregnant women with high HBV DNA levels is recommended by (i) American Association for the Study of Liver Diseases (AASLD); (ii) European Association for the Study of the Liver (EASL); (iii) Asian Pacific Association for the Study of the Liver (APASL); and (iv) Practices Recommendations of the Advisory Committee on Immunization[9]. How about the WHO? The WHO supports countries to evaluate the use of antivirals during pregnancy to further reduce MTCT of HBV, although it has not made any recommendations so far.

LITERATURE REVIEW

In the literature, there are one multicentre, open-labelled, non-randomised study conducted in Taiwan, one meta-analysis and two major multicentre randomised controlled trials (RCTs) conducted in Mainland and Thailand respectively to study the use of Tenofovir during pregnancy to prevent MTCT of HBV; they were published in top-tier medical journals in 2015, 2016 and 2018.

The Taiwan Study (2015)[10]

A total of 118 HBV infected pregnant women with HBeAg positivity, and HBV DNA load > 8 $\log_{10}$ copies/mL (or 2 x 10^7 IU/mL) were enrolled to receive either usual care without antiviral therapy vs Tenofovir 300mg daily from 30 to 32 weeks of gestation until postpartum week 4. HBsAg-positive pregnant women were enrolled based on their willingness to join the control or study arm. All infants received HBIg within 24 hours of delivery and HBV vaccination at 0, 1 and 6 months. The primary outcome was infant HBsAg positivity at six months after delivery. The infants in the Tenofovir group had lower rates of being HBsAg-positive, compared with the control group (1/65, 1.54% vs 6/56, 10.71%; p=0.048). Multivariate analysis showed that Tenofovir treatment was associated with lower risk (OR=0.10, 95% CI 0.01-0.94; p=0.043). The secondary outcome is infant HBsAg positivity at 12 months after delivery. One additional infant in the Tenofovir group became HBsAg-positive at 12 months while the HBsAg status of the other children remained unchanged. This newly infected child was born at term by Caesarean section (twin pregnancy), and the mother had amniocentesis during the pregnancy. The HBsAg-positive rate at 12 months in the Tenofovir and control groups was thus 2/65 (3.08%) vs 6/56 (10.71%); p=0.142. The study was therefore supportive of the use of short-term antiviral therapy in selected HBsAg-positive pregnant women to reduce MTCT of HBV.

The Meta-analysis (2016)[11]

This meta-analysis of 26 studies that enrolled 3,622 HBsAg-positive pregnant women found that the use of antiviral therapy (in addition to HBIg and HBV vaccination) reduced MTCT as defined by infant HBsAg seropositivity (RR=0.3, 95% CI 0.2-0.4) or infant HBV DNA seropositivity (RR=0.3, 95% CI 0.2-0.5) at 6-12 months. There was no increased risk of adverse outcomes among mothers who received antiviral therapy and their newborns. However, this study is limited by concerns regarding the quality of data (as few RCTs were available), potential bias from included cohort studies, and the overall small number of events.

Two major RCTs: The Mainland Study (2016) & the Thailand Study (2018)[12, 13]

These two major RCTs, both published in NEJM, apparently showed conflicting conclusions (Table 1). The devils or indeed the angels might lie in the details!

The negative result of the Thailand Study might have limited generalisability because of the very short median time for the administration of HBIg (1.3 hour) and 1st dose of HBV vaccine (1.2 hour) from birth and the examination of HBsAg status of infants was 6 months instead of the recommended 9 to 12 months. Furthermore, the median HBV DNA level in both groups was 8 $\log_{10}$ copies/mL, that means half of the infants might be at low risk for HBV transmission even if their mothers had not received Tenofovir. The exclusion of mothers with ALT > 30 IU/L might also contribute to the unexpectedly low rate of vertical transmission in the control group. This highlights the need for further research to delineate other potential factors that might influence the MTCT of HBV such as the timing of HBIg administration, the timing & dosage regimen of HBV vaccination, and other factors, e.g. invasive prenatal tests such as chorionic villus biopsy & amniocentesis.

Nevertheless, the MTCT of HBV were both ZERO in the Mainland Study (0/92, per-protocol) and the Thailand Study (0/147). The safety of Tenofovir in pregnancy was ascertained. And the rebound increase of ALT after stopping Tenofovir was mild in the majority of cases.

Table 1. The Mainland vs. The Thailand Studies

The Mainland Study (Pan et al., NEJM 2016) [12]	The Thailand Study (Jourdain et al., NEJM 2018) [13]
Total no. of subjects = 200	Total no. of subjects = 331
Criteria for recruitment → HBeAg +ve and HBV DNA level > 6 log10 copies/mL or 2 x 10^5 IU/mL	Criteria for recruitment → HBeAg +ve and ALT < 30 IU/L (median HBV DNA level = 8 $\log_{10}$ copies/mL or 2 x 10^7 IU/mL)
Randomised 1:1 at 30-32 weeks gestation @ Tenofovir 300 mg daily vs. no treatment Until 4 weeks postpartum (All infants received HBIg & 1st dose of HBV vaccination within 12 hours after birth; and two additional doses of HBV vaccination at 4 & 24 weeks)	Randomised 1:1 at 28 weeks gestation @ Tenofovir 300 mg daily vs. Placebo Until 2 months postpartum (All infants received HBIg & 1st dose of HBV vaccination, median time 1.3 hour & 1.2 hour after birth respectively; and four additional doses of HBV vaccination at 1,2,4 & 6 months)
Outcomes	
HBV DNA level < 6 $\log_{10}$ copies/mL at delivery: (mother) Tenofovir group = 68% (66/97) Control group = 2% (2/100) P<0.001	
MTCT at 28 weeks postpartum, i.e. HBsAg +ve infants: Tenofovir group = 5% (5/97) Control group = 18% (18/100) P=0.007 *[Intension to treat]* Tenofovir group = 0% (0/92) Control group = 7% (6/88) P=0.01 *[Per-protocol analysis]*	MTCT at 6 months postpartum, i.e. HBsAg +ve infants: Tenofovir group = 0% (0/147) Placebo group = 2% (3/147) P=0.12
Birth defects: Tenofovir group = 2% (2/95) Control group = 1% (1/88) P=1.00	
↑ ALT after stopping Tenofovir: Tenofovir group = 45% (44/97)* Control group = 30% (30/100) P=0.03 *majority of cases were mild	↑ ALT (>300 IU/L) after stopping Tenofovir: Tenofovir group = 6% (9/154) Placebo group = 3% (5/157) P=0.29
Conclusions	
Supports the use of Tenofovir to prevent MTCT of Hepatitis B	**Does NOT support the use of Tenofovir to prevent MTCT of Hepatitis B**

THE WAY FORWARD IN HONG KONG

According to a local multicentre study by Cheung et al.[5] on IF of infants born to HBsAg-positive mothers, there were 22.3% and 18.9% of pregnant subjects with HBV DNA level > 7 $\log_{10}$ copies/mL and > 8 $\log_{10}$ copies/mL at 28-30 weeks of gestation respectively. The results showed that the risk of IF with HBV DNA level > 7 $\log_{10}$ copies/mL and > 8 $\log_{10}$ copies/mL was 4.9% and 5.8% respectively and it was reflected from the study that no IF occurred when the maternal HBV DNA level was < 8 $\log_{10}$ copies/mL.

Some calculations have been made according to the prevalence rate and the study results[5] to obtain a clear picture of the current situation in Hong Kong (Table 2).

Table 2. Calculations based on the prevalence rate and local study results[5]. Assume there are 10,000 pregnant women, 520 of them are HBsAg +ve (using prevalence rate = 5.2% in 2016).

200,000 IU/mL →	Maternal HBV DNA > 6 $\log_{10}$ copies/mL	Maternal HBV DNA > 7 $\log_{10}$ copies/mL	Maternal HBV DNA > 8 $\log_{10}$ copies/mL
No. of pregnant women with high HBV DNA at 28-30 weeks of gestation	136 (26.1%)	116 (22.3%)	98 (18.9%)
No. of HBsAg +ve pregnant women to test for finding one case of high HBV DNA	3.8	4.5	5.3
No. of infants born to mothers with high HBV DNA suffer from IF	5.7 (4.2%)	5.7 (4.9%)	5.7 (5.8%)
No. of high HBV DNA mothers to treat with tenofovir for preventing one MTCT	23.8	20.3	17.2

A threshold of 2 x 10^5 IU/mL (200,000 IU/mL) is chosen as high HBV DNA which is also the recommendations by AASLD (2018), EASL (2017) & APASL (2015). Using this threshold of HBV DNA level to start Tenofovir for further prevention of MTCT of HBV, assuming a total of 60,000 pregnant women per year in Hong Kong, Tenofovir will be offered to 816 pregnant women (HBsAg +ve with HBV DNA level > 200,000 IU/mL) every year through the eight HA Hospitals with Obstetrics & Hepatology Clinics.

THE ACTION PLAN

After all the preparatory work, the Steering Committee on Prevention and Control of Viral Hepatitis has decided to adopt a universal programme to use Tenofovir to further prevent MTCT of HBV.

The programme has started as a pilot to test feasibility in 2 (QMH & PWH) of the 8 HA Hospitals with Obstetrics & Hepatology Clinics from 1st quarter of 2020. All HBsAg +ve pregnant women will be tested for HBV DNA, HBeAg, anti-HBe, and L/RFT. Women with high HBV viral load (> 200,000 IU/ml) will be given an early referral to the corresponding Hepatology Clinic to discuss starting Tenofovir by 28 weeks gestation to further reduce the risk of MTCT of HBV (irrespective of the HBeAg and LFT status). Women with low HBV viral load (<200,000 IU/ml) will also be given an appointment (triaged by HBeAg and LFT status), usually after their delivery for long term surveillance & treatment of the HBV complications.

The universal programme will be extended to all the 8 HA Hospitals with Obstetrics & Hepatology Clinics. One important aspect of this universal programme to be highlighted is that post-vaccination serological testing (HBsAg & anti-HBs) will be performed to infants after completing the full course of vaccination. This post-vaccination serological testing would be most important

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Abbreviations: GBM=glioblastoma multiforme; TMZ=temozolomide

References: 1. Data on file. Novocure. Last updated January 2019. **2.** Stupp, R. *et al.* JAMA 318, 2306–2316 (2017).

Indications for Use Optune Treatment Kit is intended for the treatment of patients with newly diagnosed GBM and for the treatment of patients with recurrent GBM. **Newly diagnosed GBM** NovoTTF-200A (Optune™) Treatment Kit is intended for the treatment of patients with newly diagnosed GBM, after surgery and radiotherapy with adjuvant Temozolomide, concomitant to maintenance Temozolomide. The treatment is intended for adult patients, 18 years of age or older, and should be started more than 4 weeks after surgery and radiation therapy with adjuvant Temozolomide. Treatment may be given together with maintenance Temozolomide (according to the prescribing information in the Temozolomide package insert) and after maintenance Temozolomide is stopped. **Recurrent GBM** NovoTTF-200A (Optune™) Treatment Kit is intended for the treatment of patients with recurrent GBM who have progressed after surgery, radiotherapy and Temozolomide treatment for their primary disease. The treatment is intended for adult patients, 18 years of age or older, and should be started more than 4 weeks after the latest surgery, radiation therapy or chemotherapy. **Contraindications** Do not use Optune Treatment Kit if you are pregnant, think you might be pregnant, or are trying to get pregnant. If you are a woman who is able to get pregnant, you must use birth control when using the device. Optune Treatment Kit was not tested in pregnant women. Do not use Optune Treatment Kit if you have significant additional neurological disease (primary seizure disorder, dementia, Progressive degenerative neurological disorder, Meningitis or encephalitis, Hydrocephalus associated with increased intracranial pressure) Do not use Optune Treatment Kit if you are known to be sensitive to conductive hydrogels like the gel used on electrocardiogram (ECG) stickers or transcutaneous electrical nerve stimulation (TENS) electrodes. In this case, skin contact with the gel used with Optune Treatment Kit may commonly cause increased redness and itching, and rarely may even lead to severe allergic reactions such as shock and respiratory failure. Do not use Optune if you have an active implanted medical device, a skull defect (such as, missing bone with no replacement) or bullet fragments. Examples of active electronic devices include deep brain stimulators, spinal cord stimulators, vagus nerve stimulators, pacemakers and defibrillators. Use of Optune together with implanted electronic devices has not been tested and may lead to malfunctioning of the implanted device. Use of Optune together with skull defects or bullet fragments has not been tested and may possibly lead to tissue damage or render Optune ineffective. Ref: EU IFU Document number QSD-EUUM-001-EN (Rev 04)

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to assess the outcome of this new universal programme using Tenofovir during pregnancy on top of HBIg & HBV vaccination to infants from HBsAg +ve pregnant women with high viral load (> 200,000 IU/mL) to further prevent MTCT of HBV in order to achieve the WHO goal to eliminate Viral Hepatitis as a public health threat by 2030.

References

1. Wong VC, Ip HM, Reesink HW, et al. Prevention of the HBsAg carrier state in newborn infants of mothers who are chronic carriers of HBsAg and HBeAg by administration of hepatitis-B vaccine and hepatitis-B immunoglobulin. Double-blind randomised placebo-controlled study. Lancet. 1984;1(8383):921–926. doi:10.1016/s0140-6736(84)92388-2
2. World Health Organization. Global Hepatitis Report 2017. Geneva: World Health Organization & Global Hepatitis Programme; 2017. Available from: http://apps.who.int/iris/bitstream/10665/255016/1/9789241565455-eng.pdf?ua=1
3. Beasley RP. Hepatitis B virus. The major etiology of hepatocellular carcinoma. Cancer. 1988;61(10):1942–1956
4. Surveillance of viral hepatitis in Hong Kong – 2016 to 2018 update report. Special Preventive Programme, Centre for Health Protection, Department of Health, December 2017, 2018 & 2019
5. Cheung KW, Seto MTY, Kan ASY, et al. Immunoprophylaxis Failure of Infants Born to Hepatitis B Carrier Mothers Following Routine Vaccination. Clin Gastroenterol Hepatol. 2018;16(1):144–145. doi:10.1016/j.cgh.2017.07.013
6. Schillie S, Walker T, Veselsky S, et al. Outcomes of infants born to women infected with hepatitis B. Pediatrics. 2015;135(5):e1141–e1147. doi:10.1542/peds.2014-3213
7. Stevens CE, Beasley RP, Tsui J, Lee WC. Vertical transmission of hepatitis B antigen in Taiwan. N Engl J Med. 1975;292(15):771–774. doi:10.1056/NEJM197504102921503
8. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67(4):1560–1599. doi:10.1002/hep.29800
9. Schillie S, Vellozzi C, Reingold A, et al. Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep. 2018;67(1):1–31. Published 2018 Jan 12. doi:10.15585/mmwr.rr6701a1
10. Chen HL, Lee CN, Chang CH, et al. Efficacy of maternal tenofovir disoproxil fumarate in interrupting mother-to-infant transmission of hepatitis B virus. Hepatology. 2015;62(2):375–386. doi:10.1002/hep.27837
11. Brown RS Jr, McMahon BJ, Lok AS, et al. Antiviral therapy in chronic hepatitis B viral infection during pregnancy: A systematic review and meta-analysis. Hepatology. 2016;63(1):319–333. doi:10.1002/hep.28302
12. Pan CQ, Duan Z, Dai E, et al. Tenofovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load. N Engl J Med. 2016;374(24):2324–2334. doi:10.1056/NEJMoa1508660
13. Jourdain G, Ngo-Giang-Huong N, Harrison L, et al. Tenofovir versus Placebo to Prevent Perinatal Transmission of Hepatitis B. N Engl J Med. 2018;378(10):911–923. doi:10.1056/NEJMoa1708131

High Resolution Anoscopy for the Management of HPV-Associated Anal Intraepithelial Neoplasia

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INTRODUCTION

Human Papillomavirus and Anal Cancer

Human papillomavirus (HPV) infections are the most common sexually transmitted infections worldwide. HPV is a non-enveloped double-stranded DNA virus that infects mucosal and cutaneous keratinocytes. There are more than 180 subtypes of HPV, of which 40 types infect the anogenital region. These subtypes can usually be categorised into high- vs low-risk in terms of their oncologic potential. Most sexually active males or females will acquire HPV soon after sexual debut. 90% of the infection is silent and will resolve spontaneously[1]. There are several factors associated with persistent infection, and they are shown in TABLE 1[2]. The longer the duration of an HPV infection, the greater the chance that it will lead to cellular changes.

The importance of persistent HPV infection lies in its association with cancer causation. Evidence for cervical cancer has been firmly established[3]. Anal intraepithelial neoplasia (AIN) is a potential precursor lesion of anal squamous cell carcinoma. Similar to cervical intraepithelial neoplasia (CIN), AIN is causally linked to persistent infections with high-risk HPV types such as HPV16 or HPV18. There is ample evidence for HPV infection as precursor infection for anal intraepithelial neoplasia (AIN) and anal cancer[4]. HPV prevalence among patients with AIN is over 90%[5]. A large meta-analysis found that among patients with cervical, vulvar and anal cancer, those with anal cancer had the highest prevalence of HPV infection (84.3%)[6]. Furthermore, the amount of HPV DNA is higher in those with high-grade AIN than low-grade AIN, suggesting its biologically plausible role in causing the malignancy[7].

Table 1. Factors associated with persistent HPV infection (Adapted from Rev Obstet Gynecol 2008 [2])

Behaviours	Multiple sexual partners Men who have sex with men Smoking Limited medical care
Medications	Immunosuppression No HPV vaccination Oral contraceptive use
Co-infection	Human immunodeficiency virus (HIV) Multiple HPV subtype infections Other sexually transmitted infections
HPV infection characteristic	High risk HPV type 16, 18 High viral load

WHO ARE THE AT RISK GROUP?

Anal cancer is uncommon, with an incidence rate of around 2 per 100,000 of the general population[8,10], but incidence rates have been steadily increasing over the last three decades[9]. It is more common in females than in males[9].

Anal cancer is increasing significantly among some groups of people[13], especially those infected with HIV, men who have sex with men (MSM)[10], women with a history of cervical, vaginal or vulvar cancer[11], tobacco smokers, and people who are immunocompromised due to organ transplants[12], steroid use, or the use of any medications that suppress the immune system. In human immunodeficiency virus (HIV)-infected MSM, anal HPV prevalence is more than 90%, and infections with multiple HPV types are common[14]. Consequently, HPV-associated anogenital malignancies occur with high frequency in patients with HIV infection. Although anal cancer is not an AIDS-defining cancer, it is 30-100 times more common in HIV-positive individuals[15]. Studies have indicated that a low CD4 count in HIV-positive individuals is a risk factor for AIN and invasive anal cancer[16].

WHAT IS ANAL INTRAEPITHELIAL NEOPLASIA AND HOW TO RECOGNISE IT?

Anal squamous dysplasia refers to a spectrum of disease ranging from low-grade intraepithelial lesions (LSIL) to high-grade squamous intraepithelial lesions (HSIL) to invasive anal squamous cell carcinoma of the anus (SCCA). They can involve both the perianal skin and anal canal. 'Intraepithelial' in anal intraepithelial neoplasia (AIN) refers to the abnormal cells not having gone further than the epithelium or the lining of the anus. AIN can either be LSIL or HSIL[17]. Inside the anal canal, the histopathologic manifestations of HPV infection are most commonly detected at the anal transition zone (ATZ), where the rectal columnar epithelium and anal squamous epithelium meet (known as the squamo-columnar junction, SCJ)[18,19].(Fig. 1) The anus and cervix also share embryological origins and susceptibility to HPV infection, which might also explain the similarities between these malignancies.

LSIL usually goes away on its own, without treatment. But some of them associated with an increased risk of HSIL are less likely to go away on their own, with approximately one in ten chance of becoming a

cancer over approximately five years[20,21]. But there is heterogeneity, and the rate is highest in high-risk populations. The rate of progression of AIN to invasive anal cancer more closely resembles the natural history of vulval intraepithelial neoplasia, with expected malignant transformation in about 10% of immunocompetent patients over five years[22].

Fig. 1. The squamo-columnar junction (SCJ) marked with a green line partially on the left side of the picture taken at HRA (Photo from personal collection of Dr Andrew TY Wong)

Patients with AIN are often asymptomatic. Symptomatic patients may present with pruritus or anal discharge. Suspicious lesions may be raised, plaques, scaly, fissured, or eczematous. The colour can be white, erythematous or pigmented[23].

Patients who describe perianal symptoms consistent with AIN or anal cancer require examination of the perineum, digital rectal examination, and examination of the inguinal area for palpable nodes. When AIN is found, it is important to examine other sites including vulva, vagina and cervix in women and the penis in men, because of the multi-zonal nature of the disease[24]. The vice-versa should apply to patients detected to have disease involving vulva, vagina and cervix to have a lower threshold of screening for AIN. There is a misconception that anal HPV infection was invariably associated with anal intercourse. In fact, sex does not have to occur for the infection to spread, and most women who have AIN or anal cancer did not have a history of anal intercourse. Skin-to-skin contact with an area of the body infected with HPV is all that is needed for infection to spread. The virus can be spread through genital-to-genital contact or even hand-to-genital contact. HPV infection can also spread from one part of the body to another, for example, from the genitals to anus[25]. The finding that it is more common in women who clean themselves from front to back after voiding urine is a case in point[26].

WHAT IS High-resolution Anoscopy?

High-resolution anoscopy, or HRA, is a procedure that allows for examination of the anal canal and surrounding skin using a colposcope. The 10-40 times magnifying power of the colposcope allows for the direct visualisation of the mucosal surface of the anal canal and the surrounding skin of the perianal area. In addition, staining up with acetic acid and Lugol's iodine will enable lesions which are otherwise invisible to the naked eyes to be picked up for biopsy for confirmation of histology.

HRA is well known for its steep learning curve, and hence quality assurance is of vital importance in ensuring proper care. For that, the International Anal Neoplasia Society (IANS) has defined minimum standards for service to guide HRA practitioners on the set-up and implementation of high-resolution anoscopy, the provision of information to patients, staffing, infection control, medical notes, and follow-up referrals to and communication with a team of specialists[27].

WHO SHOULD HAVE HRA?

- People who have a higher risk of developing anal cancer. They includes both men and women who are immunosuppressed; this could be due to HIV infection, organ transplants, long term steroid use or other medicine that suppresses immune function, or any other condition that affects the immune system.
- People who have a history of anal dysplasia (precancerous changes) or cervical or vulval dysplasia (women).

WHY IS IT DONE?

When Pap smear was first introduced to screen for precancerous changes in the cervix of women, it was based theoretically on the pathological progression of precancer changes to cancer. It was after decades of screening that revealed the usefulness of Pap smear in the reduction of cervical cancer. Biological and epidemiological evidence has demonstrated that anal cancer and cervical cancer share lots of analogy and persistent high-risk type HPV infection is even a stronger predictor for anal cancer. Clinical approach to the diagnosis of AIN also borrows from the cervical cancer model and includes the application of colposcopy to the evaluation of anal and perianal region[28]. The success of cervical cancer screening has led to the use of colposcopy as a template for anal cancer screening in high-risk groups.

A retrospective study demonstrated that anal carcinoma developed at previously biopsied sites of high-grade dysplasia in 27 out of 72 anal cancers studied (37.5%), illustrating the potential for the development of anal squamous cell carcinoma from high-grade anal dysplasia[29]. In this study, nearly half of the HIV-infected MSM with HSIL who developed anal cancer were asymptomatic[29]. Evidence to support the use of HRA for detection and treatment in the surveillance of AIN exists and strongly suggests that it is beneficial, resulting in reduced rates of cancer progression[30]. Pilot data demonstrated a 5.72-fold reduction in local disease failure rates of patients with T1-T3 tumours; these data, therefore, suggested that use of HRA for detection and treatment in surveillance of anal cancer patients will help prevent local, regional relapse at the anal site[30]. Hence the objective of HRA is to detect precancer lesion early. HRA will also allow treatment to be performed to prevent the HSIL from turning into cancer.

Anal cytology is only 47 to 70% sensitive in picking up precancerous lesions in HIV-negative MSM[31,32]. In high-risk population such as HIV-positive MSM, anal cytology can be inaccurate and has been shown not to correlate with histology[33]. Testing of high-risk human papillomavirus strains 16/18 improves specificity and positive predictive value over cytology for AIN screening. Patients testing positive for strains 16/18 are at high-risk for HSIL and should undergo high-resolution anoscopy regardless of the cytology result[34].

HRA has been recommended by some as a tool for screening in high-risk patients[35,36]. Apart from a better sensitivity and specificity for picking up abnormal lesions, HRA also allows ablative therapy to be done. However, HRA involves higher demand in terms of expertise and cost.

A large retrospective review from 2015 showed that patients followed with standard anoscopy or HRA every 3-12 months had lower rates of progression of AIN to anal cancer, compared to epidemiologic data[37,38]. Standards and protocols for anal cancer screening are not widely promulgated. The AIDS Institute of the New York State Department of Health has established formal screening guidelines for HIV-positive individuals. It recommends routine annual examination of the anus in all HIV-infected adults and cytologic (pap) testing in higher risk HIV-positive patients such as men who have sex with men (MSM), those with a history of genital infection, and women with cervical or vulvar dysplasia[39]. A colonoscopy does not screen for anal cancer and is not an acceptable alternative to HRA.

The U.S. Department of Health and Human Services (HHS) AIDS Info website in 2018 recommended that positive cytology requires follow-up with HRA and that visible lesions should be biopsied. Patients should be referred to expert centres where diagnostic and treatment procedures using HRA can be performed. The high recurrence rates of AIN also warrant ongoing post-treatment surveillance[40, 41].

For transplant patients, there is a recommendation for annual anal cytology targeting at those with a history of anal intercourse and a history of cervical dysplasia. Abnormal cytology needs a referral to HRA for biopsy and treatment[12].

HOW IS IT DONE?

There is no special preparation needed for the assessment. The procedure is performed on an outpatient basis. Starting 24 hours before the examination, avoid using any douches, enemas or creams that are applied to the anal canal. It is also important to avoid anal sex.

The patient will be asked to remove the lower half of his/her clothes and given a gown opening at the back. There are several positions for performing HRA. In the UK, it is done in a lithotomy position (Fig. 2). In the Netherlands, it is performed in lithotomy position too, but the legs are elevated much higher than those in UK (Fig. 3). In USA, it is either performed in knee-chest position (Fig. 4) or lateral position. In Australia, it is performed in a lateral position (Fig. 5). Some patients may prefer lateral position as they claim to be less vulnerable in that position. The choice of the position depends on the habits and practice of the operators as well. Personally, I find the lithotomy (especially with the end of the pelvic table tilted up considerably) or knee-chest position can expose the SCJ better as the mucosal folds tend to gravitate towards the colon end and provide a better view. Knee chest position can be challenging for some patients who have knee problems. Hence, I adopt the lithotomy position in Hong Kong (Fig. 6).

Fig. 2. HRA set up in Homerton Anal Neoplasia Service, Homerton Hospital, London, where lithotomy position is used (Photo from personal collection of Dr Andrew TY Wong)

Fig. 3. HRA set up in Amsterdam Medical Centre, Amsterdam, the Netherlands, where high lithotomy position is used.(Photo from personal collection of Dr Andrew TY Wong)

Fig. 4. HRA set up in Dr Stephen Goldstoneclinic in New York City, USA, where knee chest position is used by him to perform HRA.(Photo from personal collection of Dr Andrew TY Wong)

Fig. 5. HRA set up in St. Vincent Hospital, Sydney, Australia where lateral position is used. (Photo from personal collection of Dr Andrew TY Wong)

Fig. 6. HRA in operation in Hong Kong, where lithotomy position is used. (Photo from personal collection of Dr Andrew TY Wong)

Before the proper HRA, an anal Pap smear is performed if not done before. Taking an anal pap smear involves gently pushing a fine thin brush into the anal canal to obtain cells from the lining of the anus and collect in liquid medium for cytology. Then, the clinician will examine the anal canal with a finger to feel inside the anus and rectum for abnormal growths and will also examine the skin around the anus for any abnormalities (digital anorectal examination; DARE). As part of DARE, it is important to document any palpable mass lesion, indicating the distance from the anal verge and the proportion of the anal circumference that it occupies. Inspect the glove for blood from the anal canal.

For the HRA, a proctoscope will be coated with a lubricant and inserted about two inches into the anus. A cotton swab covered with mild (5%) acetic acid will be inserted through the proctoscope into the anus. Acetic acid is generously and continually applied during the examination to highlight areas of disease. The acetic acid on the cotton swab will cause any abnormal cells to turn white; these are called 'Acetowhite' areas. Acetowhite areas/lesions with specific vascular characteristics like punctation or honeycomb patterns are highly suggestive of high-grade disease. (Fig. 7) Lugol's iodine is then used to highlight Lugol non-uptake areas. With the use of a magnifying colposcope, the clinician performing the examination can detect abnormal areas using the characteristics described above. Should the patients want, they can observe the anoscopy image on the computer screen while the procedure is being performed. After a careful and thorough examination, the doctor will decide whether to take one or more biops(ies) from the anal canal and the perianal area. A local anaesthetic will be injected before the biopsy is taken to help minimise any discomfort.

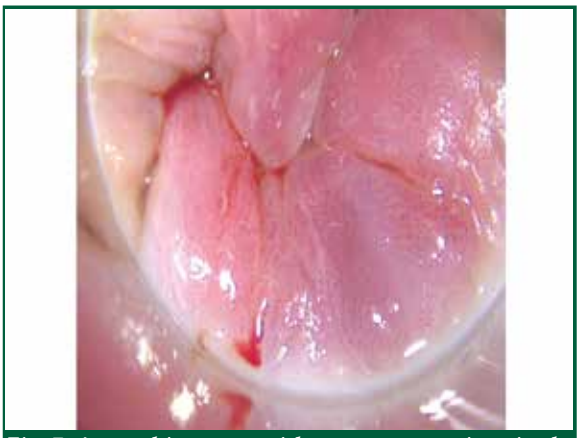

Fig. 7. Acetowhite areas with coarse punctations in the lower half of the anal canal. Biopsy showed HSIL. (Photo from personal collection of Dr Andrew TY Wong)

The total time of the procedure is between 20-40 minutes. The procedure is usually very well tolerated with mild, if any, discomfort. Significant risks, such as bleeding or infection, are extremely rare. HRA can also be used to direct therapy. Ablative therapy using infrared coagulation, hyfrecation or laser can be performed during HRA.

WHEN IS IT DONE?

Screening has been found to be cost-effective for AIN[42]. Various infectious disease societies have made recommendations for annual cytology for HIV-positive patients, especially those who are MSM, or have a history of cervical cancer[43]. For timing of subsequent surveillance, there is no established consensus, but most societies recommend yearly surveillance for HIV-positive males, and every 3-6 months for those with low- or high-grade AIN[44]. Fig. 8 showed the recommended algorithm for the diagnosis and management of AIN by Department of Health of New York State, USA[35].

When high-grade lesions are found, they can be treated either by topical agents or by ablative therapies. The primary topical agents are imiquimod, TCA, and 5-FU. Imiquimod is a synthetic immune modulator that works by upregulating the patient's immune system to combat the virus. It has been shown to downgrade high-risk lesions to low-risk lesions among HIV-positive patients[45]. In a randomised study, 61% of patients had an absence of high-risk lesions sustained at 36 months with imiquimod treatment[46]. The major side effects include treatment area reactions such as irritation and burning pain. TCA has a good safety profile with few major side effects. It can be applied during the examination, and is well-tolerated. Two retrospective

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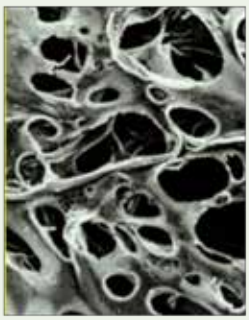

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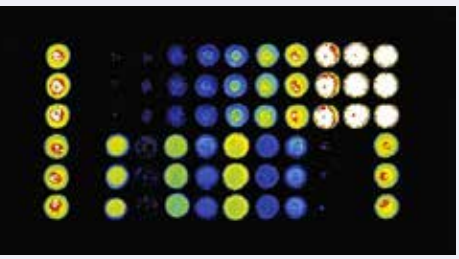

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studies of small populations of biopsy-confirmed high-grade AIN lesions reported rates of HSIL regressing to LSIL or complete resolution in 71%-79% of cases[47,48]. 5-FU is a chemotherapy agent that inhibits DNA synthesis and, when applied topically, can clear AIN. Prospective data showed complete clearance of 90%, with a recurrence rate of 50% at 6 months[49]. Side effects include hypopigmentation or skin irritation.

Ablative therapies, including infrared coagulation, cryotherapy, laser therapy, and electrocautery/hyfrecator are well tolerated. Repeated ablative treatment or a combination of treatment methods are often required for long-term clearance of AIN2-3. Infrared coagulation (IRC) was proven to have moderate efficacy in the treatment of HSIL in patients who are HIV-seropositive in a retrospective study[50]. It was safe and well-tolerated in the HIV-positive population in a prospective study[51].

Hyfrecation (electrocautery ablation) is also commonly used to treat anal HSIL. It has a similar efficacy profile to IRC[52]. Some clinicians prefer it over IRC because it may be faster than IRC, particularly for large and keratotic lesions. It is also easier to use than IRC for the perianal disease.

The efficacy of hyfrecation was addressed in a retrospective study in HIV-positive patients where at one-year post-ablation, about 45% of patients developed local recurrence. No patient developed invasive squamous cell carcinoma of the anus (SCCA)[53].

Taken together, topical therapy appears to be generally well-tolerated and offers reasonable efficacy, although a substantial portion of patients will not respond and others will recur. In many centres, topical therapy is utilised as an adjunct to local ablative therapy. At one centre, 248 patients were followed with exams and serial ablative procedures under HRA and supplemental topical treatments. 80% clearance of HSIL was demonstrated and only 1.2% of the patients developed anal cancer[54].

Currently, a prospective randomised study called Anal Cancer HSIL Outcomes Research (ANCHOR) to determine whether screening and treatment of HSIL are effective in reducing subsequent anal cancer in HIV-positive men and women compared with active monitoring via regular exams (including anal cytology combined with HRA and biopsy of any concerning lesions) vs observation is underway in 12 sites in the United States. Treatments can include imiquimod, fluorouracil, electrocautery, and laser therapy. The study will be able to answer questions like the best strategy for AIN surveillance and the efficacy and safety of different treatment modalities[55].

ROLE OF HPV VACCINATION

HPV vaccine is currently recommended only as a preventive immunisation for youth between the ages of 9 to 26. US CDC recommends it for people of all gender identities and sexual orientations, starting at age 11 or 12. Since it is intended to be given before sexual activity begins, it can be given as early as nine years of age. ACIP also recommends vaccination through age 26 years for those who were not adequately vaccinated previously, including gay, bisexual, and other men who have sex with men, transgender people, and immunocompromised persons (including those with HIV infection)[56].

A trial using quadrivalent vaccines among MSM showed that the incidence of anal SIL associated with HPV 6, 11, 16, or 18 was decreased by 78% and the incidence of persistent HPV infection of relevant types was decreased by 95% in those receiving the vaccine compared with those receiving placebo (per protocol efficacy). 165 (27.4%) men were seropositive or HPV DNA–positive for HPV-6 or 11, 99 (16.4%) for HPV16, and 68 (11.3%) for HPV-18. Hence HPV vaccine is useful for prevention of AIN and should preferably be given before sexual activity begins[57].

Administration of the vaccine after the diagnosis of AIN in order to assist with prevention in the future has been

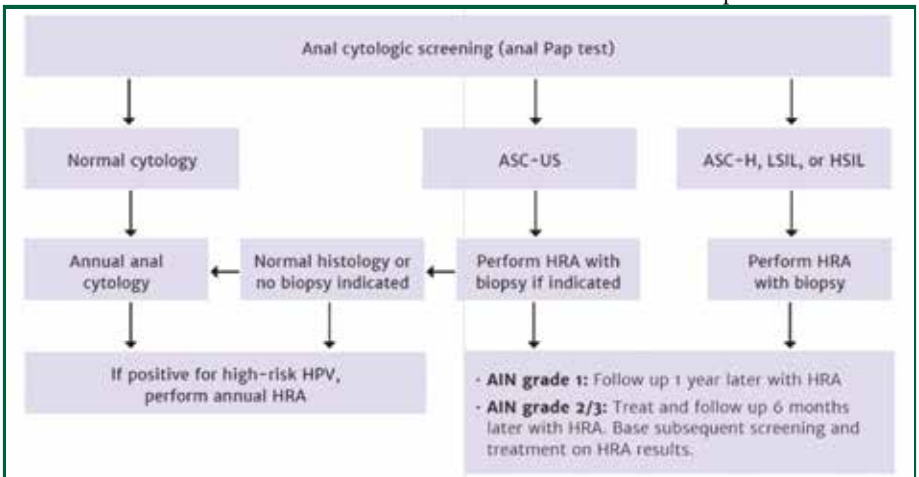

Fig. 8 A suggested algorithm for diagnosis, treatment and surveillance of anal intraepithelial neoplasia from Ref. 35. Key: AIN, anal intraepithelial neoplasia; ASC-US, atypical squamous cells of undetermined significance; ASC-H, atypical squamous cells cannot exclude HSIL; HPV, human papillomavirus; HRA, high-resolution anoscopy; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion. (Excerpted from The AIDS Institute of New York State Department of Health[39])

studied. Retrospective data showed that vaccination could lower the rates of HSIL in MSM with recurrent AIN[58]. A randomised trial involving MSM found the rates of AIN were lower in the vaccine group, while they also had a significantly lower risk for persistent HPV infection following vaccination[59]. Therefore, patients with AIN may benefit from the vaccine though it is considered an off-label use of the vaccine.

Primary prevention by administering the 9-valent HPV vaccine to girls and boys prior to the onset of sexual activity is most effective for prevention of almost all squamous cell carcinoma of the anus (SCCA). In addition, the 9v HPV vaccine may be helpful in preventing recurrent HSIL and possibly the progression to SCCA, especially in individuals at increased risk for SCCA including all HIV-positive men and women, HIV-negative MSM, and women with a history of CIN3 or cervical cancer.

FINAL REMARKS

HRA of the anal region, analogous to colposcopy of the cervix, is a technique that is not well-known in the medical and surgical fraternity. There is much potential room for improvement in general knowledge about the prevention, diagnosis and treatment of chronic HPV infection, AIN and anal cancer among medical practitioners and patients in high-risk groups alike. Specialists taking care of high-risk patients need to be aware of this disease entity and educate patients about the disease and prevention methods. This applies especially to gynaecologists and oncologists taking care of patients with other HPV-associated cancers; nephrologists or transplant physicians taking care of transplant patients ;and rheumatologists and other physicians taking care of patients on immunosuppressants.

To facilitate communication and better understand risks, healthcare providers need to learn how to comfortably take a proper sexual history in a non-judgemental way, regardless of stated or assumed sexual orientation, to better understand who is at risk. In patients with AIN or SCCA, Smoking cessation should be encouraged. Women should be made aware that anal HPV recovery does not mean anal intercourse and should be encouraged to abolish shame associated with the condition and come forwards to seek medical help if they notice any anal symptoms. There is a high correlation between cervical and anal cancer risk in women. For MSM, due to the high rate of sexually transmitted diseases and anal cancer among this population, a comprehensive STDs screening and prevention strategy inclusive for HPV should be in place.

References

1. Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2015. Other Sexually Transmitted Diseases 2015. Atlanta: US Department of Health and Human Services. https://www.cdc.gov/std/stats
2. Dempsey AF. Human papillomavirus: the usefulness of risk factors in determining who should get vaccinated. Rev Obstet Gynecol 2008;1:122-128.
3. Crosbie EJ, Einstein MH, Franceschi S, Kitchener HC. Human papillomavirus and cervical cancer. Lancet 2013;382:889-899.
4. Shah KV. Human papillomaviruses and anogenital cancers. N Engl J Med 1997; 337: 1386-1388 [PMID: 9358136 DOI: 10.1056/NEJM199711063371911]
5. Bosch FX, Broker TR, Forman D, et al. authors of ICO Monograph Comprehensive Control of HPV Infections and Related Diseases Vaccine Volume 30, Supplement 5, 2012. Comprehensive control of human papillomavirus infections and related diseases. Vaccine. 2013;31(Suppl 7):H1–H31.
6. De Vuyst H, Clifford GM, Nascimento MC, Madeleine MM, Franceschi S. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. Int J Cancer 2009;124:1626-1636.
7. Salit IE, Tinmouth J, Chong S, et al. Screening for HIV-associated anal cancer: correlation of HPV genotypes, p16, and E6 transcripts with anal pathology. Cancer Epidemiol Biomarkers Prev 2009;18:1986-1992.
8. SEER Cancer Statistics Factsheets: Anal Cancer. National Cancer Institute. Available from: URL: http//seer.cancer.gov/statfacts/html/anus.html
9. Grulich AE, Poynten IM, Machalek DA, et al. The epidemiology of anal cancer. Sex Health 2012;9:504–8.
10. Silverberg MJ, Lau B, Justice AC, Engels E, Gill MJ, Goedert JJ, Kirk GD, D'Souza G, Bosch RJ, Brooks JT, Napravnik S, Hessol NA, Jacobson LP, Kitahata MM, Klein MB, Moore RD, Rodriguez B, Rourke SB, Saag MS, Sterling TR, Gebo KA, Press N, Martin JN, Dubrow R. Risk of anal cancer in HIV-infected and HIV-uninfected individuals in North America. Clin Infect Dis 2012; 54: 1026-1034 [PMID: 22291097 DOI: 10.1093/cid/cir1012]
11. Lin C et al. Human papillomavirus types from infection to cancer in the anus: according to sex and HIV status: a systematic review and meta-analysis. Lancet Infect Dis 2018; 18:198-206.
12. Chin-Hong PV & Reid GE on behalf of AST Infectious Diseases Community of Practice. Human Papilloma Virus Infection in solid organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clinical Transplantation 2019:00: e13590
13. Roberts JR et al. Anal intraepithelial neoplasia: A review of diagnosis and management. World J Gastrointest Oncol 2017; 9: 50-61.
14. Park IU, Palefsky JM. Evaluation and management of anal intraepithelial neoplasia in HIV-negative and HIV-positive men who have sex with men. Curr Infect Dis Rep 2010;12:126-133.
15. Wasserman P, Rubin DS, Turett G. Review: Anal intraepithelial neoplasia in HIV-infected men who have sex with men: is screening and treatment justified? AIDS Patient Care STDS 2017;31:245-253.
16. Nancy F. Crum-Cianflone et al. Anal Cancers among HIV-Infected Persons: HAART Is Not Slowing Rising Incidence. AIDS. 2010; 24: 535–543. doi:10.1097.
17. Darragh TM et al. The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: Background and Consensus Recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. Archives of Pathology & Laboratory Medicine 2012 136:10, 1266-1297.
18. Alemany L, Saunier M, Alvarado-Cabrero I, et al. Human papillomavirus DNA prevalence and type distribution in anal carcinomas worldwide. Int J Cancer. 2015;136(1):98-107. doi:10.1002/ijc.28963
19. Palefsky M. Anal human papillomavirus infection and anal cancer in HIV-positive individuals: an emerging problem. AIDS. 1994;8:283.
20. Scholefield JH, Castle MT, Watson NF. Malignant transformation of high-grade anal intraepithelial neoplasia. Br J Surg 2005;92:1133-1136.
21. Watson AJ, Smith BB, Whitehead MR, Sykes PH, Frizelle FA. Malignant progression of anal intra-epithelial neoplasia. ANZ J Surg 2006;76:715-717.
22. Scholefield JH, Harris D, Radcliffe A. Guidelines for management of anal intraepithelial neoplasia. Colorectal Dis 2011;13(suppl 1):3-10.
23. Zbar AP, Fenger C, Efron J, Beer-Gabel M, Wexner SD. The pathology and molecular biology of anal intraepithelial neoplasia: comparisons with cervical and vulvar intraepithelial carcinoma. Int J Colorectal Dis 2002;17:203-15.
24. Carter JJ, Madeleine MM, Shera K, Schwartz SM, Cushing-Haugen KL, Wipf GC, et al.Human papillomavirus 16 and 18 L1 serology compared across anogenital cancer sites. Cancer Res 2001;61:1934-40.
25. American Cancer Society. Risk Factors for Anal Cancer. Assessed from https://www.cancer.org/cancer/anal-cancer/causes-risks-prevention/risk-factors.html
26. Simpson S et al. Front-to-back & dabbing wiping behaviour post-toilet associated with anal neoplasia & HR-HPV carriage in women with previous HPV-mediated gynaecological neoplasia. Cancer Epidemiol 2016; 42:124-132.
27. Hillman RJ et al. 2016 IANS International Guidelines for Practice Standards in the Detection of Anal Cancer Precursors. Journal of Lower Genital Tract Dis 2016; 20: 283-291.
28. Darragh TM, Winkler B. Anal cancer and cervical cancer screening: key differences. Cancer Cytopathol 2011;119(01):5–19.
29. Berry JM, Jay N, Cranston RD, et al. Progression of anal high-grade squamous intraepithelial lesions to invasive anal cancer among HIV-infected men who have sex with men. Int J Cancer 2014;134:1147–1155.
30. Goon P et al. High resolution anoscopy may be useful in achieving reductions in anal cancer local disease failure rates: HRA may prevent anal cancer local disease failure. European journal of cancer care. 2013; 24. 10.1111/ecc.12168.
31. Nathan M, Singh N, Garrett N, Hickey N, Prevost T, Sheaff M. Performance of anal cytology in a clinical setting when measured against histology and high-resolution anoscopy findings. AIDS 2010; 24: 373-379.
32. Palefsky JM, Holly EA, Hogeboom CJ, Berry JM, Jay N, Darragh TM. Anal cytology as a screening tool for anal squamous intraepithelial lesions. J Acquir Immune Defic Syndr Hum Retrovirol 1997; 14: 415-422.
33. Panther LA, Wagner K, Proper J, et al. High resolution anoscopy findings for men who have sex with men: inaccuracy of anal cytology as a predictor of histologic high-grade anal intraepithelial neoplasia and the impact of HIV serostatus. Clin Infect Dis 2004;38(10):1490–1492.
34. Sambursky JA, Terlizzi JP, Goldstone SE. Testing for Human Papillomavirus Strains 16 and 18 Helps Predict the Presence of Anal High-Grade Squamous Intraepithelial Lesions. Dis Colon Rectum. 2018;61:1364-1371. doi:10.1097/DCR.0000000000001143
35. Nahas CS, de Silvia Filho EV, Segurado AA, et al. Screening anal dysplasia in HIV-infected patients: is there an agreement between anal pap smear and high-resolution anoscopy-guided biopsy? Dis Colon Rectum 2009;52:1854-1860.

Dovato
dolutegravir/lamivudine

POWER REIMAGINED

AN INNOVATIVE NEW TREATMENT FOR YOUR PATIENTS LIVING WITH HIV

POWERED BY DOLUTEGRAVIR AT THE CORE

DURABLE, NON-INFERIOR EFFICACY WITH 0 RESISTANCE vs A 3-DRUG REGIMEN[1]

FEWER ANTIRETROVIRALS vs A 3-DRUG REGIMEN: **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 aminotransferase (ALT) and/or aspartate aminotransferase (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.

GlaxoSmithKline Limited
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Tel: (852) 3189 8989 Fax: (852) 3189 8931

WORKING ON BEHALF OF ViiV HEALTHCARE IN HIV

PM-HK-DLT-ADVT-200001
Date of preparation: 30/01/2020 (01/2021)

36. Shridhar, R., Shibata, D., Chan, E., Thomas, C. Anal Cancer: Current Standards in Care and Recent Changes in Practice. CA: A Cancer Journal for Clinicians 2015; 65:139-162. doi.org/10.3322/caac.21259
37. Long KC, Menon R, Bastawrous A, Billingham R. Screening, surveillance, and treatment of anal intraepithelial neoplasia. Clin Colon Rectal Surg 2016;29:57-64.
38. Crawshaw BP, Russ AJ, Stein SL, et al. High-resolution anoscopy or expectant management for anal intraepithelial neoplasia for the prevention of anal cancer: is there really a difference? Dis Colon Rectum 2015;58:53-59.
39. The AIDS Institute of New York State Department of Health. Screening for Anal Dysplasia and Cancer in Patients with HIV. Assessed at https://www.hivguidelines.org/hiv-care/anal-dysplasia-cancer/#tab_3
40. US Department of Health and Human Services. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Section on Human Papilloma Virus at AIDSInfo https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/343/human-papillomavirus-disease assessed on 1 Jun 2020.
41. Dalla Pria A, Alfa-Wali M, Fox P, et al. High-resolution anoscopy screening of HIV-positive MSM: longitudinal results from a pilot study. AIDS 2014;28:861-867.
42. Goldie SJ, Kuntz KM, Weinstein MC, Freedberg KA, Palefsky JM. Cost-effectiveness of screening for anal squamous intraepithelial lesions and anal cancer in human immunodeficiency virus-negative homosexual and bisexual men. Am J Med 2000;108:634-641.
43. Dindo D, Nocito A, Schettle M, Clavien PA, Hahnloser D. What should we do about anal condyloma and anal intraepithelial neoplasia? Results of a survey. Colorectal Dis 2011;13:796-801.
44. Siddharthana RV, Lanciaultb C, Tsikitis VL. Anal intraepithelial neoplasia: diagnosis, screening, and treatment. Ann Gastroenterol 2019; 32: 1-7.
45. Wieland U, Brockmeyer NH, Weissenborn SJ, et al. Imiquimod treatment of anal intraepithelial neoplasia in HIV-positive men. Arch Dermatol 2006;142:1438-1444.
46. Fox PA, Nathan M, Francis N, et al. A double-blind, randomized controlled trial of the use of imiquimod cream for the treatment of anal canal high-grade anal intraepithelial neoplasia in HIV-positive MSM on HAART, with long-term follow-up data including the use of open-label imiquimod. AIDS 2010; 24:2331-2335.
47. Cranston RD, Baker JR, Liu Y, Wang L, Elishaev E, Ho KS. Topical application of trichloroacetic acid is efficacious for the treatment of internal anal high-grade squamous intraepithelial lesions in HIV-positive men. Sex Transm Dis 2014; 41: 420-426.
48. Singh JC, Kuohung V, Palefsky JM. Efficacy of trichloroacetic acid in the treatment of anal intraepithelial neoplasia in HIV-positive and HIV-negative men who have sex with men. J Acquir Immune Defic Syndr 2009; 52: 474-479 .
49. Richel O, Wieland U, de Vries HJ, et al. Topical 5-fluorouracil treatment of anal intraepithelial neoplasia in human immunodeficiency virus-positive men. Br J Dermatol 2010;163:1301-1307.
50. Goldstone SE, Kawalek AZ, Huyett JW. Infrared coagulator: a useful tool for treating anal squamous intraepithelial lesions. Dis Colon Rectum. 2005;48(5):1042-1054. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15868241
51. Stier EA, Goldstone SE, Berry JM, et al. Infrared coagulator treatment of high grade anal dysplasia in HIV-infected individuals: an AIDS malignancy consortium pilot study. J Acquir Immune Defic Syndr 2008;47:56-61.
52. Marks DK, Goldstone SE Electrocautery ablation of high-grade anal squamous intraepithelial lesions in HIV-negative and HIV-positive men who have sex with men. J Acquir Immune Defic Syndr. 2012 Mar;59 :259-65.
53. Gaisa MM, Liu Y, Deshmukh AA, Stone KL, Sigel KM.Electrocautery ablation of anal high-grade squamous intraepithelial lesions: Effectiveness and key factors associated with outcomes. Cancer. 2020;126(7):1470. Epub 2020 Jan 24.
54. Pineda CE, Berry JM, Jay N, Palefsky JM, Welton ML. High-resolution anoscopy targeted surgical destruction of anal high-grade squamous intraepithelial lesions: a ten-year experience. Dis Colon Rectum 2008;51:829-835.
55. SEER Cancer Statistics Factsheets: Anal Cancer. National Cancer Institute. Bethesda, MD. Available from: URL: http//anchorstudy. org/about
56. US CDC HPV Vaccine Recommendations accessed at https://www.cdc.gov/vaccines/vpd/hpv/hcp/recommendations.html
57. Palefsky JM, Giuliano AR, Goldstone S, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. N Engl J Med. 2011;365:1576.
58. Swedish KA, Factor SH, Goldstone SE. Prevention of recurrent highgrade anal neoplasia with quadrivalent human papillomavirus vaccination of men who have sex with men: a nonconcurrent cohort study. Clin Infect Dis 2012; 54:891-8.
59. Vaccine therapy in preventing Human papillomavirus infection in young HIV-positive male patients who have sex with males. In: ClinicalTrials.gov [Internet]. Available from: https:// clinicaltrials.gov/ct2/show/NCT01209325?term=NCT01209325 NLM Identifier: NCT01209325.
60. Lin C et al. Cervical determinants of anal HPV infection and high-grade anal lesions in women: a collaborative pooled analysis. Lancet Infect Dis 2019; 19: 880-891.

ONCE-A-DAY

INVANZ®

(ertapenem, MSD) IV/IM

1 vial 1 gram ONCE Daily*

Indicated for:[1]

Treatment

- ✓ Complicated Urinary tract infections
- ✓ Complicated acquired Pneumonia
- ✓ Complicated intra-abdominal infections
- ✓ Complicated skin and skin structure infections
- ✓ Acute pelvic infections

Prophylaxis

- ✓ Prophylaxis of Surgical site infection following elective colorectal surgery

Covering a wide range of bacteria included:[1]

Gram-positive

- ✓ Staphylococcus aureus
- ✓ Streptococcus agalactiae
- ✓ Streptococcus pneumoniae
- ✓ Streptococcus pyogenes

(Note: Methicillin-resistant staphylococci are resistant to INVANZ®. Many strains of Enterococcus faecalis and most strains of *Enterococcus faecium* are resistant.)

Gram-negative

- ✓ **Escherichia coli** (+/- ESBL^)
- ✓ **Klebsiella pneumoniae** (+/- ESBL^)
- ✓ Haemophilus influenzae (including β-lactamase-producing strains)
- ✓ Moraxella catarrhalis
- ✓ Proteus mirabilis

Anaerobes

- ✓ Bacteroides fragilis
- ✓ Clostridium spp (excluding C difficile)
- ✓ Eubacterium spp
- ✓ Peptostreptococcus spp
- ✓ Prevotella spp
- ✓ Porphyromonas asaccharolytica

^ESBL = Extended Spectrum β-lactamase *For adult (aged 13 and older)

Reference: 1. Hong Kong INVANZ Product Circular

INVANZ® Selected Safety information

Indications:

- *INVANZ®* is indicated for the treatment of patients with moderate to severe infections caused by susceptible microorganisms, as well as initial empiric therapy prior to the identification of causative organisms in the infections listed below:
  - Complicated Intra-Abdominal Infections
  - Complicated Skin and Skin Structure Infections, including diabetic foot infections without osteomyelitis
  - Community Acquired Pneumonia
  - Complicated Urinary Tract Infections including pyelonephritis
  - Acute Pelvic Infections including postpartum endomyometritis, septic abortion and post-surgical gynecologic infections
- *INVANZ®* is indicated in adults for the prophylaxis of surgical site infection following elective colorectal surgery.

Contraindications:

- *INVANZ®* is contraindicated in patients with known hypersensitivity to any component of this product or to other drugs in the same class or in patients who have demonstrated anaphylactic reactions to betalactams.
- Due to the use of lidocaine HCl as a diluent, *INVANZ®* administered intramuscularly is contraindicated in patients with a known hypersensitivity to local anesthetics of the amide type and in patients with severe shock or heart block (Lidocaine HCl is the diluent for intramuscular administration of *INVANZ®*).

Precautions:

- Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with beta-lactams. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe hypersensitivity reactions when treated with another beta-lactam. Before initiating therapy with *INVANZ®*, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, other beta-lactams and other allergens. If an allergic reaction to *INVANZ®* occurs, discontinue the drug immediately. **Serious anaphylactic reactions require immediate emergency treatment.**
- Seizures and other CNS adverse experiences have been reported. Seizures, irrespective of drug relationship, occurred in 0.5% of patients during therapy plus 14 day follow-up period. Most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function. Close adherence to dosage regimen is urged in patients with factors predispose to convulsive activity. Anticonvulsant therapy should be continued. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically and the dosage of *INVANZ®* re-examined to determine whether it should be decreased or discontinued.
- The concomitant use of ertapenem and valproic acid/divalproex sodium is generally not recommended. Anti-bacterials other than carbapenems should be considered to treat infections in patients whose seizures are well controlled on valproic acid or divalproex sodium.
- As with other antibiotics, prolonged use of *INVANZ®* may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.
- Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ertapenem, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.
- Caution should be taken when administering *INVANZ®* intramuscularly, to avoid inadvertent injection into a blood vessel.

Adverse Events:

- Most adverse experiences reported in clinical studies were described as mild to moderate in severity. The most common drug –related adverse experiences reported during parenteral therapy in patients treated with ertapenem were diarrhea, infusion vein complication, nausea and headache. Other common side effects include: phlebitis/thrombophlebitis, vomiting, infusion site erythema, infusion site pain, infusion site swelling, rash, etc.
- For detailed adverse events, please consult the prescribing information.

Before prescribing INVANZ®, please read the Full Prescribing Information.

MSD

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HK-CAR-00028 08/28

Updates on COVID-19 and Therapeutics- How far does the Evidence Go?

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BACKGROUND

In December 2019, a novel coronavirus emerged in Wuhan, China, and rapidly spread throughout other cities in the Mainland. Subsequently, the virus was identified as SARS-CoV-2 by scientists in China, as the cause of a respiratory illness designated coronavirus disease, or COVID-19. Retrospective analysis revealed that the earliest confirmed cases had an epidemiological link to a wholesale food market in Wuhan, while some did not[1]. By May 29, 2020, more than 5.8 million COVID-19 cases were diagnosed worldwide. The number of patients is highest in the USA, with more than 1.7 million cases, followed by Brazil and Russia. Death tolls related to COVID-19 exceeded 360,000 globally[2]. In Hong Kong, the first patient, with a history of travel to Wuhan, was diagnosed on January 22, 2020, with fever and upper respiratory symptoms at presentation. By May 27, 2020 there was an accumulated number of 1,067 confirmed cases with four deaths[3]. The majority of patients had recovered and were discharged from the hospital.

Clinical trials of COVID-19 are ongoing and searching for a definitive therapeutic agent. Some treatments being tested are based on previously demonstrated efficacy on the severe acute respiratory disease (SARS) and middle east respiratory syndrome (MERS).

CLINICAL FEATURES AND RISK FACTORS

Transmission of COVID-19 occurs by close contact through respiratory droplets, by direct contact with infected persons, or by contact with contaminated objects and surfaces. Under certain circumstances, it may be transmitted via aerosol. The incubation period is mostly 5-6 days but can be up to 14 days. Less than 50% of confirmed patients presented with fever on admission. In a large cohort of 1,099 patients with laboratory-confirmed COVID-19 from 552 hospitals in mainland China, fever was only present in 43.8% on admission and 88.7% during hospitalisation. Cough, sputum, and fatigue were common symptoms while diarrhoea was infrequent. Lymphopenia was present in 83.2% of patients. Common comorbidities in severe cases included hypertension and diabetes. For treatment outcome, 6.1% of patients required mechanical ventilation, and the overall mortality rate was 1.4% from this cohort[4]. In another cohort involving 5,700 patients in New York City, only 30.7% of patients had a fever at triage. During hospitalisation, 14.2% required ICU care, 12.2% received mechanical ventilation. The overall mortality was 21%[5]. Loss of smell (anosmia) or loss of taste (ageusia), if present, is often noticed preceding the onset of respiratory symptoms[6]. For high-risk patients' identification, a meta-analysis revealed that patients with chronic obstructive pulmonary disease (COPD) had an increased risk of severe complications and higher mortality with COVID-19 infection[7]. Other risk factors for mortality include advancing age, obesity and comorbidities such as chronic liver disease or chronic kidney disease[8].

CLINICAL MANAGEMENT

General Management

Patients with suspected or confirmed COVID-19 infection in Hong Kong were kept in Airborne Isolation Rooms (AIIR) in hospitals. For mild disease, symptomatic treatment such as antipyretics for fever and pain, adequate nutrition and appropriate rehydration was given[9].

Empirical antibiotics should not be prescribed unless there is clinical suspicion of concomitant bacterial infection. Closely monitor patients for signs of clinical deterioration, such as rapidly progressive respiratory failure and shock and respond immediately with supportive care interventions.

ANTIVIRALS, IMMUNOMODULATORS AND OTHER ADJUNCTIVE THERAPIES

Hydroxychloroquine (HCQ) and Chloroquine (CQ)

Chloroquine is a widely used drug for malaria infection and autoimmune diseases. The pharmacological activity of CQ and HCQ was tested using SARS-CoV-2 infected Vero cells. HCQ was found to be more potent than CQ in vitro[10]. In mid-March, France approved the commencement of HCQ in severe cases of COVID-19. This was based on an open-label non-randomised clinical trial using HCQ and/or azithromycin as a treatment for COVID-19. Fourteen of 20 cases (70%) of the HCQ treated group showed a significant viral suppression to undetectable level versus the untreated group (12.5%) at day six post inclusion[11]. Subgroup analysis showed that those given HCQ + Azithromycin

(n=6) was associated with 100% viral suppression. However, more recent multinational registry analysis, comprising data from 96,032 patients from 671 hospitals in six continents revealed a contradictory finding. The use of hydroxychloroquine or chloroquine, either alone or with a macrolide, was associated with a decreased in-hospital survival and an increased occurrence of ventricular arrhythmia[12].

As a result, the World Health Organization (WHO) suspended the HCQ arm within the agency's Solidarity Trial on May 25, 2020. However, the suspension was lifted after concerns on the methodologic and data integrity of the study[13]. The three authors of the paper have since issued a statement in the 'Lancet" withdrawing the HCQ article because of the difficulty in verifying the primary data sources.

Remdesivir

Remdesivir (GS-5734), an inhibitor of the viral RNA dependent RNA polymerase with inhibitory activity against SARS-CoV and MERS-CoV, was identified as a potential candidate therapeutic for COVID-19 with in vitro activity against SARS-CoV-2[14]. A double-blind, randomised, placebo-controlled trial (RCT) done in China involving 237 patients (158 given Remdesivir & 79 given placebo) did not show any significant clinical improvement[15]. However, this study was criticised because it was underpowered. Subsequently, a bigger RCT conducted by the US National Institute of Allergy and Infectious Diseases (NIAID) enrolled 1,063 patients who were randomly assigned to receive a 10-day course of intravenous Remdesivir or placebo. This study showed a significantly better clinical outcome with Remdesivir. The median time to recovery for patients treated with Remdesivir (11 days (95% confidence interval [CI], 9 to 12)) was significantly shorter than those in the placebo group (15 days (95% CI, 13 to 19)), in adults hospitalised with COVID-19 and evidence of lower respiratory tract infection[16]. The study also demonstrated that there was no difference in clinical outcome between a 5-day and a 10-day course of Remdesivir in the treatment of severe cases of COVID-19[17]. In Hong Kong, about 30-40 patients were given Remdesivir under a clinical trial setting in 3 different centres.

Lopinavir-Ritonavir, Ribavirin and Interferon Beta-1b

Lopinavir-ritonavir, a human immunodeficiency virus (HIV) type 1 protease inhibitor, in combination with ribavirin, was shown to reduce the risk of adverse clinical outcomes among patients with SARS in 2003[18]. An animal study has demonstrated that mammals treated with Interferon (IFN) beta-1b may have a better clinical, radiological and pathological outcome than untreated animals[19]. A RCT was conducted in Wuhan, China to determine the efficacy of lopinavir-ritonavir on 199 hospitalised patients with SARS-CoV-2. No benefit was observed with treatment beyond standard care. However, the median time from symptom onset to randomisation was 13 days (interquartile range 11-16). This rather late symptom onset to randomisation day, raised the question of whether the insignificant treatment efficacy was related to late prescription in these patients (more than a week of symptom onset)[20]. Hung et al. revealed the result of a local, multicentre, prospective, open-label, randomised trial in adults with COVID-19 in Hong Kong. A total of 127 patients were recruited; 86 assigned to the combination therapy group and 41 assigned to the lopinavir-ritonavir monotherapy group as the control. Early use of triple antiviral therapy was safe, and no significant differences in the incidence of adverse events were noted. Triple antiviral therapy was superior to the control group, in terms of alleviating symptoms (4 days vs 8 days) and shortening the duration of viral shedding (7 days vs 12 days) and hospital stay (9 days vs 14.5 days) in patients with mild to moderate COVID-19. These outcomes were even more significant when the triple therapy was started less than or equal to 7 days after onset of symptoms[21]. This combination therapy strategy is still ongoing in hospitals in Hong Kong. Future clinical studies using a double antiviral therapy with interferon beta-1b as a backbone are warranted.

Tocilizumab

Monoclonal antibodies directed against inflammatory cytokines could be an adjunct therapy for severe cases of COVID-19. Tocilizumab, a monoclonal antibody Il-6 receptor antagonist, is mainly used to treat rheumatoid arthritis and cytokine release syndrome following chimeric antigen receptor T-cell therapy. Studies have shown that levels of inflammatory mediators are associated with the clinical severity of the COVID-19. It has been used in a small series of severe COVID-19 cases with the aim of alleviating cytokine storm. In one study, 21 patients received a single dose of tocilizumab. All patients became apyrexial on the first day after tocilizumab and remained stable thereafter. 75% had lowered their oxygen requirement within five days of treatment. Radiologic improvement occurred in 91% of patients. Lymphocyte counts returned to normal in 52.6% of patients[22]. Several RCTs of tocilizumab are in progress. In Hong Kong, a few ICU cases of COVID-19 were given tocilizumab.

Corticosteroids

The routine use of systemic corticosteroids in moderate to severe COVID-19 patients is not recommended[9]. Although corticosteroids can decrease the host inflammatory responses in the lungs, it also results in a delay in viral clearance and an increase in the risk of secondary infections. One systematic review showed no significant difference in survival, hospitalisation duration, ICU admission and use of mechanical ventilation among patients given systemic corticosteroids[23].

CONCLUSION

The SARS-CoV-2 pandemic continues to pose a significant threat to global public health. Most patients will recover with supportive therapy alone. However, for patients with moderate or severe diseases, especially for those with risk factors, combination therapy of interferon beta-1b and lopinavir-ritonavir may be considered. For patients with severe disease,

Remdesivir may provide a better clinical outcome. More future RCTs are needed to search for evidence of effective therapy against COVID-19 infection.

References

1. Coronavirus disease 2019 (COVID-19) Situation Report- 94. World Health Organization.
2. Coronavirus Resource Centre, John Hopkins University and Medicine. Https://coronavirus.jhu.edu/map.html
3. Local situation Dashboard. Centre for Health Protection. Https://coronavirus.gov.hk
4. Guan WJ, Ni ZY, Hu Y et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. Published online 2020 April 30.
5. Safiya R, Jamie SH, Mangala N et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA. Published online 2020 April 22.
6. Spinato G, Fabbris C, Polesel J et al. Alterations in small or taste in mildly symptomatic outpatients with SARS-CoV-2 Infection. JAMA. Published online 2020 April 23.
7. Alqahtani JS, Oyelade T, Aldhahir AM et al. Prevalence, severity and mortality associated with COPD and smoking in patients with COVID-19: A rapid systematic review and meta-analysis. PLoS ONE 2020;15(5): e0233147
8. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) 16-24 February 2020. https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf (Accessed on June 5 2020)
9. World Health Organization. Clinical management of COVID-19. Interim guidance. 2020 May 27. Accessed: https://www.who.int/publications/i/item/clinical-management-of-covid-19.
10. Yao X, Ye F, Zhang M et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis. Published online 2020 March 9.
11. Gautret P, Lagier JC, Parola P et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: a result of an open-label non-randomised clinical trial. Int J Antimicrob Agents. Published online 2020 March 20.
12. Mandeep RM, Sapan SD, Frank R et al. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet. Published online 2020 May 20.
13. Elisabeth Mahase. Covid-19: 146 researchers raise concerns over chloroquine study that halted WHO trial. BMJ 2020 June 2;369:m2197).
14. Manli W, Ruiyuan C, Leike Z et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. P 2020;30:269-71.
15. Wang Y, Zhang D, Du G et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet Published Online April 29 2020
16. Beigel JH, Tomashek KM, Mehta AK et al. Remdesivir for the treatment of COVID-19- Preliminary report. N Engl J Med. Published online 2020 May 22.
17. Goldman JD, Lye DC, Hui DS et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. N Eng J Med published online May 27 2020.
18. Chu C, Cheng V, Hung I et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax 2004;59:252-6.
19. Chan JF, Yao Y, Yeung ML et al. Treatment with Lopinavir/Ritonavir or Interferon-β1b Improves Outcome of MERS-CoV Infection in a Nonhuman Primate Model of Common Marmoset. J Infect Dis. 2015;212(12):1904-13
20. Cao B, Wang Y, Wen D et al. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. N Engl J Med. Published online 2020 May 7.
21. Hung IFN, Lung KC, Tso EYK et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet. Published online 2020 May 8.
22. Xu X, Han M, Li T et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A. 2020;117:10970-10975
23. Li H, Chen CX, Hu F et al. Impact of corticosteroid therapy on outcomes of persons with SARS-CoV-2, SARS-CoV, or MERS-CoV infection: a systematic review and meta-analysis. Leukaemia. Published online 2020 April 7.

Certificate Course for Allied Health Professionals

CME/CNE Course | Course No. C354

Certificate Course on

Mental Health 2020

(Video Lectures)

Objectives:

This course aims to introduce to the allied health professionals and Registered / Enrolled Nurses (General on the aetiology, course, and management of common psychiatric disorders in Hong Kong. Each topic will be delivered by a specialist psychiatrist who has extensive clinical expertise and academic knowledge in that particular area. After the course, the participants will have better understanding about the course, nature and current evidence-based treatments of various common psychiatric disorders. The course will be suitable for allied health professionals and Registered / Enrolled Nurses (General) working in mental health fields, general hospital settings, as well as social care settings in the community.

Jointly organised by

The Federation of Medical Societies of Hong Kong

The Hong Kong College of Psychiatrists

Date	Topics	Speakers
21 Aug 2020	Anxiety and phobias	Dr. Chung Wai-sau, Dicky Private Psychiatrist
28 Aug, 2020	Dementia	Dr. Pan Pey-chyou Private Psychiatrist
4 Sep, 2020	Insomnia and management of sleep disorders	Dr Wong Chung-hin, Willy Private Psychiatrist
11 Sep, 2020	Psychosocial approaches in psychiatry	Dr. John So Private Psychiatrist
18 Sep, 2020	Psychosis	Dr. Wong Hiu-mei Associate Consultant Tai Po Hospital
25 Sep, 2020	Common psychiatric disorders in children and adolescents	Dr. Tam Fung-ling, Venus Private Psychiatrist

Date : 21, 28 August & 4, 11, 18, 25 September, 2020 (Every Friday)
Time : 7:00 pm – 8:30 pm
Course Feature : Video lectures (with Q&A platform)
Language Media : Cantonese (Supplemented with English)
Course Fee : HK$1,000 (6 sessions)
Certificate : Awarded to participants with a minimum attendance of 70%
Enquiry : The Secretariat of The Federation of Medical Societies of Hong Kong
Tel.: 2527 8898 Fax: 2865 0345 Email: vienna.lam@fmshk.org

CME / CNE / CPD Accreditation in application
Online Application from website: http://www.fmshk.org

Sound Therapy: from Polyvagal Theory to Practice

Dr Andrew Tin-yau WONG
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Principal, International Sound Healing Academy, UK


Dr Andrew Tin-yau WONG Mr Anthony B.L. NEC

Stress is everywhere. Most people would yearn for being at peace in the midst of busy city life, a crowded and noisy environment, and most importantly, pressing daily routines and chores. Life can be especially stressful NOW when we are faced with huge uncertainties bought about by the greatest pandemic for the past 100 years.

Let us not forget that doctors work in one of the most stressful occupations. We face life, we face death, we face people, and we face long hours. Physician burnout is defined as a work-related syndrome involving emotional exhaustion, depersonalisation, and a sense of reduced personal accomplishment.

Surveys in the United States and United Kingdom[1] have found burnout rate among doctors as high as 80%! A survey[2] done in Hong Kong almost ten years ago showed that the rate for severe burnout was 30%. We believe that the current figure would be much higher now with escalating patient demand and workload! Serious and extreme burnout, if not dealt with properly, is associated with sudden death and suicide.

We also know that up to 80% of visits to doctors may have a stress-related component[3]. Chronic stress is, therefore, not only an underlying factor in physician burnout. It also underlies many of the most chronic health challenges presented to physicians by their patients.

It is our belief that being healthy is not only about 'physically not sick'. To possess a sound and peaceful mind and a sense of purpose in life are as crucial as health maintenance through physical exercise and taking nutritious food. We should not ignore the phenomenon that sleep problems are getting more prevalent, affecting general wellbeing and functioning.

The first author has been pursuing with a keen interest in various topics on mind-body medicine for the past 25 years. When faced with patients with various medical illness, I observed that the psychological aspect of care often plays an important part in the therapeutic outcome on top of the medical treatment or physical interventions we provide for them. Patients who are newly diagnosed with the critical illness have lots of fear and worries. Patients who have chronic illnesses easily become unmotivated to maintain their health.

I believe that as healthcare providers, we are doing our best to cater for the physical and psychological needs of our patients. However, wouldn't it be wonderful if there can be some simple tools that can help patients and we can teach to patients to help them relieve stress without any side effects? To this end, sound healing is becoming accepted as one of the valid methods to alleviate stress, reduce burnout, improve sleep and improve general wellbeing.

HOW DOES SOUND HEALING WORK?

There are sounds all around us. The vibrational forces of sound are emitted from the movement or vibration of all matter. They manifest in a constant cacophony of sound waves, endlessly resonating in the universal sea of consciousness. These sounds are both audible and inaudible to the human senses. Regardless of our capacity to hear or feel sound waves, they manifest as cause and effect, not only to us as human beings but also to the wider world around us. Sound waves wash over us at every second of every minute and hour of every day and continue to vibrate endlessly.

A variety of instruments and tools, including the human voice, is used in sound healing. Positive intention through our dedication and devotion when working with these media is thought to play an important part in the overall healing effect. By transforming and replacing old and unhealthy energies with new and harmonious energies, sound healing can help to balance and harmonise us. Stress, tension and disease are manifested as a state of disharmony. Positive wellbeing will ensue when our natural resonance and harmony is restored[4]. The human body is made up of 60% water on average. From the point of view of physics, the resonance created by sound can be transmitted to the water inside our body to cause vibration.

Sound healing works by :

1. Sympathetic resonance: Using a sound healing tool allows an area of imbalance to be brought back into balance through a "like vibration", a vibration that matches the original frequency a given area most naturally wants to vibrate at. Through the projection of a sound tool's pure, vibrational sounds, the waves go to the area of imbalance, the weak or dissonant frequency is transformed, and optimal resonance is restored.
2. Brainwave entrainment- Entrainment is the predisposition that two oscillating bodies have tendency to vibrate in harmony with one another. Entrainment occurs when two or more rhythmic cycles become synchronised.
3. Balancing left/right brain hemispheres.
4. Triggering the relaxation response to alleviate symptoms of chronic stress.

5. Releasing suppressed emotions associated with trauma from the past.

AUTONOMIC NERVOUS SYSTEM AND SOUND HEALING

The Autonomic Nervous System (ANS) is our body's primary control centre. With its two main divisions, the sympathetic and the parasympathetic nervous system (or vagus), the ANS represents a superordinate control centre in the body. It controls and regulates all vital functions, including heart rate, blood pressure, respiratory rate, and other body system functions. Many diseases, including chronic diseases of physical and mental health, are diseases of the autonomic nervous system (ANS).

Polyvagal Theory is a new view of the ANS, going beyond the conventional view of the ANS having two branches: sympathetic and parasympathetic. Polyvagal Theory was developed by Dr Stephen Porges PhD, a research scientist, in the early 1990s. Dr Porges is a 'Distinguished University Scientist' at the Kinsey Institute at Indiana University Bloomington, USA. He is also Research Professor in the Department of Psychiatry at the University of North Carolina at Chapel Hill; Emeritus Professor of Psychiatry at the University of Illinois at Chicago and Emeritus Professor of Human Development at the University of Maryland, College Park.

His Polyvagal framework is now increasingly used by medical doctors, psychiatrists, psychotherapists, and in other therapeutic modalities. Polyvagal Theory is the understanding of how our body reacts to various challenges. Our reactions are based on the evolution of our autonomic nervous system. During our evolutionary history as vertebrates, the autonomic nervous system has changed. As it changed, it created different circuits.

In Polyvagal Theory there are three circuits, and they function in a hierarchy[5] (Fig. 1)

1. social engagement corresponding to the ventral vagal circuit (supra-diaphragmatic vagus)
2. fight/flight corresponding to the sympathetic nervous system
3. freeze/shutdown corresponding to the dorsal vagal circuit (sub-diaphragmatic vagus)

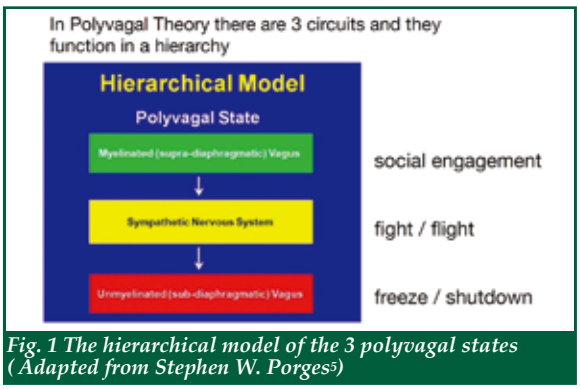

Fig. 1 The hierarchical model of the 3 polyvagal states (Adapted from Stephen W. Porges[5])

THE VENTRAL VAGAL CIRCUIT

The newer circuits can inhibit older circuits. The newest circuit is the circuit of social interaction which is linked to the uniquely mammalian vagal pathway the ventral vagal circuit. The ventral vagal circuit is the nerve going from the brain stem to the heart (CN X). The vagus nerve is linked in the brainstem to the nerves that regulate the muscles in the face and head which are involved in social engagement, including CN V (trigeminal nerve) CN VII (facial nerve). These are the muscles of vocalisation, listening, facial expressivity and gesture.

The ventral vagal circuit is the co-regulatory, interactive regulation of the autonomic state that enables our bodies to be in states that support growth, health and restoration. When that system does not work properly, we see the behaviours and the symptoms associated with physical and mental health issues. Improved flexibility and functioning of ventral vagus nerve creates a VAGAL BRAKE on dysfunctions in the spinal sympathetic nervous circuit. Such dysfunction can create a chronic mobilised state of fight/flight. Dysfunction of the dorsal vagus nervous circuit is associated with the chronic immobilised state of freeze/shutdown with fear.

Dysfunction in the nerves of the ventral vagus circuit is an underlying cause of many life impairing physiological and behavioural conditions. Learning how to correct this dysfunction and how to improve the functioning of the ventral vagal circuit is a quick, cheap and effective medical intervention[6]. This approach can eliminate the adverse effects of chronic stress arising from overstimulation of spinal sympathetic circuit. It can also eliminate the adverse effects of the shutdown and depressive behaviour arising from hyperactivity in the dorsal vagus circuit. Positive effects are cumulative. The ANS becomes more resilient each time we improve the flexibility and functioning of the ventral vagus circuit.

FROM THEORY TO PRACTICE

We have found that to successfully integrate Polyvagal theory into clinical practice; it is necessary to have a quick, cheap and reliable method of measuring the ANS.

As the heart is controlled directly by the sympathetic and parasympathetic nervous system, it acts as an effector organ to measure the autonomic nervous system. The sympathetic and parasympathetic nervous systems register and process internal and external stimuli. They initiate the proper reactions to optimally prepare the organism according to the needs of the moment (e.g. energy supply in times of sudden danger). A malfunctional ANS has an overactive sympathetic and hypoactive parasympathetic nervous system. Such state inevitably leads to a physiological change in the heart's excitation pattern. Thus, the Heart Rate Variability (HRV) - the beat-to-beat interval will be changed accordingly. This change is measurable. HRV is determined by the measurement and evaluation of the RR intervals (time period between successive heartbeats) There are commercially available software programs that allow measurement of HRV and provide analysis of the functioning of sympathetic and dorsal and ventral parasympathetic systems.

The international Sound Healing Academy has worked for three years to determine the effect of sound healing instruments and techniques on HRV, and therefore on the functioning of the ANS. With specific sound healing interventions, it is possible to improve the regulation of the ANS as shown by improved HRV and ventral parasympathetic system functioning.

PERSONAL OBSERVATIONS WITH SOUND HEALING

The first author has an avid interest in sound healing, first as a tool for personal development and relaxation; and then subsequently as a tool to help my family and friends with various issues (Fig. 2 & 3). For myself, I find that the sound emitted by various sound instruments to be very soothing (Fig. 4) and can help myself to focus on the moment by drawing my attention away from various mundane daily matters. It also facilitates me going into a meditative state more easily.

Fig. 2 Playing crystal singing bowls during a therapy session (Photo from the personal photo collection of Dr Andrew Tin-yau WONG)

Fig. 3 Use of tuning forks during a sound therapy session (Photo from the personal photo collection of Dr Andrew Tin-yau WONG)

Fig. 4 Part of the sound instruments for sound therapy, including crystal singing bowls, Tibetan singing bowls, tuning forks and gong. (Photo from the personal photo collection of Dr Andrew Tin-yau WONG)

Below is some of the anecdotal experience I had and is by no means suggesting that sound therapy is the definitive cause for the improvement in each case. Medical assessment and management is essential and cannot be bypassed.

My wife used to have chronic lower back pain requiring analgesics from time to time. I tried sound therapy for her, and after several sessions, her pain is 90% relieved, and she has not taken analgesics for the past few years.

A friend of my wife used to have chronic insomnia. She was seen by a psychiatrist and could only sleep for 1-2 hours at night even with adding to 5 medications for one year. She was exhausted when I first met her. After several sessions and my instruction to her to practice playing a tuning fork daily for practice, I was so overjoyed to hear that she could sleep for 5-6 hours in a row. Over the subsequent three months, her doctor has successfully reduced her medications to one item only. After one year, she was still well maintained on only one medication and was sleeping a few hours per night and in a brighter mood.

A friend of mine had chronic fatigue syndrome, rendering her bed-bound. She could barely support standing for 3 minutes alone at the worst of time. I diligently performed the therapy for her over ten sessions. I was so excited that she had marked improvement in her exercise tolerance progressively. She also told me that her chronic insomnia problem had markedly improved and the psychiatrist tailed down her medications gradually.

One 'side-effect' I get from performing the sessions for others is that I found that I slept very deeply on the same night that I performed the therapy. Also, I am generally more relaxed and can maintain working long hours easily without fatigue compared to before I took up this hobby.

THE NEW ERA OF HOLISTIC MEDICINE

The visionary Edgar Cayce once predicted 100 years ago that 'Sound will be the medicine of the future'. We are still far away from the stage where it is integrated as a mainstream therapy. Nevertheless, the blooming of various sound spas and sound baths especially in the West and now in Hong Kong signify that, at least for some people, the sound is appealing to them as a means to de-stress.

We believe that the Polyvagal Theory is a good scientific foundation whereby the effect on the ANS can be measured and hence quantified. We eagerly await results from a rigorous scientific study on the effect on this intervention. Even without RCTs, as a complementary therapy, sound therapy has great potential as a simple self-help therapy which can engage clients and as a 'feel-good' quick fix without side effects. As time goes by, we hope that more and more people would be opening up to experience its vast benefits.

References

1. Editorial, Physician Burnout: A Global Crisis. Lancet 2019 Jul 13;394(10193):93. doi: 10.1016/S0140-6736(19)31573-9.
2. Siu CFY, Yuen SK, Cheung A. Burnout among public doctors in Hong Kong: cross-sectional survey. Hong Kong Med J 2012;18:186–92.
3. Nerurkar A, Bitton A, Davis RB, Phillips RS, Yeh G. When Physicians Counsel About Stress: Results of a National Study. JAMA Intern Med. 2013;173(1):76-77.
4. Mitchell L. Gaynor MD. The Healing Power of Sound. Shambhala Publications 2002. ISBN: 9781570629556
5. Stephen W. Porges. The Polyvagal Theory. W.W. Norton & Company 2011. ISBN-10: 0393707008.
6. Stephen W. Porges & Deb Dana (eds). Clinical Applications of the Polyvagal Theory: The Emergence of Polyvagal-Informed Therapies. W.W. Norton & Company 2018. ISBN-10: 9781324000501.

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JUBLIA® Abbreviated Prescribing Information
Presentation: JUBLIA® (efinaconazole) topical solution, 10% w/w is a clear, colorless to pale yellow solution supplied in a white plastic bottle with an integrated flow-through brush applicator. **Indications:** Topical treatment of onychomycosis (tinea unguium) of the toenails due to Trichophyton rubrum and Trichophyton mentagrophytes. **Dosage:** Apply to affected toenails once daily for 48 weeks. When applying JUBLIA, ensure the toenail, the toenail folds, toenail bed, hyponychium, and the undersurface of the toenail plate, are completely covered. **Contraindications:** Hypersensitivity to efinaconazole or excipients or component of the container. **Precautions:** JUBLIA is for external use only and is not for ophthalmic, oral, or intravaginal use. Flammable, avoid use near heat or open flame. **Drug Interactions:** In vitro studies have shown that JUBLIA, at therapeutic concentrations, neither inhibits nor induces cytochrome P450 (CYP450) enzymes. **Adverse Reactions:** The most common adverse reactions (incidence >1%) were ingrown toenails, application site dermatitis, application site vesicles, and application site pain.
Before prescribing, please consult full prescribing information which is available upon request.

References
1. JUBLIA® Hong Kong full prescribing information (Issued: 06/2019). 2. Sugiura K, et al. Antimicrob Agents Chemother 2014;58:3837-3842. 3. Jo Siu WJ, et al. Antimicrob Agents Chemother 2013;57:1610-1616.
4. Data on File. Confidential company data. 5. Elewski BE, et al. J Am Acad Dermatol 2013;68:600-608.

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Certificate Course for Doctors, Nurses, Paramedics and Allied Health Workers • CME/CNE Course • Course No. C353

Certificate Course in

Ophthalmology 2020

(Video Lectures)

Jointly organised by

The Federation of Medical Societies of Hong Kong

The Hong Kong Ophthalmological Society

Objectives:

This course aims to provide an overview and update on the diagnosis and management of common and important eye diseases. After attending the course, attendees will learn how to deal with common ophthalmic conditions and when to refer patients to ophthalmologists.

Date	Topics	Speakers
19 Aug, 2020	Cataract and Cataract Surgery Update	Dr. CHAN Chung Yan, Tommy *FHKAM (Ophthalmology)*
	Refractive Errors, Presbyopia and Refractive Surgeries	Dr. NG Lap Ki, Alex *FHKAM (Ophthalmology)*
26 Aug, 2020	Corneal and External Eye Diseases	Dr. FAN Ching Yim, Michelle *FHKAM (Ophthalmology)*
	Glaucoma and Glaucoma Surgery Update	Prof. THAM Chee Yung, Clement *FHKAM (Ophthalmology)*
2 Sep, 2020	Neuro-Ophthalmology	Dr. HO Wing Lau *FHKAM (Ophthalmology)*
	Squint, Paediatric Ophthalmology	Dr. YUENG Chun Chun, Jane *FHKAM (Ophthalmology)*
9 Sep, 2020	Update in Orbital Diseases and Oculoplastic Surgery	Dr. LI Chi Lai *FHKAM (Ophthalmology)*
	Red Eyes, Ocular Trauma and Emergencies	Dr. CHOY Nga Kwan, Bonnie *FHKAM (Ophthalmology)*
16 Sep, 2020	Retinal Detachment and Diabetic Retinopathy	Dr. LAI Hiu Ping, Frank *FHKAM (Ophthalmology)*
	Common Macular Diseases and. Treatment	Dr. LUK Oi Jing, Fiona *FHKAM (Ophthalmology)*
23 Sep, 2020	Ophthalmic Imaging	Dr. MOHAMED Shaheeda *FHKAM (Ophthalmology)*
	Use of Laser in Ophthalmology	Dr. YUEN Shi Yin, Nancy *FHKAM (Ophthalmology)*

Date : 19, 26 August & 2, 9, 16, 23 September, 2020 (Wednesday)
Time : 7:00 p.m. – 8:30 p.m.
Course Feature : Video lectures (with Q&A platform)
Language Media : Cantonese (Supplemented with English)
Course Fee : HK$1,000 (6 sessions)
Certificate : Awarded to participants with a minimum attendance of 70%
Enquiry : The Secretariat of The Federation of Medical Societies of Hong Kong
Tel.: 2527 8898 Fax: 2865 0345 Email: vienna.lam@fmshk.org

CME / CNE / CPD Accreditation in application
Online application from website: http://www.fmshk.org

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
						* Facebook Live 1. Sexuality in COVID-19 Era 2. Unmet Need on the Management of Erectile Dysfunction and the Role of Avanafil * Facebook Live 3. Local Experience in Treatment of Erectile Dysfunction 4. Update on the Management of Premature Ejaculation **1**
2	* Certificate Course in Clinical Cytogenetics and Genetics 2020 (Video Lectures) **3**	* Evaluation of Antidepressants Efficacy and Individualized Treatment Approach (Online Symposium) * Facebook Live Abdominal Pain Management in Children **4**	* Certificate Course on Update in Clinical Sleep Medicine 2020 (Video Lectures) **5**	* Certificate Course in Allergy 2020 (Video Lectures) **6**	* Certificate Course on Complaint Management 2020 (Video Lectures) **7**	**8**
9	* Certificate Course in Clinical Cytogenetics and Genetics 2020 (Video Lectures) **10**	**11**	* The Hong Kong Neurosurgical Society Monthly Academic Meeting –COVID-19 and Neurosurgery * Certificate Course on Update in Clinical Sleep Medicine 2020 (Video Lectures) **12**	**13**	* Facebook Live Updates on IPV conference 2020 and Male HPV cancer prevention * Certificate Course on Complaint Management 2020 (Video Lectures) **14**	**15**
16	* Certificate Course in Clinical Cytogenetics and Genetics 2020 (Video Lectures) **17**	**18**	**19**	**20**	* Certificate Course on Complaint Management 2020 (Video Lectures) **21**	**22**
23	**24**	**25**	**26**	**27**	**28**	**29**
30	**31**					

THE FIRST PI-BASED STR BUILT ON THE NEWEST BACKBONE IN ARV THERAPY

Your Resilience Matters

Help protect against resistance with the barrier to rely on from the start

Symtuza®
darunavir/cobicistat/emtricitabine/tenofovir alafenamide tablets
800mg/150mg/200mg/10mg

The Only Evidence-Based STR Proven in Rapid Initiation

SYMTUZA® is the only STR that delivers these combined benefits:

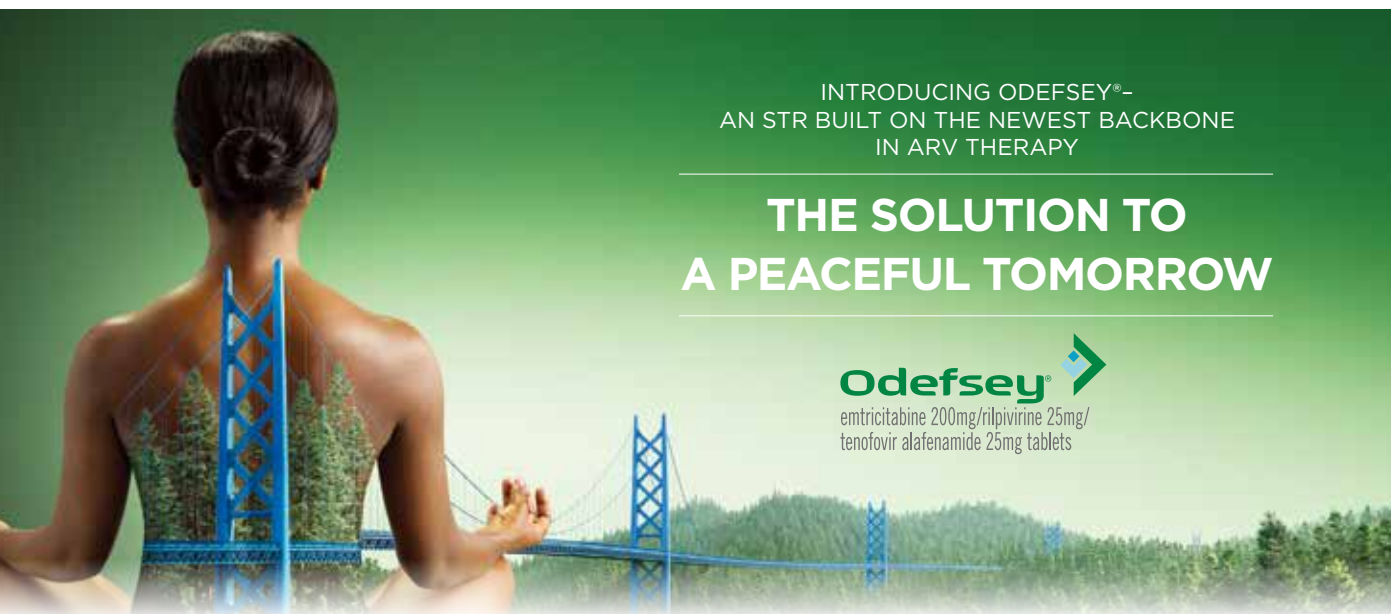
- **High Genetic Barrier of Darunavir***
- **Complete Coverage of HIV Patients†**
- STR **Formulated for Improved Tolerability‡**

* Zero treatment-emergent darunavir, primary PI, or TAF mutations across clinical trial populations. In the AMBER trial, of 362 treatment-naïve patients taking SYMTUZA®, 8 met the criteria for VF and 7 patients experiencing VF were analyzed for resistance[1]. In the EMERALD trial, of 763 virologically suppressed patients taking SYMTUZA®, 6 met the criteria for VF and 1 patient experiencing VF was analyzed for resistance[2]. Only 1 patient receiving SYMTUZA® was found to have M184I/V; this patient also had a transmitted K103N mutation at screening[1].

† Efficacy demonstrated in treatment-naïve and virologically suppressed patients, and in a rapid initiation scenario[1-3].

‡ ≤2% discontinuation rates due to adverse events through 48 weeks[1-3].

INDICATION
SYMTUZA® is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults (aged 18 years and older)[4].



INTRODUCING ODEFSEY®–
AN STR BUILT ON THE NEWEST BACKBONE IN ARV THERAPY

THE SOLUTION TO A PEACEFUL TOMORROW

Odefsey®
emtricitabine 200mg/rilpivirine 25mg/
tenofovir alafenamide 25mg tablets

INDICATION
ODEFSEY® is indicated for the treatment of adults and adolescents (aged 12 years and older with body weight at least 35 kg) infected with human immunodeficiency virus-1(HIV-1) without known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, tenofovir or emtricitabine and with a viral load ≤ 100,000 HIV-1 RNA copies/mL[5].

ARV=antiretroviral; HIV=human immunodeficiency virus; PI=protease inhibitor; STR=single-tablet regimen; TAF=tenofovir alafenamide; VF=virologic failure.

References: 1. Eron JJ, Orkin C, Gallant J, et al. A week-48 randomized phase-3 trial of darunavir/cobicistat/emtricitabine/tenofovir alafenamide in treatment-naive HIV-1 patients. AIDS. 2018;32(11):1431-42. **2.** Orkin C, Molina J-M, Negredo E, et al. Efficacy and safety of switching from boosted protease inhibitors plus emtricitabine and tenofovir disoproxil fumarate regimens to single-tablet darunavir, cobicistat, emtricitabine, and tenofovir alafenamide at 48 weeks in adults with virologically suppressed HIV-1 (EMERALD): a phase 3, randomised, non-inferiority trial. Lancet HIV. 2018;5(1):e23-e34. **3.** Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents 2019 [cited 2020 Jun 03]. Available from: https://aidsinfo.nih.gov/ contentfiles/lvguidelines/adultandadolescentgl.pdf. **4.** SYMTUZA® Hong Kong Prescribing Information. **5.** ODEFSEY® Hong Kong Prescribing Information.

Symtuza® Tablets
ABBREVIATED PRESCRIBING INFORMATION ACTIVE INGREDIENT(S): Darunavir 800mg/ cobicistat 150mg/ emtricitabine 200mg/ tenofovir alafenamide 10mg INDICATION(S): Treatment of HIV-1 infection in adults (aged 18 years and older). Genotypic testing should guide the use of Symtuza. DOSAGE & ADMINISTRATION: One tablet once daily with food. Tablet should not be crushed. May be used in patients with prior exposure to antiretroviral medicinal products but without darunavir resistance associated mutations (DRV-RAMs) and who have plasma HIV-1 RNA < 100,000 copies/mL and CD4+ cell count 100 cells x 10^6/L. Use with caution in patients above 65 years of age and patients with mild or moderate hepatic impairment. Discontinue use in patients with eGFR$_{CG}$ that declines below 30 mL/min during treatment. CONTRAINDICATIONS: Patients with severe hepatic impairment. Patients with eGFR$_{CG}$ < 30 mL/min. Treatment-experienced patients with one or more DRV-RAMs or with HIV-1 RNA 100,000 copies/mL or CD4+ cell count < 100 cells x 10^6/L. Hypersensitivity to the active substances or to any of the excipients. Carbamazepine, phenobarbital, phenytoin, rifampicin, lopinavir/ritonavir, St. John's wort (Hypericum perforatum), alfuzosin, amiodarone, dronedarone, quinidine, ranolazine, colchicine when used in patients with renal and/or hepatic impairment, rifampicin, ergot derivatives, pimozide, quetiapine, sertindole, lurasidone, triazolam, midazolam administered orally, sildenafil (when used for treatment of pulmonary arterial hypertension, avanafil, simvastatin, lovastatin and lomitapide), ticagrelor, tenofovir disoproxil (as fumarate, phosphate or succinate), lamivudine, adefovir dipivoxil (when used for treatment of HBV infection). Other antiretroviral products. Medicinal products requiring pharmacokinetic enhancement with ritonavir or cobicistat. SPECIAL WARNINGS & PRECAUTIONS: Patients co-infected with HIV and HBV or HCV: Patients with chronic hepatitis B or C treated with antiretroviral therapy are at increased risk for potentially fatal hepatic adverse reactions. Discontinuation in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis. Closely monitor these patients with both clinical and laboratory follow-up for at least several months. Do not recommend discontinuation in patients with advanced liver disease or cirrhosis. Mitochondrial dysfunction: Any child exposed in utero to nucleoside and nucleotide analogues, even HIV negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. Hepatotoxicity: Patients with pre-existing liver dysfunction have increased risk for potentially fatal hepatic adverse reactions. Conduct appropriate laboratory testing prior to initiating Symtuza and monitor patients during treatment. Consider increased AST/ALT monitoring in patients with underlying chronic hepatitis, cirrhosis, or who have pre-treatment elevations of transaminases. Consider discontinuing Symtuza if there is evidence of new or worsening liver dysfunction. Nephrotoxicity: Potential risk of nephrotoxicity cannot be excluded. Renal impairment: Cobicistat has been shown to decrease estimated creatinine clearance. Take this into consideration when Symtuza is used in patients, in whom the estimated creatinine clearance is used to guide aspects of their clinical management. Patients with co-existing conditions: Haemophiliac patients should be made aware of the possibility of increased bleeding. Severe skin reactions: Discontinue Symtuza immediately if signs or symptoms of severe skin reactions develop. Sulphonamide allergy: Use with caution in patients with a known sulphonamide allergy. Weight and metabolic parameters: For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Osteonecrosis: Advise patients to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement. Immune Reactivation Syndrome: Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Opportunistic infections: Patients receiving Symtuza should remain under close clinical observation by physicians. SIDE EFFECTS: Diarrhoea, rash, headache, nausea, fatigue, abdominal pain. Refer to the full prescribing information for other side effects. PREGNANCY & LACTATION: Treatment with darunavir/cobicistat during pregnancy results in low darunavir exposure, which may be associated with an increased risk of treatment failure and an increased risk of HIV transmission to the child. Do not initiate Symtuza during pregnancy, and women who become pregnant during therapy with Symtuza should be switched to an alternative regimen. Mothers should be instructed not to breast-feed if they are receiving Symtuza. INTERACTIONS: Substrates of transporters p-glycoprotein (P-gp), BCRP, MATE1, OATP1B1 and OATP1B3. Medicinal products primarily metabolised by CYP3A. CYP3A inducers and inhibitors. Medicinal products that are eliminated by active tubular secretion. Medicinal products that decrease renal function, or strongly affect P-gp activity and BCRP, or induce P-gp activity, or inhibit P-gp. PLEASE REFER TO FULL PRESCRIBING INFORMATION BEFORE PRESCRIBING. API version to be quoted on promotional material: Symtuza aPI ver 1.0

Odefsey® Tablets
ABBREVIATED PRESCRIBING INFORMATION
ACTIVE INGREDIENT(S): Emtricitabine 200mg/ rilpivirine 25mg/ tenofovir alafenamide 25mg INDICATION(S): Treatment of adults and adolescents (aged ≥12 years with body weight ≥35 kg) infected with HIV-1 without known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, tenofovir or emtricitabine and with a viral load ≤ 100,000 HIV-1 RNA copies/mL. DOSAGE & ADMINISTRATION: One tablet once daily with food. Do not initiate Odefsey in patients with estimated CrCl < 30 mL/min. Discontinue Odefsey in patients with estimated CrCl that declines < 30 mL/min during treatment. Odefsey should be used with caution in patients with moderate hepatic impairment. Odefsey is not recommended for use in patients with severe hepatic impairment. CONTRAINDICATIONS: Hypersensitivity to the active substances or to any of the excipients. Other antiretroviral medicinal products. Other medicinal products containing tenofovir alafenamide, lamivudine, tenofovir disoproxil or adefovir dipivoxil. Medicinal products that can result in significant decreases in rilpivirine plasma concentrations (due to cytochrome P450 [CYP]3A enzyme induction or gastric pH increase), which may result in loss of therapeutic effect of Odefsey, including: carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampicin, rifapentine, omeprazole, esomeprazole, dexlansoprazole, lansoprazole, pantoprazole, rabeprazole, dexamethasone (oral and parenteral doses), except as a single dose treatment, St. John's wort (Hypericum perforatum). SPECIAL WARNINGS & PRECAUTIONS: Virologic failure and development of resistance: Insufficient data to justify use in patients with prior NNRTI failure. Resistance testing and/or historical resistance data should guide the use of Odefsey. Cardiovascular: Odefsey should be used with caution when co-administered with medicinal products with a known risk of Torsade de Pointes. Patients co-infected with HIV and hepatitis B or C virus: Patients with chronic hepatitis B or C treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. Patients co-infected with HIV and HBV who discontinue Odefsey should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. Liver disease: Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy (CART) and 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: In HIV infected patients with severe immune deficiency at the time of institution of CART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Opportunistic infections: Patients receiving Odefsey may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases. Osteonecrosis: Cases of osteonecrosis have been reported particularly in patients with advanced HIV disease and/or long-term exposure to CART. Advise patients to seek medical advice if experience joint aches and pain, joint stiffness or difficulty in movement. Excipients: Odefsey contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take Odefsey. SIDE EFFECTS: Nausea, diarrhea, headache, dizziness, abnormal dreams, insomnia. Refer to the full prescribing information for other side effects. PREGNANCY & LACTATION: It is preferable to avoid the use of Odefsey during pregnancy. It is recommended that HIV infected women do not breast-feed their infants under any circumstances. INTERACTIONS: CYP enzyme inhibitors. QT prolonging medicinal products. PLEASE REFER TO FULL PRESCRIBING INFORMATION BEFORE PRESCRIBING. Odefsey aPI ver 1.0

Janssen, a division of Johnson & Johnson (HK) Ltd
13/F Tower 1, Grand Century Place, 193 Prince Edward Road West, Mongkok, Hong Kong.
Tel: 27361711 Fax: 2736 1926

Janssen Infectious Diseases
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

CP-160430 Jun 2020 AIC-13448

Date / Time	Function	Enquiry / Remarks
1 SAT 2:00 PM	**Facebook Live** **1. Sexuality in COVID-19 Era** **2. Unmet Need on the Management of Erectile Dysfunction and the Role of Avanafil** Organiser: Hong Kong Medical Association; Speaker: Prof Emmanuele A. JANNINI	HKMA CME Department 2527 8285 1 CME Point
3:00 PM	**Facebook Live** **3. Local Experience in Treatment of Erectile Dysfunction** **4. Update on the Management of Premature Ejaculation** Organiser: Hong Kong Medical Association; Speaker: Dr Siu-king MAK, Dr Victor Hip-wo YEUNG	HKMA CME Department 2527 8285 1 CME Point
3 MON 7:00 PM	**Certificate Course in Clinical Cytogenetics and Genetics 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr WONG Wai-shan	Ms. Vienna LAM Tel: 2527 8898
4 TUE 1:30 PM	**Evaluation of Antidepressants Efficacy and Individualized Treatment Approach (Online Symposium)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Prof. Michael LANDGREBE	Ms. Gloria CHEUNG Tel: 2527 8898
2:00 PM	**Facebook Live** **Abdominal Pain Management in Children** Organiser: Hong Kong Medical Association; Speaker: Dr Philip Chak-on SHAM	HKMA CME Department 2527 8285 1 CME Point
5 WED 7:00 PM	**Certificate Course on Update in Clinical Sleep Medicine 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Wing-chi CHAN	Ms. Vienna LAM Tel: 2527 8898
6 THU 7:00 PM	**Certificate Course in Allergy 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Marco Hok-kung HO	Ms. Vienna LAM Tel: 2527 8898
7 FRI 7:00 PM	**Certificate Course on Complaint Management 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Ms Suk-chong LEUNG, Ms Asha SHARMA, Ms Janice DAO	Ms. Vienna LAM Tel: 2527 8898
10 MON 7:00 PM	**Certificate Course in Clinical Cytogenetics and Genetics 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Anita KAN	Ms. Vienna LAM Tel: 2527 8898
12 WED 7:30 AM	**The Hong Kong Neurosurgical Society Monthly Academic Meeting –COVID-19 and Neurosurgery** Organizer: Hong Kong Neurosurgical Society; Speaker(s): Dr CHEUNG Yuk Hong, Eric Chairman: Dr CHEUNG Fung-ching; Venue: Conference Room, F2, Department of Neurosurgery, Queen Elizabeth Hospital; or via Zoom meeting	1.5 points College of Surgeons of Hong Kong Name: Dr Calvin MAK Tel: 2595 6456 Fax. No.: 2965 4061
7:00 PM	**Certificate Course on Update in Clinical Sleep Medicine 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Yat-bong YEUNG	Ms. Vienna LAM Tel: 2527 8898
14 FRI 2:00 PM	**Facebook Live** **Updates on IPV conference 2020 and Male HPV cancer prevention** Organiser: Hong Kong Medical Association; Speaker: Dr Tin-yau WONG	HKMA CME Department 2527 8285 1 CME Point
7:00 PM	**Certificate Course on Complaint Management 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Kai-ming CHOW	Ms. Vienna LAM Tel: 2527 8898
17 MON 7:00 PM	**Certificate Course in Clinical Cytogenetics and Genetics 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Chris Tsun-leung CHAN	Ms. Vienna LAM Tel: 2527 8898
21 FRI 7:00 PM	**Certificate Course on Complaint Management 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Kim-lian ONG	Ms. Vienna LAM Tel: 2527 8898

Answers to Radiology Quiz

Answers:

1. The adrenal glands appear as a pair of V-shaped structures superior and anteromedial to the kidneys on CT scan. The adrenal limbs are thin in calibre (<5mm) and any focal or diffuse thickening is considered abnormal.

2. A small nodule is shown at the lateral limb of the left adrenal gland. The risk of malignancy of an incidental adrenal nodule/ mass is extremely low, reported being 0.0007% in a meta-analysis of 1,040 lesions by Sullivan and colleagues in BMJ in 2018. For comparison, the risk of malignancy of incidental breast, renal and colon masses are quoted as 42%, 25% and 17% respectively in the same paper.

3. The low attenuation of the nodule indicates the presence of fat, favouring a benign lesion such as adenoma or myelolipoma. If the lesion shows no definite fat attenuation, a dedicated triphasic adrenal CT can be performed to calculate the washout ratio to differentiate between adenomas and other lesions.

4. Catheter-guided adrenal venous sampling can be performed at an interventional radiology unit. In this procedure, blood samples are taken from bilateral adrenal veins, and the peripheral venous blood and cortisol and aldosterone levels are measured. Normalised aldosterone levels and lateralisation indices (LI) can then be calculated. A LI greater than four is generally considered sufficient evidence for a culprit functioning adrenal adenoma. Contralateral gland suppression is advocated by some authors as a confirmatory test.

Dr Yan-lin LI
FRCR
Department of Radiology, Queen Mary Hospital

MSD

Delstrigo®

doravirine/lamivudine/ tenofovir disoproxil fumarate

Convenient Dosing[1]

DELSTRIGO

Complete regimen

Tablet not shown at actual size.

* Can be administrated with or without food

- Free to be taken once daily, any time of day
- Free of food restrictions*
- Free of HIV boosters

- Efficacy regardless of baseline viral load[2]
- Significantly fewer neuropsychiatric adverse events vs. comparator in three pre-specified categories[2,#]
- Convenient dosing[1]

Dizziness, Sleep disorders/disturbances and Altered sensorium

Study Design

DRIVE-AHEAD is a phase 3, randomized, non-inferiority trial. Antiretroviral treatment-naive adults were randomized (1:1) to once-daily, fixed-dose DOR at 100 mg, lamivudine at 300 mg, and tenofovir disoproxil fumarate (TDF) at 300 mg (DOR/3TC/TDF) or to efavirenz at 600 mg, emtricitabine at 200 mg, and TDF at 300 mg (EFV/FTC/TDF) for 96 weeks. The primary efficacy endpoint was the proportion of participants with <50 HIV-1 RNA copies/mL at week 48.

Delstrigo Selected Safety Information

Indications: Delstrigo (doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg) is indicated for the treatment of adults infected with HIV-1 without past or present evidence of resistance to the NNRTI class, lamivudine, or tenofovir.

Contraindications: • Hypersensitivity to the active substances or to any of the excipients. Co-administration with medicinal products that are strong cytochrome P450 (CYP)3A enzyme inducers is contraindicated as significant decreases in doravirine plasma concentrations are expected to occur. For the list of contraindicated medicines, please consult the full prescribing information.

Precautions: • NNRTI substitutions and use of doravirine - Doravirine has not been evaluated in patients with previous virologic failure to any other antiretroviral therapy. There is not sufficient clinical evidence to support the use of doravirine in patients infected with HIV-1 with evidence of resistance to the NNRTI class. • Severe acute exacerbation of hepatitis B in patients co-infected with HIV-1 and HBV - All patients with HIV-1 should be tested for the presence of hepatitis B virus (HBV) before initiating antiretroviral therapy. Patients who are co-infected with HIV-1 and HBV should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment with Delstrigo. • New onset or worsening renal impairment - Delstrigo should be avoided with concurrent or recent use of nephrotoxic medicinal products (e.g., high dose or multiple NSAIDs). Persistent or worsening bone pain, pain in extremities, fractures, and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in at risk patients. • Bone loss and mineralization defects - The effects of tenofovir disoproxil associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Assessment of BMD should be considered for HIV-1 infected adult patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. • Co-administration with other antiviral products - Doravirine/lamivudine/tenofovir disoproxil must not be co-administered with other medicinal products containing lamivudine, or with medicinal products containing tenofovir disoproxil, or tenofovir alafenamide, or with adefovir dipivoxil. Use with CYP3A inducers - Caution should be given to prescribing doravirine with medicinal products that may reduce the exposure of doravirine. • Immune reactivation syndrome - Immune reactivation syndrome has been reported in patients treated with combination antiretroviral therapy.

• Lactose - Delstrigo contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Adverse events: • The most frequently reported adverse reactions considered possibly or probably related to doravirine were nausea (4%) and headache (3%). Other common adverse events (≥1% to <10%) associated with doravirine/lamivudine/tenofovir disoproxil include abnormal dreams, insomnia, headache, dizziness, somnolence, cough, nasal symptoms, nausea, diarrhoea, abdominal pain, vomiting, flatulence, alopecia, rash, musculoskeletal pain, fatigue, fever and elevated amylase/lipase. For detailed side effects, please consult the full prescribing information.

Drug interactions: Delstrigo is a complete regimen for the treatment of HIV-1 infection; therefore, Delstrigo should not be administered with other antiretroviral medicinal products. *Effects of other medicinal products on doravirine, lamivudine, and tenofovir disoproxil* • Doravirine - Doravirine is primarily metabolized by CYP3A, and medicinal products that induce or inhibit CYP3A are expected to affect the clearance of doravirine. • Lamivudine - Because lamivudine is primarily eliminated by the kidneys through a combination of glomerular filtration and active tubular secretion, co-administration of drugs (sulfamethoxazole) administered with medicinal products that reduce renal function or compete for active tubular secretion may increase serum concentrations of lamivudine. • Tenofovir disoproxil - Because tenofovir is primarily eliminated by the kidneys through a combination of glomerular filtration and active tubular secretion, co-administration of doravirine/lamivudine/tenofovir disoproxil with medicinal products that reduce renal function or compete for active tubular secretion via OAT1, OAT3 or MRP4 may increase serum concentrations of tenofovir. *Effects of doravirine, lamivudine, and tenofovir disoproxil on other medicinal products* • Doravirine - Doravirine at a dose of 100 mg once daily is not likely to have a clinically relevant effect on the plasma concentrations of medicinal products that are dependent on transport proteins for absorption and/or elimination or that are metabolised by CYP enzymes. • Lamivudine - Lamivudine does not inhibit or induce CYP enzymes. • Tenofovir - Based on the results of in vitro experiments and the known elimination pathway of tenofovir, the potential for CYP-mediated interactions involving tenofovir with other medicinal products is low.

Before prescribing, please consult the full prescribing information.

References: 1. Delstrigo (MK). **2.** Orkin C, Squires KE, Molina JM, et al; and DRIVE-AHEAD Study Group. Doravirine/lamivudine/tenofovir disoproxil fumarate is non-inferior to efavirenz/emtricitabine/tenofovir disoproxil fumarate in treatment-naive adults with human immunodeficiency virus-1 infection: week 48 results of the DRIVE-AHEAD trial. *Clin Infect Dis*. 2019;68(4):535-544.

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ω-3 enriched PN – proven to improve clinical outcomes with excellent safety profile[1]:

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- Significantly reduced infection rate by **39%**

- Available in different bag sizes (Central: 493/986/1477/1970 ml, Peripheral: 1206/1448/1904 ml)
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- All PN prescriptions should include a daily dose of multi-vitamins and trace elements[2,3]
- After surgery, in those patients who are unable to be fed via the enteral route, and in whom total or near total parenteral nutrition is required, a full range of vitamins and trace elements should be supplemented on a daily basis[3]

Approved for children ≥ 2 years

References:
1. L. Pradelli et al. (Clinical Nutrition 33 (2014) 785-792
2. Singer et al. (2009) ESPEN Guidelines on parenteral nutrition: Intensive Care. Clinical Nutrition 28: 387-400
3. Braga et al. (2009) ESPEN Guidelines on Parenteral Nutrition: Surgery. Clinical Nutrition, 28: 378-386
4. Bassaiki HK. Gastroenterology 2009;137(5):92-104
http://www.espen.org/espenguidelines.html

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SMOFlipid® – A 4-oil mix with a well-balanced fatty acid pattern containing purified natural fish oil

+ additional vitamin E
(approx. 200 mg α-tocopherol/liter) to counteract lipid peroxidation and oxidative stress[4]

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EXPERT INTERVIEW

Prof. Liam O'Mahony
Departments of Medicine and Microbiology
APC Microbiome Ireland
National University of Ireland
Cork, Ireland

Read the full interview at:

https://hongkong.wyethnutritionsc.org/expert-interview

The Latest Evidence Linking Early Nutrition and Childhood Allergy Outcomes

What are the mechanisms that link the diet, microbiome and metabolism to the development of the immune system?

Does diversity of the diet play a role in protecting against allergies?

Practical tips for optimising the lifelong health of infants?

Key Points from Prof. O'Mahony

- Microbes in the gut metabolise dietary fibre to produce short chain fatty acids (SCFA), which program and modulate both the innate and adaptive immune system
- Similarly, human milk oligosaccharides (HMOs) are preferentially utilised by bifidobacteria in the infant's gut, and studies show that certain HMO profiles may offer protection against food allergies
- A diverse diet high in fibre, fermented foods and omega-3 fatty acids is recommended to safeguard against childhood allergies and help support the development of a healthy, optimised microbiome

Insert

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1

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2

Nutrition resources for your patients

FULL VERSION

Here is a quick preview to the WNSC HK Immunity Info Card. A full version will be available with nearly 20 other resources in the **WNSC HK Nutrition Toolkit** ! Request a copy now after registering below.

References: 1. Prentice S. Front Immunol. 2018;8:1641. 2. Department of Health. Proteins. Available at: https://www.change4health.gov.hk/en/healthy_diet/facts/calories_nutrients/proteins/index.html. Accessed on 02May2018. 3. Department of Health. Healthy eating during pregnancy and breastfeeding. Available at: http://www.fhs.gov.hk/english/health_info/woman/20036.html. Accessed on 02May2018. 4. Department of Health. Vitamins and health. Available at: https://www.elderly.gov.hk/english/healthy_ageing/healthy_diet/vitamins_and_health.html. Accessed on 02May2018. 5. Department of Health. Vitamins. Available at: https://www.studenthealth.gov.hk/english/health/health_dn/health_dn_vit.html. Accessed on 02May2018. 6. Centre for Food Safety. Nutrient information inquiry. Available at: http://www.cfs.gov.hk/english/nutrient/nutrient.php. Accessed on 02May2018. 7. Australian Government National Health and Medical Research Council. Selenium. Available at: https://www.nrv.gov.au/nutrients/selenium. Accessed on 02May2018.

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