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Infectious Diseases

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Reference: 1. https://www.federalregister.gov/documents/2017/01/12/2017-00199/microbiology-devices-reclassification-of-influenza-virus-antigen-detection-test-systems-intended-for Federal Registrar website with Jan 12, 2017 communication on reclassification entitled "Microbiology Devices; Reclassification of Influenza Virus Antigen Detection Test Systems Intended for Use Directly with Clinical Specimens."

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The Cover Shot

This picture was taken at the Etosha National Park at the end of the Namibia trip. We were patrolling in the park on a jeep with open cabin at the back. There were not as many animals as in the Great Migration in Kenya but there were enough to excite us and to demand extra memory cards for our cameras. Big lens is not required for good photos.

This photo was taken with a 70-200mm F4 lens, with no cropping. The pair of giraffes were spotted strolling leisurely while nibbling fleshy leaves from spiny trees. Our presence immediately alerted them and they cast a suspicious look at us. This interesting composition (with necks crossing) lasts only seconds; you have to be very attentive and quick to capture the moment.

Dr Chun-bon LAW
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Chinese New Year Message from the President

Dr Mario Wai-kwong CHAK

President
The Federation of Medical Societies of Hong Kong

Dr Mario Wai-kwong CHAK

送狗迎豬
祝大家豬年進步！一團和氣！身體健康！

In an auspicious gesture to welcome the Chinese New Year, I would like to share with you what the Federation has accomplished in the past one year.

The Federation of Medical Societies of Hong Kong, as an umbrella society comprising 141 medical, dental, nursing and allied health societies, has remained fully committed to our mission of promoting high-quality medical and health care, advancing medical knowledge, as well as coordinating various continuing educational activities.

For example, a total of 15 certificate courses have been held jointly with respective member societies last year, covering diverse topics and areas with encouraging attendance and positive feedback. Our publication, the Hong Kong Medical Diary, which is delivered to the doorsteps of all registered medical professional colleagues free of charge every month, has continued to provide concise reviews and updated knowledge on specific specialty/subspecialty. The variety of topics covered has aroused ongoing interest in our medical community. The Federation has also continued to pursue the tradition of archiving our Medical Diary in two ways: a bound hard-copy annual edition, as well as incorporating the electronic copies into our website and the internet, adding onto a large body of archived e-copies dating back to the very beginning of the Medical Diary.

In the year 2018, the Federation collaborated with RTHK to run a 12-week series on medical information talk in "Healthpedia"「精靈一點」. The issue editors and one of the authors of each monthly issue of the Hong Kong Medical Dairy were invited to attend the interviews to disseminate medical and healthcare knowledge on the latest patient care concepts and knowledge to the general public.

At the Annual Scientific Meeting 2018, under the theme of "Medical Advances in Community Health", experts coming from the fields of medical ethics and community medicine, for example, Dr Derrick Au, Director of the CUHK centre for Bioethics, Medical Faculty, the Chinese University of Hong Kong, delivered a talk on "Ethical Issues in Community Health" and Professor Tai-hing Lam, Chair Professor of Community Medicine, The University of Hong Kong, delivered a talk on "Electronic Cigarette & New Tobacco products: To Ban or To let free?" All the expert speakers graced the occasion updating our participants on the latest knowledge on and development in various aspects of community health.

To foster the development of palliative and end-of-life services for advanced diseases in Hong Kong, a "Care for the Advanced Diseases Consortium" (Chinese name of the consortium: 晚期病患醫療及各界關顧聯盟), aiming at raising public awareness and uniting key stakeholders, was formed last year. Founding members and advisors include leaders in medicine, nursing, non-governmental organisations and patient associations. Another objective of this consortium is to gather broader views from healthcare professionals, patients and carers. In August 2018, the consortium drafted and submitted a proposal to the Government Policy Innovation and Co-ordination Office.

Apart from offering continuing education, the Federation also provides other important services to our member societies. One of the services of the Federation that is greatly appreciated by member societies is our meeting and conference organising service. In the past one year, the Federation has been invited to be the conference organiser of a total of eleven symposiums and annual scientific meetings for our member societies. One of the highlights last year was the invitation by the Hong Kong Nutrition Association to act as the conference organiser for The 7th Asian Congress of Dietetics held at the Hong Kong Polytechnic University in July 2018, which involved over 700 overseas conference attendees.

To protect the health of our community, especially the health of the younger generations in Hong Kong, a Joint Press Conference for a total ban on e-cigarettes was held on 27 September 2018 to strongly urge the Government to issue a total ban of electronic cigarettes and other new tobacco products, as well as to draw up a timeline for a total ban of conventional cigarette smoking. The press event was met with positive feedback as reflected in our HKSAR Chief Executive policy address.

On the charity side, the Federation's Foundation arm has continued to organise public talks on important health issues such as diabetes mellitus.

Finally, I would like to thank all our Officers, Exco members, Foundation directors, council members and staff of the secretarial board for their stellar efforts and support in past one year. We could not have accomplished all as described above without your kind and dedicated contribution, counting on which we are confident in further excelling in the coming Chinese New Year of the Pig. We look forward to working alongside with you all in the near future.

Once again, on behalf of the Federation, I wish you and your family all the best, and may you all have a happy, healthy, wealthy and prosperous Chinese Year of Pig.

Editorial

Dr Kai-ming CHAN

MBBS(HK), MRCP(UK), DTM&H(UK), PDipID(HK), FHKAM(Medicine), FHKCP, M Sc (Epidemiology and Biostatistics)(CUHK)

Specialist in Infectious Disease

Editor

Dr Kai-ming CHAN

It's my honour to be the Issue Editor of the present issue of the Hong Kong Medical Diary entitled Infectious Disease.

The winter surge of seasonal flu started in Hong Kong in December 2018 and would probably continue as we enter the Year of Swine 2019. I am afraid the Hong Kong healthcare systems are still struggling with the infamous swine flu, which has now been named as pandemic (H1N1) influenza 2009. The best strategy against the seasonal influenza surge is believed to be yearly wide coverage of the influenza vaccines for the high risk groups[1,2]. Along with the advances in diagnostic molecular methods, the identification of pathogens for the upper respiratory tract infections are now becoming precise and accurate. It can be done in an outpatient setting at an affordable cost. I would like to express my gratitude to Dr Julian W. Tang for sharing his views on the clinical utility of Point-of-Care testing in the clinic and at the emergency department. Dr Julian W. Tang is a renowned virologist in Hong Kong, United Kingdom and Singapore with special interests in influenza, and other respiratory viruses, HIV, HCV, CMV and enteric viruses.

Up to 15% of congenital cytomegalovirus (CMV)-infected neonates will develop some form of sensorineural deafness[3]. Thanks once again to Dr Julian W. Tang, who has doubly contributed to this issue by sharing his expertise on congenital CMV infection with us.

HIV infection and related complications in the field of infectious disease is always a hot topic for discussion. Nowadays, HIV infection is managed in a way similar to diabetes mellitus. Median survival of HIV-infected individuals has dramatically improved. In 1996, a 20-year-old newly infected HIV patient was expected to live till the age of 39. In 2011, a 20-year-old newly infected HIV patient is expected to live till 70 years old. The treatment regimens of HIV-infected individuals are also changing from complicated clumsy multiple dosing to once daily. The treatment direction is shifting to balance the cost-effectiveness and side-effects: dual antiretroviral therapy is hence emerging in the new guidelines. I would like to express my heartfelt thanks to Dr Nicholas H. Wong for sharing his experience in and knowledge on these emerging treatment regimens.

Acute diarrhoea is most commonly seen in family medicine and emergency department. The main state of therapy is rehydration and symptomatic support. Antibiotic therapy is not usually indicated and may at times worsen the outcome. Thank you to Dr Chi-ho Ng, a very experienced gastroenterologist, for enlightening us with a practical approach to antibiotic therapy in acute diarrhoea.

Last but not the least, my gratitude goes to Dr Chun-bon LAW, a geriatrician with busy clinical and administrative commitment. Dr Law demonstrated a harmonic balance between heavy clinical work, and family life, while enjoying his leisure and travelling pursuits. In the Section on Lifestyle, Dr Law shared with us his wonderful travel experience in Namibia and thanks to him for sharing his beautifully taken photos. I am indebted to Dr Law for contributing to the cover

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page with a nicely caught precious moment when two giraffes were curiously staring at the camera.

In this month, we celebrate our Chinese Lunar New Year 2019. I would like to take this opportunity to wish all our readers a prosperous year of the Swine. Pig is one of the Zodiac animals representing compassion, generosity and diligence. This year, there is the challenge of African Swine Fever (ASF)[4] sweeping around nearby areas. It is very contagious and can cause extensive financial losses. ASF is a disease of the pig caused by a large DNA virus of the Asfarviridae family, which also infects ticks of the genus Ornithodoros. The good news is that the virus causing ASF luckily does not infect humans. I would like to take this opportunity to wish all our readers a prosperous Year of the Swine.

References

1. WHO position paper on influenza vaccines. Available from: https://www.who.int/wer/2012/wer8747.pdf?ua=1 [Accessed 07/01/2019]
2. Postma MJ et al. Further evidence for favorable cost-effectiveness of elderly influenza vaccination. Expert Review of Pharmacoeconomics and Outcomes Research, 2006, 6:215–227.
3. Shah T, Luck S, Sharland M, Heath P, Lyall H. Fifteen-minute consultation: diagnosis and management of congenital CMV. Arch Dis Child Educ Pract Ed. 2016 Oct; 101(5):232-5. doi: 10.1136/archdischild-2015-309656.
4. World Organisation of Animal Health. African Swine Fever. Available from: http://www.oie.int/en/animal-health-in-the-world/animal-diseases/african-swine-fever/ [Accessed 03/01/2019]

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References:
1. TRUVADA Hong Kong prescribing information (HK-SEP16-US-MAR16). 2. Baeten JM, et al. N Engl J Med 2012;367:399-410. 3. Grant RM, et al. N Engl 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 May 8, 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/arv-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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Congenital Cytomegalovirus (CMV) Infection

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OVERVIEW / INTRODUCTION

Congenital cytomegalovirus (CMV) infection is now recognised as the most important infective cause of undiagnosed sensorineural hearing loss and developmental delay[1,2]. Infection of the foetus can occur at any time during pregnancy via maternal primary or reactivated CMV infection, resulting in disease of varying severity in the foetus.

Cost effectiveness analyses have long shown that antenatal screening for past CMV infection is not sustainable, unlike the same for hepatitis B and HIV infections. This is partly due to the absence of any effective intervention for maternal primary or reactivated CMV infection during pregnancy, and the inability of CMV IgG antibodies to completely protect the mother (and subsequently the foetus) against congenital (i.e. transplacental) CMV infection[3]. Although the severity of disease is likely increased during the first trimester, disease of varying severity (including microcephaly, intracranial calcifications, cataracts, chorioretinitis and blindness, encephalitis, pneumonitis, myocarditis, hepatitis, pancreatitis, thrombocytopaenia, petechial rash, sensorineural deafness, developmental delays), can occur throughout pregnancy[1,4].

Currently, the available interventions for treating maternal primary CMV infection are limited to intravenous immunoglobulin (IVIG) since the standard anti-CMV antiviral drugs (foscarnet, ganciclovir) are contraindicated during pregnancy. However, the evidence for the efficacy of IVIG in treating maternal primary CMV infection is unconvincing[5,6]. Interventions for the newborn with congenital CMV infection are also limited, i.e. to intravenous or oral valganciclovir for 6 weeks to 6 months, and only for babies who have evidence of CMV disease at birth or shortly after (e.g. failed hearing test and/or intracranial calcifications on ultrasound). Yet, there is now increasing evidence of the benefit of longer-term postnatal treatment with ganciclovir and valganciclovir, in terms of reducing the severity of both the hearing loss and developmental delay[1,7,8]. Although a CMV vaccine and other anti-CMV antiviral drugs are in development[9-13], not all expectant mothers or newborns will have access to these; so clinician awareness, careful diagnosis and follow-up of congenital CMV-infected babies, with appropriate and timely treatment, is still essential for optimizing clinical outcomes and quality of life for these congenitally CMV-infected children.

PRIMARY CMV INFECTION

Cytomegalovirus(CMV) is an enveloped, double-stranded DNA (230-240 kbp genome), betaherpesvirus, in the family Herpesviridae. It is usually acquired during childhood asymptomatically, transmitted by contact with infected body fluids, such as saliva (e.g. from mother to child via kissing), as well as via other infectious body fluids (including blood transfusion and organ transplantation), and breast-feeding. The incubation period is thought to be at least 2-3 weeks, which forms the basis for the screening age cut-off in newborns for diagnosing congenital infection, i.e. within the first 3 weeks of life. By child-bearing age (teenagers and young adults), the seropositivity rate can be as low as 40-50% in some populations, increasing to 100% in others[14], thus making a new (primary) CMV infection in pregnancy in CMV-naïve women, a very real possibility in specific populations. Unfortunately, the source of a new CMV infection in the mother is often from the first-born child, who has been infected by other children at their kindergarten or nursery, who then infects the mother whilst she is pregnant with their younger sibling.

As already mentioned, there is currently no licensed vaccine against CMV at present, though several candidates are in development[9,10]. Licensed antiviral drugs against CMV include foscarnet (intravenous only), ganciclovir (intravenous and oral as valganciclovir - but not during pregnancy), and cidofovir (intravenous only - but not during pregnancy). Newer drugs such as maribavir and letermovir are under investigation and/or are in the process of being licensed (letermovir) in some countries now for treatment and prophylaxis (maribavir) or prophylaxis only (letermovir) – though all of these are currently contraindicated in pregnancy[11-13].

RISKS OF CONGENITAL CMV INFECTION

The risk of transplacental transmission of CMV is about 30-40% in primary CMV infection, which drops to about 1% for reactivated CMV infection. Of those babies infected, only about 10% will show overt signs of CMV disease ('symptomatic' disease) at birth, and of these, 60-70% may develop long-term neurological deficits. For the remaining 90% of babies with congenital CMV infection, who are born looking normal at birth ('asymptomatic' disease), up to 15% of these will develop some form of sensorineural hearing loss[1]. Hence, most congenitally-CMV infected babies will

remain asymptomatic and develop normally, without manifesting CMV disease.

DIAGNOSING CONGENITAL CMV INFECTION – IN MOTHER AND BABY

There are generally two phases to diagnosing congenital CMV infection – the diagnosis of maternal CMV infection then the diagnosis of foetal CMV infection. Generally, if there is no maternal CMV infection during pregnancy, congenital CMV infection of the foetus cannot occur.

Pregnant women are not routinely screened for CMV IgG at antenatal booking. Usually screening of the mother-to-be (hereafter referred to as the 'mother') for possible CMV infection arises when an abnormality has been detected during the pregnancy, e.g. during the 20 week morphology scan, or at any time if the mother develops any glandular fever-like, or other febrile rash illness, or deranged liver function tests, with or without other signs of liver disease, such as jaundice, itchy skin and abdominal pain.

Ultrasound findings are notoriously non-specific for congenital CMV infection, and may include echogenic bowel, polyhydramnios (or 'increased liquor volume' or an increased amniotic fluid index), intracranial or other calcification. Such findings will trigger a 'TORCH' serology screen, consisting of paired serological testing of the antenatal booking blood together with a current blood (from around the time of the 20-week morphology scan).

Other viruses to be screened on this serum pair typically include rubella, parvovirus B19 (PB19) as well as CMV, IgG and IgM. If the two sera show differing serological profiles (i.e. different from past CMV and PB19 infection – indicated by CMV or PB19 IgG POS, IgM NEG on both sera), then further investigations may be required – including CMV IgG avidity and amniocentesis with CMV PCR to check for foetal infection. For example, if the booking blood showed CMV IgG NEG, IgM NEG, but the current (20 week) blood shows CMV IgG POS, IgM NEG, this is indicative of CMV IgG seroconversion consistent with primary CMV infection during pregnancy. A CMV IgG avidity test can be performed on the CMV IgG POS sample to check for when the primary CMV infection occurred, e.g. if the CMV IgG avidity is HIGH, then primary CMV infection is unlikely to have occurred within the 3-4 months prior to the CMV IgG POS sample collection date[15], (this open access reference also includes a useful management flowchart).

If maternal CMV infection in pregnancy is confirmed using paired sera and CMV IgG avidity testing, then the question arises of whether the foetus itself has actually been infected, i.e. if transplacental CMV infection has occurred.

Depending on local protocols and the assays and facilities available, once confirmation of maternal primary CMV infection has been obtained, the infected mother may be offered amniocentesis (i.e. invasive sampling of the amniotic fluid for testing for CMV infection – usually by the polymerase chain reaction - PCR) after 20 weeks' gestation, to allow for foetal renal maturity (when CMV will be reliably shed into the amniotic fluid and can be detected)[15]. However, amniocentesis will only be offered if this has the potential to change her decision of whether or not to continue the pregnancy to term. Some mothers will continue their pregnancy to term regardless of any congenital CMV infection risk, and for these mothers, there is no need to offer amniocentesis, which has a low (generally quoted as ~1%, but is operator-dependent) but real risk of foetal loss associated with the procedure. For mothers who decide to carry their pregnancy to term, and instead screen the baby postnatally, a urine or saliva sample should be taken within 3 weeks of birth to test for CMV DNA by PCR[15]. Such mothers may be more willing to accept the low risk of congenital CMV infection which causes disease, and are happy to screen their baby postnatally for congenital CMV infection to allow them to be followed up appropriately – rather than terminate the pregnancy.

LABORATORY TESTING

Nowadays there are many kits and platforms commercially available for testing CMV IgG, IgM, IgG avidity and CMV DNA PCR. Repeat confirmation of maternal sera tested on one or more assays is required to confirm maternal primary CMV infection – prior to amniocentesis being offered. In addition, amniocentesis should not take place until maturation of the foetal renal system, i.e. after 20 weeks' gestation, has occurred. This ensures that a false negative CMV PCR result is not obtained in the case of an immature foetal renal system, if sampled before 20 weeks' gestation. In addition, amniocentesis should not take place until 4-6 weeks after primary maternal CMV infection or after the maternal blood becomes CMV PCR negative, to avoid a false positive result due to the potential contamination of the amniotic fluid by any CMV still circulating in the maternal blood through which the amniotic needle must pass.

In the event that a request for screening for congenital CMV infection is received after the baby has reached 3 weeks of age, if no earlier urine or blood sample has been archived, CMV PCR testing of the Guthrie (dried blood spot) card is the only option.

Not uncommonly, CMV IgG or IgM equivocal serology results are received on the maternal sera. If the profile has not progressed between the booking and the more recent TORCH screen sera, these may be non-specific reactions and careful discussion and further CMV IgG avidity testing on one or both samples may be required, in consultation with the Virology team. This will ensure accurate interpretation of results and appropriate follow up with the local obstetric and/or foetal medicine teams.

FOLLOW-UP AND MANAGEMENT OF CONGENITAL CMV-INFECTED NEONATES

Most babies congenitally (i.e. transplacental or *in utero*) infected with CMV will not be affected by disease. However, there is currently no means to identify which babies will fall into the affected and unaffected category.

The most common manifestations of CMV disease in babies born looking otherwise well are some degree of sensorineural deafness (either unilateral or bilateral) and developmental delays. Thus, any follow-up programme for these babies needs to be long enough (at least several years) to be able to detect these abnormalities. Regular audiology and developmental assessment is a key part of monitoring such children[1,15], but the availability and frequency of such testing will depend on the local resources and expertise available.

Unfortunately, such babies (who appear otherwise normal at birth) may not be screened for congenital CMV infection and may therefore miss the opportunity for early postnatal treatment. Often such screening is performed when a hearing abnormality is detected, but by this time, the optimal treatment window will have passed - usually within the first month of life[1]. In the absence of a universal neonatal screening programme for congenital CMV infection, this is one of the main obstacles to timely detection and treatment of congenital CMV infection, i.e. that abnormalities caused by CMV often take a while to appear by which time, the optimal early treatment window will have passed. As a consequence of this, some countries are now considering universal screening for congenital CMV infection for all newborns, using saliva or urine[16].

References

1. Shah T, Luck S, Sharland M, Kadambari S, Heath P, Lyall H. Fifteen-minute consultation: diagnosis and management of congenital CMV. Arch Dis Child Educ Pract Ed. 2016 Oct;101(5):232-5. doi: 10.1136/archdischild-2015-309656.
2. Williams EJ, Gray J, Luck S, Atkinson C, Embleton ND, Kadambari S, Davis A, Griffiths P, Sharland M, Berrington JE, Clark JE. First estimates of the potential cost and cost saving of protecting childhood hearing from damage caused by congenital CMV infection. Arch Dis Child Fetal Neonatal Ed. 2015 Nov;100(6):F501-6. doi: 10.1136/archdischild-2014-306756.
3. Walker SP, Palma-Dias R, Wood EM, Shekleton P, Giles ML. Cytomegalovirus in pregnancy: to screen or not to screen. BMC Pregnancy Childbirth. 2013 Apr 18;13:96. doi: 10.1186/1471-2393-13-96.
4. Foulon I, Naessens A, Foulon W, Casteels A, Gordts F. Hearing loss in children with congenital cytomegalovirus infection in relation to the maternal trimester in which the maternal primary infection occurred. Pediatrics. 2008 Dec;122(6):e1123-7. doi: 10.1542/peds.2008-0770.
5. James SH, Kimberlin DW. Advances in the prevention and treatment of congenital cytomegalovirus infection. Curr Opin Pediatr. 2016 Feb;28(1):81-5. doi: 10.1097/MOP.0000000000000305.
6. Minsart AF, Smiljkovic M, Renaud C, Gagné MP, Lamarre V, Kakkar F, Boucher M, Boucoiran I. Use of Cytomegalovirus-Specific Hyperimmunoglobulins in Pregnancy: A Retrospective Cohort. J Obstet Gynaecol Can. 2018 Jun 21. pii: S1701-2163(18)30124-5. doi: 10.1016/j.jogc.2018.03.013. [Epub ahead of print]
7. Amir J, Wolf DG, Levy I. Treatment of symptomatic congenital cytomegalovirus infection with intravenous ganciclovir followed by long-term oral valganciclovir. Eur J Pediatr. 2010 Sep;169(9):1061-7. doi: 10.1007/s00431-010-1176-9.
8. Bilavsky E, Shahar-Nissan K, Pardo J, Attias J, Amir J. Hearing outcome of infants with congenital cytomegalovirus and hearing impairment. Arch Dis Child. 2016 May;101(5):433-8. doi: 10.1136/archdischild-2015-309154.
9. Fu TM, An Z, Wang D. Progress on pursuit of human cytomegalovirus vaccines for prevention of congenital infection and disease. Vaccine. 2014 May 7;32(22):2525-33. doi: 10.1016/j.vaccine.2014.03.057.
10. Plachter B. Prospects of a vaccine for the prevention of congenital cytomegalovirus disease. Med Microbiol Immunol. 2016 Dec;205(6):537-547.
11. Melendez DP, Razonable RR. Letermovir and inhibitors of the terminase complex: a promising new class of investigational antiviral drugs against human cytomegalovirus. Infect Drug Resist. 2015 Aug 5;8:269-77. doi: 10.2147/IDR.S79131.
12. Britt WJ, Prichard MN. New therapies for human cytomegalovirus infections. Antiviral Res. 2018 Nov;159:153-174. doi: 10.1016/j.antiviral.2018.09.003.
13. Frange P, Leruez-Ville M. Maribavir, brincidofovir and letermovir: Efficacy and safety of new antiviral drugs for treating cytomegalovirus infections. Med Mal Infect. 2018 Dec;48(8):495-502. doi: 10.1016/j.medmal.2018.03.006.
14. Cannon MJ, Schmid DS, Hyde TB. Review of cytomegalovirus seroprevalence and demographic characteristics associated with infection. Rev Med Virol. 2010 Jul;20(4):202-13. doi: 10.1002/rmv.655.
15. Anonymous. Congenital Cytomegalovirus Infection: Update on Treatment: Scientific Impact Paper No. 56. BJOG. 2018 Jan;125(1):e1-e11. doi: 10.1111/1471-0528.14836.
16. Gantt S, Dionne F, Kozak FK, Goshen O, Goldfarb DM, Park AH, Boppana SB, Fowler K. Cost-effectiveness of Universal and Targeted Newborn Screening for Congenital Cytomegalovirus Infection. JAMA Pediatr. 2016 Dec 1;170(12):1173-1180. doi: 10.1001/jamapediatrics.2016.2016.

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Clinical Utility of Point-of-Care Testing for Influenza and Other Respiratory Viruses

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INTRODUCTION / BACKGROUND

The use of point-of-care tests (POCTs) for the rapid diagnosis of respiratory viruses at the patient bedside has increased significantly in recent years. This is partly due to a wider awareness of such testing and also improvements and a greater availability of such tests, as well as a general recognition that an earlier diagnosis helps with clinical management, e.g. limiting antibiotic use, and earlier discharge, thus freeing up beds[1-3].

Seasonal respiratory viruses include: influenza A (IAV, with currently circulating influenza A/H1N1pdm09 and A/H3N2 subtypes) and B viruses (IBV), respiratory syncytial virus (RSV), parainfluenza viruses types 1-4 (PIV 1-4), adenoviruses (AdVs), human metapneumoviruses (hMPV), human coronaviruses (HCoVs, which include OC43, 229E, HKU1 and NL63 species) and human rhinoviruses (HRVs, of which there are over 100 serotypes).

Depending on the patient condition, these viruses can cause just mild illness in the otherwise healthy individual, or more severe and even life-threatening illness in those with multiple comorbidities (e.g. diabetes, chronic heart, lung and renal diseases, etc.), the immunocompromised (including transplant patients and those on chemotherapy and other forms of immunosuppression), those in intensive care units, and the very old and very young[4].

OPTIONS FOR POCTS

There are two kinds of kits on the market, the cheaper, and usually quicker (less sensitive) antigen-based tests[5,6] versus the more expensive (more sensitive), relatively slower (though this difference is decreasing) molecular tests[7,8]. In addition, the number of virus targets detectable varies significantly between kits, from just IAV and IBV and/or respiratory syncytial virus (RSV) on some, to 15-20 targets on others, with an increased cost per test, accordingly[9].

Generally, the more targets detected, the longer the assay takes and the more it will cost per sample. Most teams just require IAV and IBV and sometimes RSV testing on the POCTs, where immediate treatment (e.g. for influenza) and/or isolation or cohorting (e.g. for RSV bronchiolitis) are required. For immunocompromised patients, testing for PIVs and AdVs are also useful as antiviral treatment in these more severely immunocompromised patients is possible (e.g. with ribavirin and cidofovir, respectively), if needed.

The cost of the POCT per sample is an important consideration. In a hospital setting, clinical teams may be paying twice for testing on the same sample – once on the POCT at the bedside, and again for the laboratory test, which can cover more targets, but which will only be reported out a few days later. Thus, the hospital teams need to consider carefully what the role of the POCT will be and estimate its cost effectiveness in their specific patient settings, e.g. having a POCT result showing an influenza A infection on a throat swab whilst in the Emergency Department (ED) may allow the patient to be discharged home on a treatment course of oseltamivir (Tamiflu), which will save a significant admission cost. Ultimately, the way the POCT is used and its estimated cost-effectiveness will vary between different health care funding environments i.e. whether the patients, insurance company, or government pays fully or partially for the testing and any need for hospitalisation[10-12].

WHERE ARE THEY USED?

Perhaps the most important factor to consider is where the POCT will be placed, for what patients and in what setting, e.g. a primary care (community) setting such as a general practitioner's (GP's) clinic, a hospital ward or outpatient setting, or an ED, as each will use these POCTs for different reasons.

For GPs and other community clinics, a more comprehensive POCT that detects multiple targets may be useful to avoid the lengthy process of taking a sample to be sent to the local diagnostic laboratory and waiting for the report[13]. This usually takes days, after which the result is less relevant to the patient's immediate management. If a result is available within an hour, this is much more clinically useful to the patient and the doctor, and can lead to a reduction in the use of antibiotics as well as early reassurance for the patient that the illness is due to a seasonal viral infection, without the need for a visit to the hospital[14,15]. The cost of the POCT in this situation may not be much different than the laboratory testing (including sample transport and processing), and the earlier diagnosis may avoid the unnecessary use of empirical antibiotics.

In a hospital ward or emergency department setting, such POCTs are often used for a 'diagnose and isolate on treatment' or a 'diagnose and discharge on treatment' pathway for influenza (where antiviral therapy is available), or a 'diagnose and isolate/discharge' pathway, when other, currently untreatable, respiratory viruses (like RSV, PIV, AdV, hMPV, HCoV and HRVs)

are detected. More vulnerable patients, such as those with cystic fibrosis and other forms of chronic lung disease, or the immunocompromised, may be treated with systemic antivirals, and/or still need antibiotic cover (with or without admission), to safeguard against secondary bacterial infections that commonly follow seasonal respiratory virus infections[16,17].

POCTS VERSUS LABORATORY TESTING?

Depending on the status of the institution (regional teaching hospital and/or tertiary referral centre, or local district general hospital, or community GP practice, etc.), there may also be an established diagnostic laboratory that will run its own panel of respiratory virus PCR tests. Although these respiratory panel tests typically include many more virus targets[9,18], the testing at these routine laboratories can take several days (including sample pick-up and transport time), by which time, the patient may have already recovered or deteriorated and already be admitted to hospital.

In a hospital setting, the laboratory testing can be performed on the same residual sample, once the POCT is complete. Thus, the POCT will give a much quicker result (usually within an hour) that can be used for the immediate patient management, whereas the laboratory test can give a wider spectrum of results, including the other (non-influenza, non-RSV) respiratory viruses. The laboratory testing also provides valuable surveillance data for the patient population tested, and for most patients, the results may explain the presenting symptoms sufficiently well to avoid the prescription or ongoing use of unnecessary antibiotics.

POCT EVALUATION, IMPLEMENTATION AND MONITORING

When bringing in a new POCT for the first time, it is important to evaluate its performance within the patient population in which it will be used. Whilst reference to published studies related to the POCT concerned are useful to make the initial choice about which kit to consider for evaluation, local variations in the circulating viruses and other local institutional, patient and staff-related factors (e.g. how samples are taken, the understanding and compliance of the staff in response to the training, work intensities, ability to link the POCT test data into the local laboratory information system network, location of the POCT relative to the staff that need to use it, etc.), may impact on the actual clinical utility and performance of that POCT in that environment.

Within a hospital setting, if the existing diagnostic laboratory already has a routine 'gold standard' assay of the same type (antigen- or molecular- based) against which the POCT can be compared and monitored, this will be ideal.

For the community (GP) clinics, where there is usually no other reference standard, they will necessarily have to rely on the data reported in the kit's user manual, which would have been used for the initial licensing of the POCT, e.g. with the US Food and Drug Administration (i.e. FDA approval), or the European CE-marking schemes. Although most clinics can still send samples to their local reference laboratory for testing to confirm any POCT results, these may take some time to come back.

SUMMARY

Point-of-care-tests can improve patient flow in both hospital and community clinic settings, and if used appropriately, can save both the hospital and patient unnecessary admission and use of antibiotics. However, the selection and application of the POCT in different clinical areas and specialties requires careful consideration to achieve all these benefits – and a poorly performing POCT can cause multiple problems with not only patient flow, but inappropriate isolation and treatment in those who are not truly infected, with false positive results produced by less specific tests; or, perhaps worse, result in missed opportunities for early isolation and treatment, with false negative results produced by less sensitive tests – potentially leading to outbreaks caused by undiagnosed (and therefore untreated and un-isolated) infected index cases being managed on open bays[19].

References

1. Moore C. Point-of-care tests for infection control: should rapid testing be in the laboratory or at the front line? J Hosp Infect. 2013 Sep;85(1):1-7. doi: 10.1016/j.jhin.2013.06.005.
2. Nakao A, Hisata K, Matsunaga N, Fujimori M, Yoshikawa N, Komatsu M, Kikuchi K, Takahashi H, Shimizu T. The clinical utility of a near patient care rapid microarray-based diagnostic test for influenza and respiratory syncytial virus infections in the pediatric setting. Diagn Microbiol Infect Dis. 2014 Apr;78(4):363-7. doi: 10.1016/j.diagmicrobio.2013.11.005.
3. Avril E, Lacroix S, Vrignaud B, Moreau-Klein A, Coste-Burel M, Launay E, Gras-Le Guen C. Variability in the diagnostic performance of a bedside rapid diagnostic influenza test over four epidemic seasons in a pediatric emergency department. Diagn Microbiol Infect Dis. 2016 Jul;85(3):334-337. doi: 10.1016/j.diagmicrobio.2016.03.015.
4. Tang JW, Lam TT, Zaraket H, Lipkin WI, Drews SJ, Hatchette TF, Heraud JM, Koopmans MP; INSPIRE investigators. Global epidemiology of non-influenza RNA respiratory viruses: data gaps and a growing need for surveillance. Lancet Infect Dis. 2017 Oct;17(10):e320-e326. doi: 10.1016/S1473-3099(17)30238-4.
5. Hurt AC, Alexander R, Hibbert J, Deed N, Barr IG. Performance of six influenza rapid tests in detecting human influenza in clinical specimens. J Clin Virol. 2007 Jun;39(2):132-5.
6. Herzum I, Lutz T, Koch F, Geisel R, Gehrt A. Diagnostic performance of rapid influenza antigen assays in patients infected with the new influenza A (H1N1) virus. Clin Chem Lab Med. 2010;48(1):53-6. doi: 10.1515/CCLM.2010.022.
7. Novak-Weekley SM, Marlowe EM, Poulter M, Dwyer D, Speers D, Rawlinson W, Baleriola C, Robinson CC. Evaluation of the Cepheid Xpert Flu Assay for rapid identification and differentiation of influenza A, influenza A 2009 H1N1, and influenza B viruses. J Clin Microbiol. 2012 May;50(5):1704-10. doi: 10.1128/JCM.06520-11.
8. Nolte FS, Gauld L, Barrett SB. Direct Comparison of Alere i and cobas Liat Influenza A and B Tests for Rapid Detection of Influenza Virus Infection. J Clin Microbiol. 2016 Nov;54(11):2763-2766.
9. Babady NE, England MR, Jurcic Smith KL, He T, Wijetunge DS, Tang YW, Chamberland RR, Menegus M, Swierkosz EM, Jerris RC, Greene W. Multicenter Evaluation of the ePlex Respiratory Pathogen Panel for the Detection of Viral and Bacterial Respiratory Tract Pathogens in Nasopharyngeal Swabs. J Clin Microbiol. 2018 Jan 24;56(2). pii: e01658-17. doi: 10.1128/JCM.01658-17.
10. Nelson RE, Stockmann C, Hersh AL, Pavia AT, Korgenksi K, Daly JA, Couturier MR, Ampofo K, Thorell EA, Doby EH, Robison JA, Blaschke AJ. Economic analysis of rapid and sensitive polymerase chain reaction testing in the emergency department for influenza infections in children. Pediatr Infect Dis J. 2015 Jun;34(6):577-82. doi: 10.1097/INF.0000000000000703.
11. Nshimyumukiza L, Douville X, Fournier D, Duplantie J, Daher RK, Charlebois I, Longtin J, Papenburg J, Guay M, Boissinot M, Bergeron MG, Boudreau D, Gagné C, Rousseau F, Reinharz D. Cost-effectiveness analysis of antiviral treatment in the management of seasonal influenza A: point-of-care rapid test versus clinical judgment. Influenza Other Respir Viruses. 2016 Mar;10(2):113-21. doi: 10.1111/irv.12359.

12. You JHS, Tam LP, Lee NLS. Cost-effectiveness of molecular point-of-care testing for influenza viruses in elderly patients at ambulatory care setting. PLoS One. 2017 Jul 27;12(7):e0182091. doi: 10.1371/journal.pone.0182091.
13. Green DA, Hitoaliaj L, Kotansky B, Campbell SM, Peaper DR. Clinical Utility of On-Demand Multiplex Respiratory Pathogen Testing among Adult Outpatients. J Clin Microbiol. 2016 Dec;54(12):2950-2955.
14. Bhavnani D, Phatinawin L, Chantra S, Olsen SJ, Simmerman JM. The influence of rapid influenza diagnostic testing on antibiotic prescribing patterns in rural Thailand. Int J Infect Dis. 2007 Jul;11(4):355-9.
15. Tillekeratne LG, Bodinayake CK, Nagahawatte A, Vidanagama D, Devasiri V, Arachchi WK, Kurukulasooriya R, De Silva AD, Østbye T, Reller ME, Woods CW. Use of Rapid Influenza Testing to Reduce Antibiotic Prescriptions Among Outpatients with Influenza-Like Illness in Southern Sri Lanka. Am J Trop Med Hyg. 2015 Nov;93(5):1031-7. doi: 10.4269/ajtmh.15-0269.
16. Ballinger MN, Standiford TJ. Postinfluenza bacterial pneumonia: host defenses gone awry. J Interferon Cytokine Res. 2010 Sep;30(9):643-52. doi: 10.1089/jir.2010.0049.
17. Weinberger DM, Klugman KP, Steiner CA, Simonsen L, Viboud C. Association between respiratory syncytial virus activity and pneumococcal disease in infants: a time series analysis of US hospitalization data. PLoS Med. 2015 Jan 6;12(1):e1001776. doi: 10.1371/journal.pmed.1001776.
18. Banerjee D, Kanwar N, Hassan F, Essmyer C, Selvarangan R. Comparison of Six Sample-to-Answer Influenza A/B and Respiratory Syncytial Virus Nucleic Acid Amplification Assays Using Respiratory Specimens from Children. J Clin Microbiol. 2018 Oct 25;56(11). pii: e00930-18. doi: 10.1128/JCM.00930-18.
19. Tang JW, Blount J, Bradley C, Donaghy B, Shardlow C, Bandi S, Baxter C, Hunter A, Range S, Lam TT. Impact of a poorly performing point-of-care test during the 2017-2018 influenza season. J Infect. 2018 Nov 5. pii: S0163-4453(18)30318-9. doi: 10.1016/j.jinf.2018.10.013. [Epub ahead of print]

Radiology Quiz

Radiology Quiz

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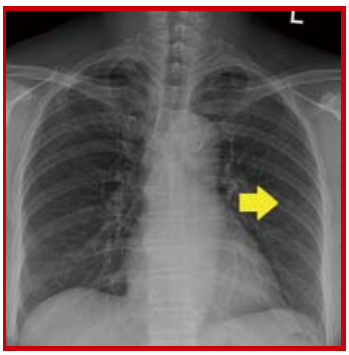

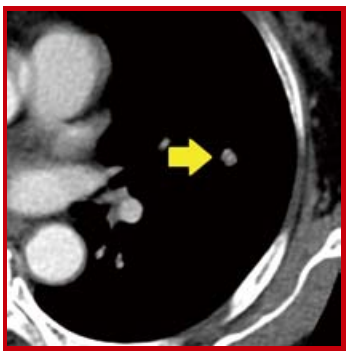

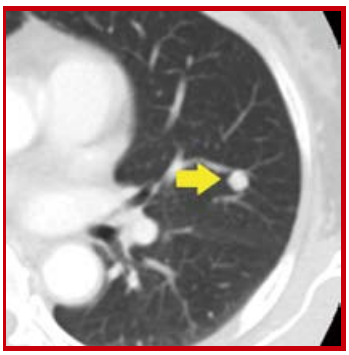

Questions

1. What are the imaging findings in this elderly female patient?
2. What is the diagnosis?
3. What is the treatment?

(See P.32 for answers)

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Two-drug Regimens for HIV – An Old Idea for the Modern Era

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INTRODUCTION

The advent of effective and convenient anti-retroviral therapy (ART) for patients living with HIV has led to significant improvements in life expectancy, which has continued to increase over time.[1] The standard of care since 1996 has generally comprised of a combination of at least three drugs, most commonly two nucleoside analogue reverse transcriptase inhibitors (NRTIs) with either a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), or an integrase inhibitor(INI).[2] During the early years of the HIV pandemic, the use of single and dual NRTI regimens was associated with rapid development of drug resistance and treatment failure[3], and so their use in this manner was not recommended. However, with the arrival of newer, more potent treatment options with higher genetic barriers to resistance, evidence is mounting that some two-drug regimens can be used for long-term management in certain groups of patients.

WHY SHOULD TWO-DRUG REGIMENS BE CONSIDERED?

With the combined effects of improved access to testing, earlier diagnosis and ART, people living with HIV are living much longer lives than before.[4] In the United States, for example, approximately half of all patients living with HIV are over the age of 50,[5] and in Hong Kong, approximately 14% of patients were aged 50 or over at the time of their diagnosis.[6]

As the HIV-positive population ages, other co-morbidities become more common, e.g. hypertension, dyslipidaemia, ischaemic heart disease, osteoporosis, chronic liver disease and osteoporosis.[4] Despite their efficacy in controlling HIV, certain antiretroviral drugs are associated with side effects that can worsen these co-morbidities (e.g. protease inhibitors and dyslipidaemia,[7] tenofovir disoproxil fumarate (TDF) and reduced bone mineral density[8]) and HIV clinicians have a responsibility to maintain a holistic view of their patients' health. Therefore, selecting ART regimens should take all co-morbidities into account. In addition, by reducing the number of medications, the side effects associated with polypharmacy are reduced, as is the potential for drug-drug interactions.[9]

A final reason to consider two-drug regimens is cost – assuming equal effectiveness, it would seem logical to select lower cost options where possible: one trial of 35 treatment-experienced patients who were switched to a combination of dolutegravir (DTG) and rilpivirine (RPV) showed no virological rebound in previously suppressed patients with a €665 drop in annual-per-patient ART costs.[10] A modelling study of dual therapy with DTG and lamivudine (3TC) estimated savings of over US$ 3 billion if 25% of virologically suppressed patients in the USA were switched to DTG + 3TC.[11]

EARLIER TRIALS OF TWO-DRUG REGIMENS

Trials of two-drug regimens in the 1990s generally indicated inferior outcomes for patients on two-drug initiation or maintenance therapy. The ACTG 343 study, completed in 1997, randomised patients who had been virologically suppressed following six months of zidovudine (AZT)/lamivudine (3TC)/indinavir (IDV) to maintenance therapy with either the same regimen (serving as the control), AZT/3TC dual therapy, or IDV monotherapy.[12] Significantly higher failure rates were noted in the dual therapy and monotherapy arms,[13] prompting an early discontinuation of the trial. The inferiority of dual therapy with older protease inhibitors and NRTIs or dual-NRTI therapy was further reinforced by the Trilège trial[14] – in this study, 29 out of 93 patients receiving AZT/3TC and 21 out of 94 patients receiving AZT/IDV developed detectable viral loads having previously been suppressed, compared to 8 out of 92 patients maintained on AZT/3TC/IDV.

EARLY LIMITED SUCCESS WITH DUAL THERAPY

As ART options increased over the following years, different two-drug regimens from different classes were tested. An earlier study in the mid-2000s randomised virologically suppressed patients (n=236) to either lopinavir/ritonavir (LPV/r) + efavirenz (EFV) or two NRTIs + EFV.[15] After over two years of follow up, significantly higher rates of virological failure and adverse effects requiring drug discontinuation were noted in the LPV/r + EFV group.

The SPARTAN study, published in 2012, assigned treatment-naïve patients to either twice daily atazanavir (ATV) + raltegravir (RAL) or ATV/r + TDF/emtricitabine (FTC).[16] 74.6% (47/63) in the ATV + RAL group and 63.3% (19/30) in the ATV/r + TDF/FTC group were virologically suppressed (HIV RNA <50 copies/ml) at 24 weeks, indicating comparable efficacy, but higher rates of hyperbilirubinaemia and mutations associated

with RAL resistance were observed in the ATV + RAL group. Given that four out of the six patients with viral loads above 400 copies/ml at 24 weeks developed RAL resistance, the authors felt further clinical development of this regimen was not warranted.

A larger trial, the NEAT001 study, randomised 805 treatment-naïve patients into two groups, with 401 patients commenced on RAL + darunavir/ritonavir (DRV/r) and 404 patients on DRV/r + TDF/FTC.[17] Treatment failure was observed in 19% and 15% of each group respectively, with a similar frequency of adverse events noted. Five patients in the RAL arm developed INI resistance, while no PI resistance was observed in the TDF/FTC arm. Higher rates of treatment failure in the dual therapy arm were noted in patients with baseline CD4 counts <200 cells/μL or HIV RNA >100,000 copies/ml. A different study involving patients taking DRV/r + RAL also showed higher rates of integrase resistance mutations occurring with viral loads >100,000 copies/ml.[17]

FURTHER DEVELOPMENTS

In more recent years, further trials have demonstrated the potential for two-drug regimens, particularly the combinations of 3TC + boosted PIs or DTG, or DTG combined with other classes. Two main groups have been studied: treatment-naïve patients initiating treatment and suppressed, treatment-experienced patients requiring continuation therapy.

The GARDEL study, published in 2014, demonstrated dual therapy with 3TC + LPV/r was non-inferior to LPV/r + 2 NRTIs in treatment-naïve patients and was also associated with few discontinuations due to side effects.[3] Further proof of effectiveness with 3TC + boosted PI combinations was found in the ANDES trial, which randomised treatment-naïve patients to either 3TC + DRV/r or 3TC/TDF/DRV/r. In this study of 145 patients, only one virological failure was noted in the triple therapy group, with 95% and 97% of the respective groups achieving undetectable viral loads at 24 weeks.[18]

The combination of DTG + RPV has also shown promise, with a recent review of over 900 patients across multiple studies demonstrating over 90% of previously suppressed patients switching to DTG + RPV maintaining suppression along with an improved side effect profile.[19] DTG/RPV is now available as a fixed dose combination (see Fig.1 for a timeline of the approval dates of the various ARVs and combinations available). Additionally, the non-inferiority of DTG + 3TC compared to triple therapy has been supported by the PADDLE-1 and PADDLE-2 trials, which randomly assigned a total of 1,433 treatment-naïve patients with viral loads <500,000 copies/ml to either DTG + 3TC or DTG + TDF/FTC.[18] After 48 weeks of treatment, 91% vs 93% of patients in the respective groups were suppressed.

WHEN CAN A TWO-DRUG REGIMEN BE CONSIDERED?

Key considerations for using two-drug regimens include the patient's CD4 count, current viral load, treatment history, previous resistances, hepatitis B status and, depending on the agents used, the likelihood of pregnancy.

Current national/international guidelines differ slightly in their recommendations on dual therapy. For initiation of treatment, guidelines from the US Department of Health and Human Services only recommend dual therapy options in patients where Abacavir (ABC), tenofovir alafenamide (TAF) and TDF cannot be used[18]. The first recommended two drug regimen is 3TC + DTG in treatment-naïve patients with viral loads <5,000,000 copies/ml. DRV/r + 3TC is listed as an alternative option, but is less strongly recommended. DRV/r + RAL is also recommended in patients with viral loads <100,000 and a CD4 count of over 200 cells/mm^3. Finally, LPV/r + 3TC is listed as a final option where none of the previous combinations can be used. The European AIDS Clinical Society (EACS) also lists 3TC + DTG and boosted DRV + RAL as possible initiation regimens with the same conditions as those detailed in the US guidelines.[20] Conversely, the British HIV Association (BHIVA) only recommends the DRV/r + RAL regimen, but under the same circumstances.[17]

For suppressed patients requesting a regimen switch, the US guidelines list DTG + RPV as an option for patients without chronic hepatitis B, evidence of resistance to either drug and any drug-drug interactions. The fixed dose combination of DTG/RPV is licensed as a replacement regimen in suppressed patients, approved by both the US Food and Drug Administration and the European Commission. Consideration is also given to regimens with boosted PIs and either 3TC or FTC. Two-drug regimens are not recommended at present for patients with any history of treatment failure, even if currently suppressed. This approach is similar to that recommended by EACS, which lists DTG + RPV or 3TC + boosted PI as dual therapy options. BHIVA guidelines only suggest a boosted PI with 3TC as an alternative to a three-drug regimen in suppressed patients.

Specific combinations to avoid when formulating a two-drug regimen are listed by EACS. These include: single NRTI + single NNRTI or unboosted PI or RAL, dual NRTIs, maraviroc (MVC) + RAL, MVC + boosted PIs, and RAL + boosted ATV.[20]

CONCLUSION

While previously associated with treatment failure and the development of resistance, two-drug regimens using new combinations of ART classes have been demonstrated as viable treatment options, particularly for lower risk patients. In particular, their use can be considered in virologically suppressed patients requiring treatment simplification, and significant cost savings may result from wider use of two-drug regimens for HIV. It remains essential, however, to take individual patient circumstances into account when offering this as the treatment option. Additional, larger trials of dual therapy are needed to ensure long-term outcomes are equivalent to the gold standard of triple therapy.

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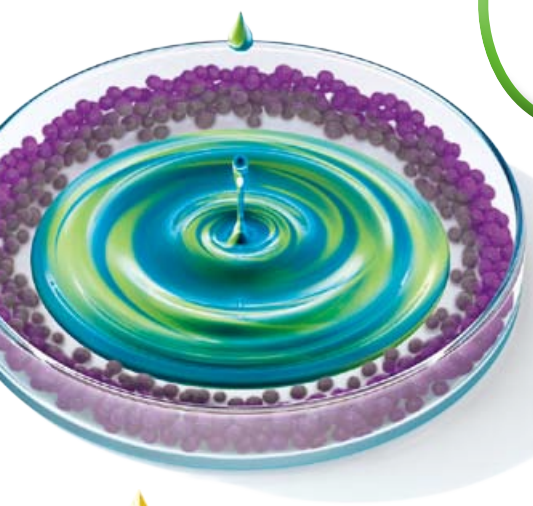

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References:

1. Lodise TP, Low DE. *Drugs* 2012;72:1473–1493. **2.** Laudano JB. *J Antimicrob Chemother* 2011;66(Suppl 3):iii11–iii18. **3.** Frampton JE. *Drugs* 2013;73:1067–1094. **4.** Zhong N, et al. *Lancet Infect Dis* 2015;15:161–171. **5.** ZINFORO™ (ceftaroline fosamil) Prescribing Information. Pfizer Corporation Hong Kong Limited: Version July 2017.

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PRESENTATION: Each vial contains ceftaroline fosamil acetic acid solvate monohydrate equivalent to 600 mg ceftaroline fosamil. **INDICATIONS:** Treatment for complicated skin and soft tissue infections (cSSTI) and community-acquired pneumonia (CAP) in adults and children from the age of 2 months. **DOSAGE: Age >12 years with bodyweight ≥33kg:** 600 mg administered q12h by intravenous infusion over 60 minutes. Increase to 600 mg q8h using 2 hours infusion for treatment of cSSTI due to S. aureus with ceftaroline MIC is 2 or 4 mg/L. **Age ≥ 12 years to < 18 years with body weight <33kg:** 12 mg/kg q8h over 60 minutes. **Age ≥ 2 years to < 12 years:** 12mg/kg q8h over 60 mins. **Age ≥ 2 months to < 2 years:** 8mg/kg q8h over 60 minutes. The recommended treatment duration for cSSTI is 5 to 14 days and for CAP is 5 to 7 days. Please refer to prescribing information for dose adjustment in patients with creatinine clearance ≤ 50 ml/min. **CONTRAINDICATIONS:** Hypersensitivity to ceftaroline fosamil or any excipients (e.g. arginine). Hypersensitivity to the cephalosporin class of antibacterials. Immediate and severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial agent (e.g. penicillins or carbapenems). **WARNINGS & PRECAUTIONS:** Hypersensitivity reactions. In patients with history of hypersensitivity reaction to cephalosporins, penicillins or other beta-lactam antibacterials. *Clostridium difficile*-associated diarrhea. In patients with pre-existing seizure disorders. Possible development of a positive direct antiglobulin test (Coombs test) and potential risk of haemolytic anaemia. **INTERACTIONS:** The interaction potential of ceftaroline or ceftaroline fosamil on medicinal products metabolized by CYP450 enzymes is expected to be low since they are not inhibitors nor inducers of CYP450 enzymes *in vitro*. Ceftaroline or ceftaroline fosamil are not metabolized by CYP450 enzymes *in vitro*, therefore co-administered CYP450 inducers or inhibitors are unlikely to influence the pharmacokinetics of ceftaroline. Ceftaroline is neither a substrate, nor an inhibitor of renal uptake transporters (OCT2, OAT1, and OAT3) *in vitro*. Therefore, interactions of ceftaroline with medicinal products that are substrates or inhibitors of these transporters would not be expected. **PREGNANCY AND LACTATION:** Limited data for use in pregnant women. Preferable to avoid the use during pregnancy unless treatment with an antibiotic with Zinforo's antibacterial profile required. It is unknown whether ceftaroline fosamil or ceftaroline is excreted in human milk. Discontinue either breast-feeding or Zinforo therapy taking into account the benefit of therapy for the woman. **COMMON SIDE EFFECTS:** Coombs direct test positive, rash, pruritus, headache, dizziness, diarrhoea, nausea, vomiting, abdominal pain, increased transaminases, pyrexia, infusion site reactions (erythema, phlebitis, pain).
Reference: ZINFORO HK PI (version: July 2017)
Date of preparation: Dec 2017
Identifier number: ZINF1217
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ECIL = European Conference on Infections in Leukemia. IDSA = Infectious Diseases Society of America. IMPACT = Interhospital multi-disciplinary programme on antimicrobial chemotherapy.

References
1. Ho PL, et al. (ed). 2017. Reducing bacterial resistance with IMPACT, 5th edition, Hong Kong. 2. Pappas PG, et al. Clin Infect Dis 2016;62:e1-e50. 3. Tissot F, et al. Haematologica 2017;102:433-444. 4. Reboli AC, et al. N Engl J Med 2007;356:2472-2482. 5. Ruhnke M, et al. Clin Microbiol Infect 2012;18:680-687. 6. Kett DH, et al. Critical Care 2011;15:R253. 7. Kofla G and Ruhnke M. Eur J Med Res 2011;159-166. 8. Raasch RH. Anti-infect Ther 2004;2:499-508. 9. Eraxis® (anidulafungin) Prescribing Information. Pfizer Corporation Hong Kong Limited Version February 2017.

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1. TRADE NAME: ERAXIS (anidulafungin) POWDER FOR INJECTION **2. PRESENTATION:** Each vial contains 100 mg anidulafungin. Refrigerate at 2°C to 8°C. Do not freeze. **3. INDICATIONS:** Treatment of invasive candidiasis in adult patients. **4. DOSAGE & ADMINISTRATION:** Single 200mg loading dose on Day 1, followed by 100mg daily dose thereafter. Antifungal therapy should be based on the patient's clinical response but generally should continue for at least 14 days after last positive culture. Must be reconstituted with sterile water for injection and subsequently diluted only with 5% Dextrose Inj., USP or 0.9% NaCl Injection, USP (normal saline). No dosage adjustments are required for patients with any degree of renal/ hepatic insufficiency or those in other special populations (see full prescribing information for more details) **5. CONTRAINDICATIONS:** Known hypersensitivity to active substance, any of the excipients, or other echinocandins. **6. WARNINGS & PRECAUTIONS:** Hepatic effects: monitor for evidence of worsening hepatic function and evaluate for risk/benefit of continuing therapy. Anaphylactic reactions. Infusion-related reactions. Patients with rare hereditary problems of fructose intolerance should not take this medicine. **7. INTERACTIONS:** Not a clinically relevant substrate , inducer, or inhibitor of cytochrome P450 isoenzymes. No dosage adjustment of either drug is recommended when anidulafungin is co-administered with voriconazole,tacrolimus,amphotericin B,rifampin or ciclosporine. **8. PREGNANCY AND LACTATION:** Not recommended in pregnancy. Animal studies have shown excretion of anidulafungin in breast milk. A decision on whether to continue/discontinue breast-feeding or therapy with anidulafungin should be made taking into account the benefit of breast-feeding to the child and the benefit of anidulafungin to the mother. **9. COMMON SIDE EFFECTS:** Hypokalaemia, diarrhea, nausea, hyperglycaemia, convulsion, headache, hypotension, hypertension, bronchospasm, dyspnea, vomiting, alanine aminotransferase increased, blood alkaline phosphatase increased, aspartate aminotransferase increased, blood bilirubin increased, cholestasis, rash, pruritus, blood creatinine increased.
Reference: HK PI (version date FEB2017) Date of preparation: OCT2017 Identifier number: ERAW1017
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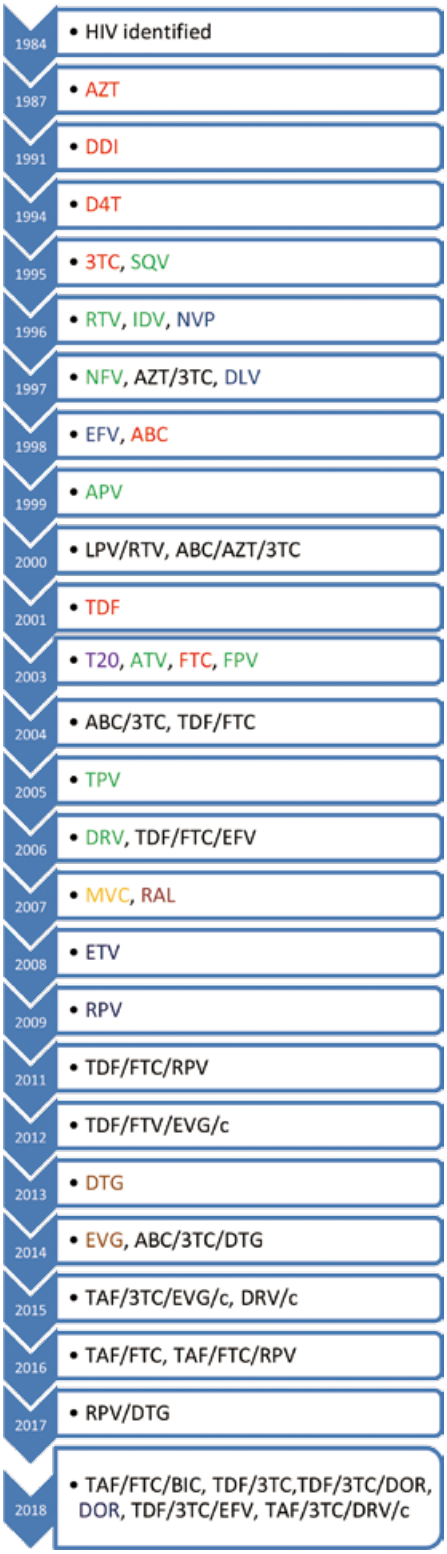

Fig. 1. Timeline of ARVs by year of FDA approval. Key: NRTI, NNRTI, PI, fusion inhibitor, INI, CCR5 inhibitor, fixed dose combination (Timeline Summerised from reference 21,22)

References

1. Teeraananchai S, Kerr SJ, Amin J, et al. Life expectancy of HIV-positive people after starting combination antiretroviral therapy: a meta-analysis. HIV Med. 2017 Apr;18(4):256-266.
2. World Health Organisation, July 2018. Updated Recommendations on First-Line and Second-Line Antiretroviral Regimens and Post-Exposure Prophylaxis and Recommendations on Early Infant Diagnosis of HIV. Available from: http://www.who.int/hiv/pub/guidelines/ARV2018update/en/ [Accessed 21/10/2018]
3. Baril JG, Angel JB, Gill MJ,et al. Dual Therapy Treatment Strategies for the Management of Patients Infected with HIV: A Systematic Review of Current Evidence in ARV-Naive or ARV-Experienced, Virologically Suppressed Patients. PLoS One. 2016 Feb 5;11(2):e0148231
4. Wing EJ. HIV and Ageing. Int J Infect Dis. 2016 Dec;53:61-68.
5. Centers for Disease Control and Prevention, September 2018. HIV Among People Aged 50 and Older. Available from: https://www.cdc.gov/hiv/group/age/olderamericans/index.html [Accessed 23/10/18]
6. Virtual AIDS Office of Hong Kong, August 2018. HIV Surveillance and Epidemiology. https://www.aids.gov.hk/english/surveillance/latest_stat.htm [Accessed 23/10/18]
7. Feeney ER, Mallon PWG. HIV and HAART-Associated Dyslipidemia. Open Cardiovasc Med J. 2011; 5: 49–63.
8. Grant PM, Cotter AG. Tenofovir and Bone Health. Curr Opin HIV AIDS. 2016 May; 11(3): 326–332.
9. Yendewa GA, Salata RA. Hot News: Ready for HIV Dual Therapy? - New Data from International HIV/AIDS Society 2017. AIDS Rev. 2017 Oct-Dec;19(3):167-172.
10. Revuelta-Herrero JL, Chamorro-de-Vega E, Rodríguez-González CG et al. Effectiveness, Safety, and Costs of a Treatment Switch to Dolutegravir Plus Rilpivirine Dual Therapy in Treatment-Experienced HIV Patients. Ann Pharmacother. 2018 Jan;52(1):11-18.
11. Girouard MP, Sax PE, Parker RA, et al. The Cost-effectiveness and Budget Impact of 2-Drug Dolutegravir-Lamivudine Regimens for the Treatment of HIV Infection in the United States. Clin Infect Dis. 2016 Mar 15;62(6):784-91.
12. ClinicalTrials.gov, US National Library of Medicine. A Study of Three Treatment Combinations Using Zidovudine Plus Lamivudine Plus Indinavir in HIV-Infected Patients. Available from: https://clinicaltrials.gov/ct2/show/NCT00001084 [Accessed 21/10/2018]
13. Bowersox J. ACTG 343: three drugs better than two for maintaining HIV suppression. NIAID AIDS Agenda. 1998 Mar:1-2, 10-1.
14. Pialoux G, Raffi F, Brun-Vezinet F, et al. A randomized trial of three maintenance regimens given after three months of induction therapy with zidovudine, lamivudine, and indinavir in previously untreated HIV-1-infected patients. Trilège (Agence Nationale de Recherches sur le SIDA 072) Study Team. N Engl J Med. 1998 Oct 29;339(18):1269-76.
15. Fischl MA, Collier AC, Mukherjee AL, et al. Randomized open-label trial of two simplified, class-sparing regimens following a first suppressive three or four-drug regimen. AIDS. 2007 Jan 30;21(3):325-33.
16. Kozal MJ, Lupo S, DeJesus E, et al. A nucleoside- and ritonavir-sparing regimen containing atazanavir plus raltegravir in antiretroviral treatment-naïve HIV-infected patients: SPARTAN study results. HIV Clin Trials. 2012 May-Jun;13(3):119-30.
17. British HIV Association. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015 (2016 interim update). Available at: https://www.bhiva.org/file/RVYKzFwyxpgiI/treatment-guidelines-2016-interim-update.pdf [Accessed 15/11/18]
18. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Department of Health and Human Services. Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf Accessed [14/11/18] Timeline References:
19. Casado JL, Monsalvo M, Rojo AM et al. Dolutegravir and rilpivirine for the maintenance treatment of virologically suppressed HIV-1 infection. Expert Rev Clin Pharmacol. 2018 Jun;11(6):561-570.
20. European AIDS Clinical Society. Guidelines Version 9.1 October 2018. Available at http://www.eacsociety.org/files/2018_guidelines-9.1-english.pdf [Accessed 15/11/18] Timeline references:
21. US Food and Drug Administration, Aug 2018. HIV Timeline and History of Approvals. Available from: https://www.fda.gov/forpatients/illness/hivaids/history/default.htm [Accessed 3/11/2018]
22. US Department of Health and Human Services, AIDSinfo. September 2018. FDA Approval of HIV Medicines. Available from: https://aidsinfo.nih.gov/understanding-hiv-aids/infographics/25/fda-approval-of-hiv-medicines [Accessed 3/11/2018]

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Antibiotic Treatment in Acute Diarrhoea: A Practical Approach

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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 28 February 2019.

INTRODUCTION

Acute infective diarrhoea (AID) is defined as acute onset (onset of < 14 days) diarrhoea (passing of minimum of three loose stools per day) due to infective aetiology (detection of viral, bacterial or parasite pathogens in stool). In Hong Kong, AID remains a very common problem encountered in our daily practice[1]. The aim of this article is to review the management of acute infective diarrhoea in adults in the industrialised society, with special focus on the role of antibiotics. The management of chronic diarrhoea or acute diarrhoea in children is beyond the scope of this article.

Acute infective diarrhoea (AID) can be subdivided into community-acquired diarrhoea, traveller's diarrhoea and hospital-acquired diarrhoea.

COMMUNITY-ACQUIRED AID

In industrialised countries, the leading causes of community-acquired bacterial diarrhea include non-typhoidal Salmonella, non-cholera Vibrio species, Enteropathogenic Escherichia coli (EPEC), Campylobacter and Enteroaggregative Escherichia Coli (EAEC)[2]. Other common pathogens include Plesiomonas species, Aeromonas species and Shigella species[3].

Most cases of AID are self-limiting and do not required medical attention. Microbiological testing for the cause of diarrhoea is usually not necessary except for those with severe disease (e.g. fever > 72 hours, dysentery or dehydration). The initial treatment of acute diarrhoeal illness must include rehydration with oral electrolyte solutions or intravenous fluids. Antibiotics are not required in most cases and any consideration of antibiotic treatment must be carefully weighted against potential adverse consequences. Nonetheless, empirical antibiotic treatment can be useful in certain circumstances with good understanding of the local disease epidemiology and resistance pattern of enteropathogens.

Quinolones, which have been extensively used as empirical antibiotic for AID, are effective against all the usual bacterial causes of infective diarrhoea: Escherichia coli, Salmonella, Shigella, Vibrio parahaemolyticus, Yersinia, Aeromonas and Plesiomonas (except for Campylobacter, which will be discussed below). Previous studies have demonstrated that empirical treatment with short course of oral fluoroquinolone (e.g. 5 days) in the early stage of disease has favourable effect on disease severity and duration, independent of cultures results[4]. However, empirical treatment approach has been associated with several drawbacks: First, metanalysis has confirmed that antibiotics cannot reduce the length of illness in otherwise healthy patients with non-severe disease caused by non-typhoidal salmonella[5]. In addition, in those infections caused by non-typhoidal salmonella, usage of antibiotics delays the elimination of bacteria. Secondly, empirical antibiotics induces resistance in Campylobacter. Global data showed that the percentage of Campylobacter isolates that are resistant to quinolones has significantly risen in the past few decades. Thirdly, there are data suggesting a relationship between the use of antibiotics and the development of haemolytic uraemic syndrome (HUS) in patients infected with Escherichia coli O157:H7 or other Shiga toxin-producing Escherichia Coli (STEC), especially in the children group.

Because of these reasons, empirical antimicrobials should be considered only in selected patient groups: six or more stools per day, fever, bloody diarrhoea, symptoms persisting for >1 week, or immunocompromised status. In United states, empirical treatment options include azithromycin, fluoroquinolones, and Rifaximin. The common antibiotic regimens suggested by The American College of Gastroenterology are summarised as follows (Table1) reproduced from Ref 6:

Table 1. Common antibiotic regimens for AID [6] (reproduced from Ref 6)

Antibiotic	Oral Daily dose	Treatment duration
Levofloxacin	500mg	1 day or 3 days
Ciprofloxacin	750 mg	1 day
	500 mg	3 days
Azithromycin Δ	1000 mg	1 day
	500 mg	3 days
Rifaximin ©	200 mg three times per day	3 days

Δ Preferred regimen for dysentery or febrile diarrhoea
© Do not use if there is clinical suspicion of Campylobacter, Salmonella, Shigella or other causes of invasive diarrhoea.

SPECIFIIC PATHOGENS

CAMPYLOBACTER

Most Campylobacter species can infect humans and cause disease. The bacterium's main reservoir is

poultry; humans can contract the disease by eating contaminated food or by coming in contact with asymptomatic animal. More than a dozen species of Campylobacter have been implicated in human disease, with C. jejuni and C. coli being the most common.

Campylobacter is sensitive to the acidic environment of stomach and therefore the infective dose is relatively high in normal individuals with intact stomach acid production. On the other hand, those with impaired stomach acidity, including people taking proton pump inhibitor or post-gastrectomy patients are more susceptible to the infection. The incubation period is 24–72 hours. The sites of tissue injury include the jejunum, the ileum, and the colon. The organism produces diffuse, bloody, oedematous, and exudative enteritis. Typically, it induces an inflammatory type of diarrhoeal symptoms with fever, abdominal pain and bloody diarrhoea. However, diarrhoea can be minimal or absent in some cases, especially in young children. The overall feature can mimic appendicitis (called Pseudo-appendicitis) with intense pain and right lower quadrant tenderness due to acute ileocecitis. Campylobacter infection can also lead to two late complications, namely reactive arthritis, Guillain–Barré syndrome and rarely gut perforation.

Owing to the introduction of fluoroquinolones in veterinary medicine, fluoroquinolone-resistant campylobacter strains have become increasingly prevalent. The resistance problem is more prominent in Asian countries. A study from Thailand showed that up to 85% of Campylobacter strains are resistance to fluoroquinolones. Laboratory analysis of isolates of Campylobacter jejuni from Hong Kong showed similar rate of resistance to fluoroquinolones[7]. Given the self-limiting nature of disease and high rate of antibiotic resistance, treatment of campylobacter enteritis with antibiotic is warranted only for those severe disease (e.g. bloody diarrhoea, high fever, extraintestinal manifestation) or high-risk patients (e.g. elderly, pregnant, immunocompromised). Azithromycin should be the drug of choice given the high rate of fluoroquinolone resistance in most part of the word.

NONTYPHOIDAL SALMONELLA

Nontyphoidal Salmonella are a major cause of gastroenteritis in Hong Kong. It is commonly due to ingestion of contaminated poultry, eggs and milk products. The incubation is around 8 to 72 hours and the clinical features are indistinguishable from gastroenteritis induced by other pathogens. Since less than 5 percent of salmonella-infected patients develop invasive disease like bacteraemia, antibiotics are usually not required in immunocompetent individuals without clinical features of severe disease. In addition, previous study has shown that antibiotic usage may prolong the excretion of bacteria and cause more relapse of diarrhoea. The paradoxical finding has been thought to be due to deleterious effect of the antibiotics on normal bowel flora, which protects against the colonisation with enteric pathogen. If antibiotics is warranted, fluoroquinolones can be considered first choice because of its high tissue and intracellular penetration. Other options include trimethoprim-sulfamethoxazole and azithromycin. For those with severe disease who require intravenous therapy, third generation cephalosporin and fluoroquinolones can be considered.

ENTEROHAEMORRHAGIC E COLI (EHEC)

Enterohaemorrhagic Escherichia coli (EHEC) strains pose a specific virulence property, namely Shiga toxin, and therefore they are also referred to as Shiga toxin-producing E. Coli (STEC). In general, Shiga producing E Coli can be divided into serotype O157:H7 and Non O157 serotype. The pathogenesis of EHEC consists of bacterial attachment to the intestinal epithelium and secretion of Shiga toxin that causes vascular damage and systemic symptoms. The toxin invades the endothelial cell of vessels, podocytes, renal epithelium and thalamus of brain, which in turn lead to haemolysis, thrombosis, acute renal injury, thrombocytopenia and neurological manifestation of haemolytic uraemic syndrome. Treatment of EHEC is mainly supportive. There may be a role for plasma exchange and eculizumab (a monoclonal antibody that blocks complement activity by cleavage of C5) in patients with central nervous system involvement.

Treatment of EHEC with antibiotics does not ameliorate the infection, and in some studies, antibiotics treatment has been associated with development of HUS, especially in children. The plausible reason of such association is because antibiotics increase the release of Shiga toxin from injured bacteria in the intestine, making the toxin more available for absorption. It is important to avoid antibiotics in children who may be infected with EHEC.

TRAVELLERS' DIARRHOEA

Between 20% and 50% of travellers from industrialised countries to resource-restricted nations experienced travellers' diarrhoea[8]. Bacterial enteropathogens account for 80% of the cases of travellers' diarrhoea. Enterotoxigenic E. coli (ETEC), Enteroinvasive E. coli (EIEC) and Enteroaggregative E. coli (EAEC) are implicated in most cases, followed by Campylobacter, Salmonella and Shigella[9]. Parasitic agents are uncommon causes of acute travellers' diarrhoea but should be suspected in the case of a subacute or chronic illness.

PROPHYLAXIS

Antimicrobial prophylaxis should not be used routinely in travellers because of concerns about the development of antibiotic resistance, the demonstrated limited efficacy of empiric therapy after the development of symptoms, and the associated potential adverse effects. It should be considered in travellers at high risk of health-related complications, such as in immunosuppressed patients or HIV patients with CD4< 200. Three agents have been proven to be useful in preventing travellers' diarrhoea, namely Bismuth Subsalicylate, Rifaximin and Fluoroquinolones. Bismuth subsalicylate (BSS) has been studied using four divided doses of either 2.1 g/day or 4.2 g/day (with meals and at bedtime). A lower divided dose of 1.05 g/day has also been shown to be preventive, although it is unclear whether it is as effective as the higher doses. However, its usage has been limited by its side effects. Fluoroquinolones, which were consistently demonstrated to be effectiveness in preventing travellers' diarrhoea in the past, are now fading out

because of its association with tendinopathies and its systemic broad-spectrum nature causing selection of resistance strains. Rifaximin may be the best option in view of its good safety profile and non-systemic absorption.

TREATMENT

Most of the travellers' diarrhoea do not require specific treatment. Severe and persistent disease or immunodeficient travellers can be treated with antibiotics plus loperamide combination. Trimethoprim–sulfamethoxazole (TMP-SMZ) were used in the past but the development of resistance decreases the efficacy of treatment and therefore are no longer recommended. Currently, three drugs are commonly prescribed to travelers as self-medication: Fluoroquinolones, Azithromycin, and Rifaximin.

As empiric therapy, the fluoroquinolones e.g. ciprofloxacin, levofloxacin, are proven to be effective, and it allows single dose regimen. However, increasing microbial resistance among Campylobacter isolates has limited their usefulness in many destinations, particularly in South and Southeast Asia. Moreover, increasing fluoroquinolone resistance has been reported in other destinations and in other bacterial pathogens, including Shigella and Salmonella. More importantly, the safety concern of fluoroquinolones has rendered it a less favourable option for treating travellers' diarrhoea.

Rifaximin, a non-absorbed rifamycin, has been shown to be effective in the treatment of travellers' diarrhoea caused by non-invasive pathogens. However, its usage has been limited by the concern of the development of rifampin-resistant staphylococci strain. Moreover, since it is often difficult for travellers to distinguish between invasive and noninvasive diarrhoea, and they would have to carry a backup drug in the event of invasive diarrhoea, the overall usefulness of rifaximin as empiric self-treatment remains to be determined.

Azithromycin may be the best option for treating traveller's diarrhoea of undetermined type and without the access of laboratory or microbiology investigation. Azithromycin taken as single dose of 1000 mg appeared to be as effective as quinolones for the treatment of travellers' diarrhoea[10], but side effects (mainly nausea) may limit the acceptability of this large dose. Giving azithromycin as 2 divided doses on the same day may limit this adverse event.

Consensus guidelines have been developed by the International Society of Travel Medicine and are summarised as follows (Table 2 & 3)[11]:

Table 2. Severity grading of traveller's diarrhoea (reproduced from Ref 11)

Grading of severity of travellers' diarrhoea
Mild: diarrhoea that is tolerable, is not distressing, and does not interfere with planned activities.
Moderate: diarrhoea that is distressing or interferes with planned activities.
Severe: diarrhoea that is incapacitating or completely prevents planned activities; all dysentery is considered severe.

Table 3. Travellers' diarrhoea treatment recommendations (reproduced from Ref 11)

Mild disease:
Antibiotic treatment is not recommended in patients with mild travellers' diarrhoea. Loperamide may be considered in the treatment of mild travellers' diarrhoea.
Moderate disease:
Antibiotics may be used to treat cases of moderate travellers' diarrhoea. Options include: Fluoroquinolones, Azithromycin and Rifaximin Loperamide may be used as adjunctive therapy for moderate to severe travellers' diarrhoea.
Severe disease:
Antibiotics should be used to treat severe travellers' diarrhoea. Azithromycin is preferred to treat severe travellers' diarrhoea. Fluoroquinolones may be used to treat severe, non-dysenteric travellers' diarrhoea. Rifaximin may be used to treat severe, non-dysenteric travellers' diarrhoea.

HOSPITAL ACQUIRED DIARRHOEA

Diarrhoea is common among hospitalised patients, and the causes are distinct from those of diarrhoea in the community. Clinicians should recognise that most cases of nosocomial diarrhoea have a noninfectious aetiology, including medications, underlying illness, alternation of bowel anatomy due to surgery, and enteral feeding.

Toxigenic Clostridium Difficile Infection (CDI) is a major cause of infective nosocomial diarrhoea. Since the spore of the bacteria can survive outside the host for months, the hospital environment can be contaminated for a long period of time. In addition to causing nosocomial AID, toxigenic Clostridium Difficile Infection (CDI) has also emerged as a cause of community-acquired diarrhoeal illness, with many patients lacking typical risk factors (e.g. recent antibiotic usage)[12].

Symptoms of CDI usually begin soon after colonisation (with a median of 2-3 days), with the time from antibiotic exposure to onset of symptoms ranging from 1 day to 6 weeks[13]. Risk factors for contracting CDI include exposure to antibiotics, advanced age, prolonged hospitalisation, cancer chemotherapy and manipulation of the gastrointestinal tract (e.g. by surgery or tube feeding).

In general, CDI 's disease severity can be categorised as follows: Non-severe disease (white cell count <15,000 cells/ml and serum creatinine < 88 umol/L), severe disease (white cell count > 15,000 cells/ml or serum creatinine > 88 umol/L) and fulminant disease (presence of hypotension, ileus or megacolon)[14].

MANAGEMENT OF C. DIFFICILE COLITIS

For patients infected with C. difficile, the goal of therapy is to alleviate the acute symptoms of colitis and to restore the normal bacterial flora of the gut. The initial therapy is to discontinue all inciting antibiotics and monitor the patient's progress. About 20% of patients with C difficile infection will resolve within 2-3 days of discontinuing the antibiotic to which the patient was

previously exposed. If symptom is severe or persistent, or when the culprit antibiotics cannot be discontinued, appropriate antibiotics, such as metronidazole, vancomycin, or fidaxomicin, can be used.

Traditionally, 10 days' course of oral metronidazole is considered as first-line therapy for patients with mild to moderately severe CDI and oral vancomycin has been reserved for patients who do not respond to or tolerate metronidazole and for patients with multiple recurrences of CDI or severe disease. However, recent clinical data showed that the symptomatic response rate after treatment with metronidazole were inferior to those after treatment with vancomycin[15]. In addition, metronidazole should be avoided in patients who are frail or with underlying inflammatory bowel disease due to its potential side effect profile. Oral vancomycin (125 mg orally four times per day) is now considered to be the first treatment of choice. Oral vancomycin is not absorbed systemically and achieves high level in bowel. Intravenous vancomycin has no effect on CDI as it is not excreted into colon and should not be used.

Fidaxomicin, a new class of narrow spectrum macrocyclic antibiotic derived from the fermentation product of the actinomycete Dactylosporangium Aurantiacum, provides a new alternative for treatment of CDI. Fidaxomicin carries several advantages compared with metronidazole and vancomycin. First, Fidaxomicin is a bactericidal agent while both metronidazole and vancomycin are bacteriostatic. In addition, it is non-systemic, meaning it is minimally absorbed into the bloodstream. Third, Fidaxomicin has demonstrated selective eradication of pathogenic Clostridium difficile with minimal disruption to the bacteria that make up the normal, healthy intestinal flora. The maintenance of normal physiological conditions in the colon can reduce the probability of CDI recurrence. Fidaxomicin treatment (oral 200 mg twice daily for 10 days) was associated with lower recurrence rate but are more expensive and not widely available.

Rifaximin, a derivative of rifamycin, has been widely used to treat traveller's diarrhoea, irritable bowel syndrome, and hepatic encephalopathy. It has also poor absorption when taken by mouth. Small scale study has proved that 10 days course of Rifaximin is effective as first-line treatment for CDI but more prospective data are warranted to confirm it therapeutic role in CDI patients.

For patients with fulminant disease, enteric vancomycin (500 mg four times per day) plus parenteral metronidazole (500 mg every 8 hours) should be used. In ileus cases, vancomycin (500 mg in 100 ml normal saline) can be administered as rectal enema every 6 hours.

Recurrent CDI is defined by reappearance of symptom within 2-8 weeks after treatment completion. For patients with recurrence following treatment with metronidazole for the initial episode, treatment with vancomycin is recommended. For patients who were initially treated with oral vancomycin and developed the recurrent infection, retreatment with oral vancomycin in pulse-tapered fashion (125 mg four times per day for 2 weeks, 125 mg two times per day for 1 week, 125 mg daily for 1 week, 125 mg alternative day for 2 weeks) is indicated. The rationale of the vancomycin pulse-tapered regimen is based upon the theory that relapses are believed due to the presence of spores that survive the antibiotic therapy. Intermittent antibiotic allows the spores to germinate on the days when no antibiotics are given. Once the spores have geminated to become vegetative toxin-producing form, they are susceptible to the killing effect of the antibiotics administered.

Vancomycin followed by rifaximin (sequential regimen) serves as an alternative for recurrent CDI. This latter approach has been evaluated by a prospective study showing that the addition of 2 to 3 weeks of rifaximin 400mg three time per day after completion of standard oral course of vancomycin was associated with significantly lower rate of recurrent CDI compared with placebo[16].

CONCLUSION

As most cases of community-acquired gastroenteritis are self-limiting, routine empirical use of antibiotics is not recommended. Empirical antibiotics should only be considered in selected groups of patients, such as patients with severe or prolonged symptoms or patients who are immunocompromised. Options for empirical treatment include oral fluoroquinolones or oral azithromycin. For travellers' diarrhoea, routine chemoprophylaxis is not recommended. Prophylaxis can be considered in high risk groups and oral rifaximin is the best option of choice. A short course of oral antibiotics (fluoroquinolones, azithromycin) with loperamide can be used in treating moderate to severe travellers' diarrhoea. For hospitalacquired diarrhoea, possibility of clostridium difficile infection should always be considered. Inciting antibiotics leading to CDI should be taken off if clinical condition allows. Treatment of confirmed cases with oral vancomycin instead of oral metronidazole leads to higher treatment success rate. The approach to treatment of adult patients with AID is summarised in Fig. 1.

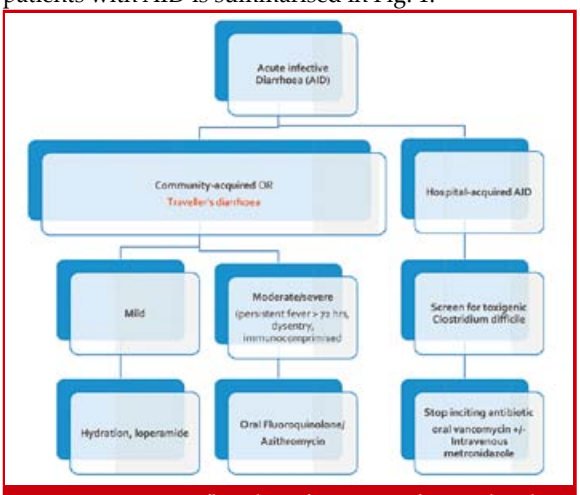

Fig. 1. Management flowchart for acute infective diarrhoea (AID) (summarized from Ref 6, 9, 11, 14)

References

1. Ho SC, Chau PH, Fung PK, Sham A et al. Epidemiology and Infection, 2010, v. 138 n. 7, p. 982-991
2. Spina A, Kerr KG, Cormican M, Barbut F, et al. Spectrum of enteropathogens detected by FilmArray® GI Panel in a multi-centre study of community-acquired gastroenteritis. Clin Microbiol Infect. 2015;21(8):719-28.
3. Chan SSW, Ng KC, Lyon DJ, et al. Acute bacterial gastroenteritis: a study of adult patients with positive stool cultures treated in the emergency department. Emerg Med J, 2003;20(4)>335-8.

4. Wistrom J, Jertborn M, Ekwall E, et al. Empiric treatment of acute diarrheal disease with norfloxacin. A randomized, placebo-controlled study. Swedish Study Group. Ann Intern Med, 117 (1992): 202-208
5. Sirinavin S, Garner P. Antibiotics for treating salmonella gut infections. Cochrane Database Syst Rev (2000), p. CD001167
6. Riddle MS, DuPont HI, Connor BA. ACG clinical guideline: Diagnosis, treatment, and Prevention of acute diarrheal infections in Adult. Am J Gastroenterology 2016; 111:602-622.
7. Chu YW, Chu MY, Luey KY, et al. Genetic Relatedness and Quinolone resistance of Campylobacter jejuni strains isolated in 2002 in Hong Kong. J Clin Microbiol. 2004;42(7):3321-3323.
8. Hill DR. Health problems in a large cohort of Americans traveling to developing countries. J Travel Med, 7 (2000): 259-266
9. Pawlowski SW, Warren CA, Guerrant R. Diagnosis and treatment of acute or persistent diarrhea. Gastroenterology, 136 (2009): 1874-1886
10. Sanders JW, Frenck RW, Putnam SD, et al. Azithromycin and loperamide are comparable to levofloxacin and loperamide for the treatment of traveler's diarrhea in United States military personnel in Turkey. Clin Infect Dis, 45 (2007):294-301
11. Riddle MS, Connor BA, Beeching NJ, et al. Guidelines for the prevention and treatment of travellers' diarrhoea: a graded expert panel report. J Travel Med. 2017:24(supp1): S57-74
12. Noren T, Akerlund T, Back E, Sjoberg L, et al. Molecular epidemiology of hospital-associated and community-acquired Clostridium difficile infection in a Swedish country. J Clin Microbiology 2004; 42:3635-43.
13. Poutanen SM, Simor AE. Clostridium difficile-associated diarrhea in adults. CMAJ. 2004;171(1):51-8.
14. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adult and children: 2017 Update by the Infectious disease Society of America (IDSA) and Society for Helathcare Epidemiology of America (SHEA). Clin Infect Dis. 2018;66(7): e1
15. Johnson S, Louie TJ, Gerding GN, et al. Vancomycin, metronidazole, or tolevamer for Clostridium difficile infection: results from two multinational, randomized, controlled trials. Clin Infect Dis. 2014;59(3): 345
16. Garey KW, Ghantoji SS, Shah DN, et al. A randomised, double-blind, placebo-controlled pilot study to assess the ability of rifaximin to prevent recurrent diarrhoea in patients with Clostridium difficile infection. J Antimicrob Chemother. 2011 Dec;66(12):2850-5.

MCHK CME Programme Self-assessment Questions

Please read the article entitled "Antibiotic Treatment in Acute Diarrhoea: A Practical Approach" by Dr Chi-ho NG 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 28 February 2019 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. **Viral infection is the major cause of traveller's diarrhoea.**
2. **Microbiological workup including stool saving and blood test is recommended in majority of children who suffer from acute onset diarrhoea.**
3. **Antibiotic treatment cannot reduce the length of disease caused by non-typhoidal salmonella-related acute infective diarrhoea.**
4. **Treatment of Enterohaemorrhagic E coli (EHEC) with antibiotics does not ameliorate the infections, and in some studies, it has been associated with development of HUS, especially in pregnant women.**
5. **Human Immunodeficiency Virus (HIV)-infected patients with CD4 count < 100 require antimicrobial prophylaxis when travelling to high-risk areas.**
6. **Rifampicin is effective in treating traveller's diarrhoea caused by non-invasive pathogens.**
7. **Oral metronidazole is the first step in treating Clostridium Difficile Infection (CDI)-related diarrhoea.**
8. **Intravenous vancomycin can be used in treating severe or refractory Clostridium Difficile infection (CDI)-related colitis.**
9. **Oral Azithromycin is one of the antibiotic choices in patients with acute severe diarrhoea even in the absence of stool microbiology investigation.**
10. **The main route of Campylobacter transmission is generally believed to be foodborne, most commonly via undercooked seafood as well as contaminated shellfish.**

ANSWER SHEET FOR FEBRUARY 2019

Please return the completed answer sheet to the Federation Secretariat on or before 28 February 2019 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Antibiotic Treatment in Acute Diarrhoea: A Practical Approach

Dr Chi-ho NG

MBChB(CUHK), MRCP(UK), FHKCP, FHKAM(Medicine), DPD(Wakes), MSc(Epidermiology & Biostatistics)(CUHK), FRCP(Edin)

Specialist of Gastroenterology and Hepatology

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

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Answers to January 2019 Issue

Medical Expert Witness – Duty, Independence, and Immunity

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

Department of Orthopaedics and Traumatology
Faculty of Medicine
The Chinese University of Hong Kong
香港中文大學 醫學院 矯形外科及創傷學系

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2019年5月30日（兼讀制）

Enquiry 查詢
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The Chinese University of Hong Kong
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An Exotic Astrophotography Trip to Africa, Namibia

Dr Chun-bon LAW

Dr Chun-bon LAW

MBBS, FHKAM, FRCP (London, Glasgow, Edinburgh)
Specialist in Geriatric Medicine

Namibia (納米比亞) is in the south western part of Africa and this is my first trip to the continent. I travelled in a group tour with several medic friends. The flight to Johannesburg was not particularly long, just over 12 hours. We then took a short flight to Windoheck (溫特和克), capital of Namibia. From there, a five-hour bus-ride on a sandy, non-paved road took us to the first scenic spot, Keetmanshoop Quivertree Forest (箭袋樹), where we stayed in a lodge. It was dark when we arrived. The sky was cloudless and sparkled in a sea of countless stars. In the middle of the sky lied the Milky Way, shone like a dreamy river glistening in silvery-white. I could see all the major planets: Venus, Jupiter, Mercury, Mars and Saturn. Nebulae and star clusters, hardly visible in Hong Kong, were easily spotted with naked eyes. The Large and Small Magellanic Clouds (大小麥哲倫星雲), the Southern Cross (南十字座) and the Coal Sac (煤袋星雲), off-limit to the sky-watchers of the northern hemisphere, were high up in the sky. Even though we were tired, we were so excited that as soon as we finished dinner, we geared up for our first night-photo session. Under the instruction of our photo master, I learnt how to do light painting and took portraits with a backdrop of the Milky Way. It was fun, and I went on till well past mid-night.

Spitzkoppe Arch. A small aperture was used to create the sun-star. Canon 6DM2, 24-70 F2.8, ISO 320, f16, 1/100

Panorama of the Southern Milky Way against the silhouette of Quiver Tree – a native tree of the Namibia dessert. Numerous stars totally disorientated me and I had a hard time recognizing individual constellation.
Canon 6DM2, Irix 15mm prime, ISO 1600, F f.8, 30 seconds exposure, 3 photos stitched by Lightroom

On the next day, we woke up early for a rare adventure. A pair of wild cheetahs came near to the lodge for breakfast and we had the opportunity to meet them outside the protective fence of the lodge – face to face and within feet. (The owner of the lodge explained that cheetahs are not as dangerous as other wild cats because their jaw is not strong enough to inflict fatal wounds!) No time for bed, we spent the rest of the day with our drones and cameras. Soon after dark, we were photographing the night sky again! That night was unforgettable. The first time in my life, I successfully identified the southern polar star, the Sigma Octantis, a very dim star – the first step of polar alignment. Aligning my instrument to the southern celestial pole proved difficult. Even with the help of my friend, the job took me four hours. After that, I set up my gear for a series of photos of the Large Magellanic Cloud – a 20 billion stars' "dwarf" galaxy that was one hundred and fifty thousand light years away – and my first DSO (Deep Sky Object) photo. I went to bed only just before dawn.

The cheetah is wild but used to humans as she is fed regularly. We are within 20 feet of her, without protection. The picture was taken back-lit to catch the morning light against her beautiful silhouette.
Canon 6DM2, 70-200 F4, ISO 400, f4, 1/800

The brightest, reddish star just above the tree is Mars. It was around opposition (大衝), when Mars was closest to earth.
Canon 6DM2, Irix 15mm, ISO 3200, f2.8, 30 seconds.

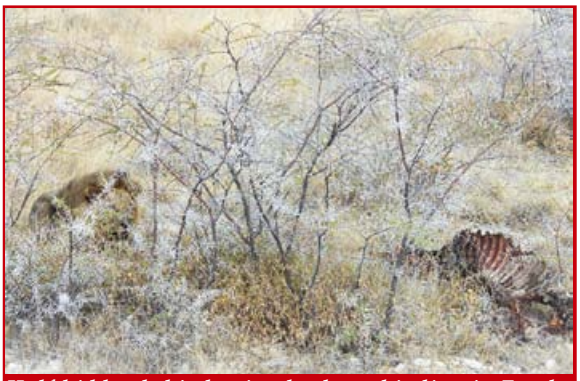
We spent the next few days in Sossusvlei (索蘇斯弗雷), a desert with orange and red sand, in Namibia. (The word Sossusvlei means dead end marsh.) The first stop was Kolmankop, a deserted ghost town invaded by sand after diamonds were exhausted from the area. Namibia once accounted for 80% of the world's diamond production. The warm glowing evening sun casting eerie shadows through shattered windows into the sand-filled houses made excellent photographic subjects. We came back next morning to catch the morning sun rays that filled the haunted houses. Next, we visited the Dead Valley – a must-go destination for Namibia visitors. It was a valley beamed with life eight hundred years ago until sand dunes cut off its feeding river. Lonely semi-ossified trees stood aloft among massive dunes of sand in red and yellow. In a backdrop of blue sky and white clouds, these dead trees looked paradoxically beautiful. We spent a night in a chateau hotel. It came out from nowhere in an endless land of sand. You simply did not expect a good-looking hotel (with candlelight dinner) in a desert. The night was originally meant for the sky but unfortunately, thunderstorm, being extremely rare in the desert, disrupted our plan. We were consoled by the manager's invitation to watch the final match of the World Cup in his lodge.

The next stop was the Skeleton Coast. The Coast had its name because skeleton of whales could be found along the shore. Two and a half million of brown fur seals and millions of sea-faring birds inhabited the area. Large flocks of flamingos can be seen afar in lakes that scattered in the lifeless desert of Namibia. We had the chance of seeing these creatures real close. Pelicans and seals were especially aggressive - they boarded our cruising boat as if they were the only rightful passengers and boldly walked passed us. Seals were super agile. I was amazed by a young fur seal chasing after our boat in great speed for 10 minutes, swimming effortlessly like a torpedo and jumping out of the water to fetch fishes from the hand of the boat captain with pin-point accuracy. The town where we stayed was fairly urbanised. We had a wonderful dinner in a restaurant built on a pier 200 metres into the Atlantic Ocean. Oyster was their specialty.

We spent the last two days in the Etosha National Park (埃托沙國家公園). The park was huge, about the size of several dozens of Hong Kong. It took us a full-day (including occasional stop for animals) to travel by bus across, from its eastern to the western border. Typical African animals can be seen roaming among the spiny bushes, walking on vast arid grassland or resting in the shade of dwarf, weird-looking trees. We saw lions, leopards, elephants, giraffes, springbok, wildebeests, kudus and zebras. Usual sites where one could find animals were the water holes. I was amazed by the extremely sharp eyesight of our tour guide, a native African. He was able to spot a leopard a mile away when we had difficulty locating it with our binoculars – it only showed up as a tiny silhouette under a tree, half hidden in the bushes.

Ghost town at Kolmanskop. Photo was taken at dusk to catch the golden light of the setting sun in the sand-invaded, ghostly house. It was extremely windy and camera must be well protected from the sandy gale.
Canon 6DM2, 24-70 F2.8, ISO 1600, f8, 1/200

Fossilized trees in the "Dead Vlei" (Dead Valley). These trees were eight hundred years old.
Canon 6DM2, 24-70 F2.8, ISO 400, f13, 1/800



Half hidden behind spiny bushes, this lion in Etosha National Park probably just had a full meal. The photo was taken through the window pane of our bus. I wish I could get off the bus for a better angle…
Canon 6DM2, 70-200 F2.8, ISO 400, f6.3, 1/640

Springbok, abundant in the national park.
Canon 6DM2, 70-200 F4, ISO 400, f13, 1/500

It was an exotic and unforgettable journey. The natural beauty of Namibia, the pristine wilderness and the jaw-dropping photographs of my companions (they were true masters of photography) had intoxicated my wife. Before our return to Hong Kong, she had already enrolled herself into photography classes and was planning to buy cameras! Our next destination – Vanuatu!

Our team of Medic friends and photo enthusiasts, with their better halves. We were advised to wear colorful clothes but avoid orange and yellow, the color of the desert.

AQ

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17	* FMSHK Certificate Course on Osteoporosis 2019 18	* HKMA Yau Tsim Mong Community Network and the Centre for Health Protection of the Department of Health - Antibiotic Stewardship Programme in Primary Care * FMSHK Certificate Course on Complaint Management 2019 19	* HKMA Central, Western & Southern Community Network - Physiotherapy for Common Orthopaedic Conditions (Part 2) 20	* HKMA Kowloon East Community Network - Improving Dyslipidaemia Management An Update on International Guideline and More * HKMA New Territories West Community Network - The Current Situation and Latest Management of Nasopharyngeal Carcinoma in Hong Kong 21	* HKMA Kowloon City Community Network and the Centre for Health Protection of the Department of Health - Antibiotic Stewardship Programme in Primary Care * FMSHK Certificate Course on Mental Health 2019 22	23
24	* FMSHK Certificate Course on Osteoporosis 2019 25	* HKMA Kowloon West Community Network - Antibiotic Stewardship Programs (ASP) in Primary Care * FMSHK Certificate Course on Complaint Management 2019 26	* Course on Community Nephrology (Facebook CME Live) 27	* FMSHK Executive Committee Meeting * FMSHK Council Meeting 28		

Date / Time	Function	Enquiry / Remarks
1 FRI 9:00 AM	**HKMA Council Meeting** Organiser: The Hong Kong Medical Association; Chairman: Dr. HO Chung Ping, MH, JP; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, HK	Ms. Christine WONG Tel: 2527 8285
12 TUE 8:00AM	**FMSHK Officers' Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Gallop, 2/F, Hong Kong Jockey Club Club House, Shan Kwong Road, Happy Valley, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
13 WED 7:30AM	**The Hong Kong Neurosurgical Society Monthly Academic Meeting –Minimally Invasive Epilepsy Surgery** Organiser: Hong Kong Neurosurgical Society; Chairman: Dr Dr POON Tak Lap; Speaker: Dr SEE Ka Wing, Michael; Venue: Seminar Room, G/F, Block A, Queen Elizabeth Hospital	Dr. WONG Sui To Tel: 2595 6456 Fax. No.: 2965 4061 1.5 points College of Surgeons of Hong Kong
2:00 PM	**Course on Community Nephrology (Facebook CME Live)** Organiser: The Hong Kong Medical Association; Chairman: Dr. HO Chung Ping, MH, JP; Speaker: Dr. TAM Chun Hay, Ivan; Venue: N/A	Mr. Jeff CHENG Tel: 2527 8285 1 CME Point
18 MON 7:00 PM	**FMSHK Certificate Course on Osteoporosis 2019** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Lecture Hall, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wan Chai, Hong Kong	The Secretariat of FMSHK Tel: 2527 8898 Fax: 2865 0345
19 TUE 1:00 PM	**HKMA Yau Tsim Mong Community Network and the Centre for Health Protection of the Department of Health - Antibiotic Stewardship Programme in Primary Care** Organiser: HKMA Yau Tsim Mong Community Network and the Centre for Health Protection of the Department of Health; Chairman: Dr. HO Kit Man, Carmen; Speaker: Dr. Leo LUI; Venue: Diamond Room, 5/F, The Cityview Hong Kong, 23 Waterloo Road, Kowloon	Ms. Candice TONG Tel: 2527 8285 1 CME Point
7:00 PM	**FMSHK Certificate Course on Complaint Management 2019** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Lecture Hall, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wan Chai, Hong Kong	The Secretariat of FMSHK Tel: 2527 8898 Fax: 2865 0345
20 WED 1:00 PM	**HKMA Central, Western & Southern Community Network - Physiotherapy for Common Orthopaedic Conditions (Part 2)** Organiser: HKMA Central, Western & Southern Community Network; Chairman: Dr. TSANG Chun Au; Speaker: Prof. WONG Kam Hung, Francis; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, HK	Miss Antonia LEE Tel: 2527 8285 1 CME Point
21 THU 1:00 PM	**HKMA Kowloon East Community Network - Improving Dyslipidaemia Management An Update on International Guideline and More** Organiser: HKMA-Kowloon East Community Network; Chairman: Dr. CHU Wen Jing, Jennifer; Speaker: Dr. CHEUNG Ling Ling; Venue: V Cuisine, 6/F., Holiday Inn Express Hong Kong Kowloon East, 3 Tong Tak Street, Tseung Kwan O	Miss Antonia LEE Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA New Territories West Community Network - The Current Situation and Latest Management of Nasopharyngeal Carcinoma in Hong Kong** Organiser: HKMA New Territories West Community Network; Chairman: Dr. CHEUNG Kwok Wai, Alvin; Speaker: Dr. LAM Wing Hung, Eddy; Venue: Atrium Function Rooms, Lobby Floor, Hong Kong Gold Coast Hotel, 1 Castle Peak Road, Gold Coast, Hong Kong	Miss Antonia LEE Tel: 2527 8285 1 CME Point
22 FRI 1:00 PM	**HKMA Kowloon City Community Network and the Centre for Health Protection of the Department of Health - Antibiotic Stewardship Programme in Primary Care** Organiser: HKMA Kowloon City Community Network and the Centre for Health Protection of the Department of Health; Chairman: Dr. CHAN Man Chung, JP; Speaker: Dr. Leo LUI; Venue: President's Room, Spotlight Recreation Club, 4/F., Screen World, Site 8, Whampoa Garden, Hunghom, Kowloon	Ms. Candice TONG Tel: 2527 8285 1 CME Point
7:00 PM	**FMSHK Certificate Course on Mental Health 2019** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Lecture Hall, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wan Chai, Hong Kong	The Secretariat of FMSHK Tel: 2527 8898 Fax: 2865 0345
25 MON 7:00 PM	**FMSHK Certificate Course on Osteoporosis 2019** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Lecture Hall, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wan Chai, Hong Kong	The Secretariat of FMSHK Tel: 2527 8898 Fax: 2865 0345
26 TUE 1:00 PM	**HKMA Kowloon West Community Network - Antibiotic Stewardship Programs (ASP) in Primary Care** Organiser: HKMA Kowloon West Community Network; Chairman: Dr. LEUNG Gin Pang; Speaker: Dr. Leo LUI; Venue: Fulum Palace, Shop C, G/F, 85 Broadway Street, Mei Foo Sun Chuen	Miss Antonia LEE Tel: 2527 8285 1 CME Point
7:00 PM	**FMSHK Certificate Course on Complaint Management 2019** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Lecture Hall, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wan Chai, Hong Kong	The Secretariat of FMSHK Tel: 2527 8898 Fax: 2865 0345
27 WED 2:00 PM	**Course on Community Nephrology (Facebook CME Live)** Organiser: The Hong Kong Medical Association; Chairman: Dr. HO Chung Ping, MH, JP; Speaker: Dr. MA King Wing, Terry; Venue: N/A	Mr. Jeff CHENG Tel: 2527 8285 1 CME Point
28 THU 7:00 PM	**FMSHK Executive Committee Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
8:00 PM	**FMSHK Council Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898

Answers to Radiology Quiz

Answers:

1. The frontal chest radiograph demonstrates the presence of a subcentimetre solitary round nodule at the left mid zone. No consolidation or pleural effusion is noted. Dedicated contrast-enhanced CT scan of the thorax confirms the presence of the nodule. It is well-demarcated with several clumps of calcification seen in a "pop-corn" configuration. Tiny lucencies seen within the lesion could represent fat density. No significant interval change was noted in subsequent surveillance imaging.

2. Pulmonary hamartoma.

3. Pulmonary hamartoma is a benign neoplasm, and accounts for up to 6% of solitary pulmonary nodules. They are usually asymptomatic and present as incidental findings, as per this patient. These tumours are composed of cartilage, connective tissue, muscle, fat and bone in a disorganised fashion. Malignant transformation is extremely rare, and a small peripheral hamartoma, as per this case, can usually be safely left alone with infrequent surveillance to exclude growth.

Dr Victor Siang-hua CHAN
MBBS, LMCHK, FRCR
Department of Radiology, Queen Mary Hospital

Chronic Disease Patients — High Risk of Pneumonia[1#]

Prevenar 13®

Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)

Advanced Protection to Your Patients[2*]

Elderly aged 65+ with chronic diseases are more likely to develop pneumococcal pneumonia:

DIABETES

2.8 folds[1]

CHRONIC CVD†

3.8 folds[1]

CHRONIC LUNG DISEASE

7.7 folds[1]

\# Compared with healthy individuals aged 65 or above

* Conjugate vaccine induces immune memory and provides long-term protection[3,4]

† Chronic cardiovascular disease

References: 1. Shea KM, et al. Open Forum Infect Dis. 2014. doi:10.1093/ofid/ofu024. 2. Pneumococcal polysaccharide conjugate vaccine, 13-valent adsorbed Prescribing Information. Pfizer Corporation Hong Kong Limited. (Version Dec 2015). 3. Pollard AJ et. al., Nature Reviews. Immunology. 2009; 9: 213-220. 4. Goldblatt D. Clin Exp Immunol. 2000; 119:1-3.

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Website: www.pfizer.com.hk

Vaccination Helps Protect against Pneumococcal Pneumonia[2] — Your Role is KEY

PREVENAR 13® ABBREVIATED PACKAGE INSERT **1. TRADE NAME:** PREVENAR 13® **2. PRESENTATION:** A homogeneous white suspension for injection. **3. INDICATIONS:** Active immunisation for the prevention of pneumococcal disease caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F in adults and children aged more than 6 weeks of age. The use of Prevenar 13 should be guided by official recommendations. **4. DOSAGE:** Intramuscular administration only. The immunisation schedules should be based on official recommendations. Infants aged 6 weeks - 6 months: The primary infant series consists of three doses, with the first dose usually given at 2 months of age and with an interval of at least 1 month between doses. The first dose may be given as early as six weeks of age. A fourth (booster) dose is recommended after 12 months of age, and at least 2 months after the third dose. Unvaccinated children aged 7-11 months: 3 doses. Unvaccinated children aged 12-23 months: 2 doses. Unvaccinated children aged 24 months to 17 years: One single dose. Adults: One single dose. For more dosage information, please refer to the full package insert. **5. CONTRAINDICATIONS:** Hypersensitivity to the active substances or to any of the excipients, or to diphtheria toxoid. Allergic reaction or anaphylactic reaction following prior administration of Prevenar (7-valent). **6. WARNINGS & PRECAUTIONS:** Not for intravenous or intravascular administration; as with other vaccines, the administration should be postponed in subjects suffering from acute moderate or severe febrile illness; should not be given to individuals with thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injection unless the potential benefit clearly outweighs the risk of administration; will not protect against Streptococcus pneumoniae serotypes other than those included in the vaccine nor other microorganisms that cause invasive disease, pneumonia, or otitis media; may not protect all individuals receiving the vaccine from pneumococcal disease. Individuals with impaired immune responsiveness may have reduced antibody response to active immunisation. Safety and immunogenicity data for Prevenar 13 are available for certain high-risk groups such as children and adolescents with sickle cell disease and children and adults with HIV infection or with a haematopoietic stem cell transplant. Data are not currently available for individuals in other immunocompromised groups (e.g., malignancy, or nephrotic syndrome) and vaccination should be considered on an individual basis. Children below 2 years old should receive the appropriate-for-age Prevenar 13 vaccination series. The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunisation series to very premature infants (born ≤ 30 weeks of gestation), and particularly for those with a previous history of respiratory immaturity. Antipyretic treatment should be initiated according to local treatment guidelines. Prophylactic antipyretic medication is recommended for children with seizure disorders or with a prior history of febrile seizures and for all children receiving Prevenar 13 simultaneously with vaccines containing whole cell pertussis. **7. INTERACTIONS:** Infants and children aged 6 weeks to 5 years: Can be given with any of the following vaccine antigens, either as monovalent or combination vaccines: diphtheria, tetanus, acellular or whole cell pertussis, Haemophilus influenzae type b, inactivated poliomyelitis, hepatitis B, meningococcal serogroup C, measles, mumps, rubella and varicella. In clinical trials, where there was concomitant administration of Prevenar 13 and rotavirus vaccine, no change in the safety profiles of these vaccines was observed. When Prevenar 13 is administered concomitantly with Infanrix hexa (DTaP HBV-IPV/Hib), the rates of febrile reactions are similar to those seen with concomitant administration of Prevenar (7-valent) and Infanrix hexa. Children 6 to 17 years of age and adults 18 to 49 years of age: No data are currently available regarding concomitant use with other vaccines. Adults aged 50 years and older: May be administered concomitantly with seasonal trivalent inactivated influenza vaccine. Different injectable vaccines should always be given at different injection sites. **8. PREGNANCY AND LACTATION:** Prevenar 13 is not indicated or recommended for use in pregnant women and has not been evaluated for potential harmful effects during pregnancy in humans. Safety during lactation has not been established. **9. SIDE EFFECTS:** Children: Decreased appetite; fever; irritability; drowsiness/increased sleep; restless sleep/decreased sleep; any vaccination-site erythema, induration/swelling or pain/tenderness; vaccination-site pain/tenderness interfering with movement; diarrhoea, vomiting; rash. Children and adolescents aged 5 to 17 years of age: Decreased appetite; irritability; any vaccination-site erythema; induration/swelling or pain/tenderness; drowsiness/increased sleep; restless sleep/decreased sleep; vaccination-site tenderness (including impaired movement); fever; headache; rash; urticaria/urticaria-like rash; vomiting; diarrhoea. Adults: decreased appetite; headache; diarrhoea; vomiting; rash; chills; fatigue; vaccination-site erythema; vaccination-site induration/swelling; vaccination-site pain/tenderness; limitation of arm movement; joint pain; muscle pain; fever. (Please refer to the full Prescribing Information for details). **Reference:** HK Pneumococcal polysaccharide conjugate vaccine, 13-valent adsorbed (version December 2015). **Date of preparation:** APR 2017 **Identifier number:** PR13-0417_Hong Kong **FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.**

PP-PRE-HKG-0006

OUR TOMORROW STARTS WITH 2

MAKE TIVICAY + LAMIVUDINE THEIR FIRST HIV REGIMEN

POWERFUL EFFICACY
non-inferior to a traditional 3-drug regimen[1]

0 RESISTANCE
up to 48 weeks[1]

REDUCED ARV EXPOSURE
and potential for associated toxicities[2,3]

BECAUSE NO ONE SHOULD TAKE MORE MEDICINES THAN THEY NEED

For your treatment-naïve adult patients

Tivicay + lamivudine
dolutegravir

POWERED BY DTG AT THE CORE

To learn more about the next step in the 2-drug regimen era, visit www.viivexchange.com

Abbreviated prescribing information[2,3]

Tivicay Tablets (Dolutegravir) 50mg **Therapeutic indication:** Indicated in combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected adults and adolescents above 12 years of age. **Posology and method of administration:** *Patients infected with HIV-1 without documented or clinically suspected resistance to the integrase class:* Tivicay 50 mg (1 tablet) orally once daily. Co-administered some medicines for example efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin: twice daily. *Patients infected with HIV-1 with resistance to the integrase class (documented or clinically suspected):* Tivicay 50 mg twice daily. Avoid co-administration of Tivicay with efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin. Missed doses: Take Tivicay as soon as possible, providing next dose is not due within 4 hours. If next dose is due within 4 hours, patient should not take the missed dose and simply resume the usual dosing schedule. *Adolescents (aged from 12 to 17 years and weighing ≥ 40 kg) infected with HIV-1 without resistance to the integrase class:* Tivicay 50mg once daily. Elderly: Limited data available. No evidence that elderly patients require a different dose than younger adult patients. *Renal impairment:* No dosage adjustment required for patients with mild, moderate or severe (CrCl <30 mL/min, not on dialysis) renal impairment. *Hepatic impairment:* No dosage adjustment required in patients with mild or moderate hepatic impairment (Child-Pugh grade A or B). Use with caution in patients with severe hepatic impairment (Child-Pugh grade C). *Children aged <12 years or weighing <40 kg:* Safety and efficacy not yet established. Oral use. Taken with or without food. In the presence of integrase class resistance, Tivicay should preferably be taken with food to enhance exposure (particularly in patients with Q148 mutations). **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Co-administration with dofetilide. **Warnings & precautions:** *Integrase class resistance of particular concern:* Decision to use dolutegravir in the presence of integrase class resistance should take into account that dolutegravir activity is considerably compromised for viral strains harbouring Q148+≥2 secondary mutations from G140A/C/S, E138A/K/T, L74I. *Hypersensitivity reactions:* Discontinue dolutegravir and other suspect agents 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. *Immune Reactivation Syndrome:* Monitoring of liver biochemistries is recommended in patients with hepatitis B and/or C co-infection. Particular diligence should be applied in initiating or maintaining effective hepatitis B therapy when starting dolutegravir-based therapy in hepatitis B co-infected patients. Opportunistic infections: Patients remain under close clinical observation of these associated HIV diseases by physicians. Drug interactions: Avoid factors that decrease dolutegravir exposure in the presence of integrase class resistance (e.g. magnesium/ aluminium-containing antacid, iron and calcium supplements, multivitamins and inducing agents, etravirine (without boosted protease inhibitors), tipranavir/ritonavir, rifampicin, St. John's wort and certain antiepileptic drugs). A dose adjustment of metformin should be considered when starting and stopping coadministration of dolutegravir with metformin. Osteonecrosis: Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement. Interactions: Avoid factors that decrease dolutegravir exposure in the presence of integrase class resistance. Medicinal products that induce enzymes UGT1A3, UGT1A9, CYP3A4, Pgp, and BCRP may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir. Co-administration of dolutegravir and other medicinal products that inhibit these enzymes may increase dolutegravir plasma concentration. Absorption of dolutegravir is reduced by certain anti-acid agents. Co-administration with St. John's wort is strongly discouraged. Magnesium/aluminium-containing antacid, calcium supplements, iron supplements or multivitamins should be taken well separated in time from the administration of dolutegravir (minimum 2 hours after or 6 hours before). **Pregnancy & lactation:** Limited amount of data in pregnant women. 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: Insomnia, Abnormal dreams, Depression, Dizziness, Vomiting, Flatulence, Upper abdominal pain, Abdominal pain, Abdominal discomfort, Rash, Pruritus, Fatigue, Alanine aminotransferase (ALT) and/or Aspartate aminotransferase (AST) elevations, Creatine phosphokinase (CPK) elevations. **Overdose:** No specific treatment for overdose. Patient should be treated supportively with appropriate monitoring as necessary. Abbreviated Prescribing Information based on PI version GDS06v1(hk)/ EMEA20150818.

3TC 150 mg film-coated tablets (Lamivudine). **Therapeutic indication:** 3TC is indicated as part of antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infected adults and children. **Posology and method of administration:** 3TC may be administered with or without food. The tablet(s) should ideally be swallowed without crushing. 3TC oral solution is available for children over three months of age and who weigh less than 14 kg or for patients who are unable to swallow tablets. Alternatively, for patients who are unable to swallow tablets, the tablet(s) may be crushed and added to a small amount of semi-solid food or liquid, all consuming immediately. Adults, adolescents and children (weighing at least 25kg), the recommended dose of 3TC is 300 mg daily. This may be administered as either 150 mg twice daily or 300 mg once daily. Children weighing ≥ 20 kg to <25 kg, the recommended dose is 225 mg daily. Children weighing 14 to <20 kg, the recommended dose is 150 mg daily. Children from three months of age: it is recommended that the 3TC 150 mg scored tablet formulation is used. Children less than three months of age, the limited data available are insufficient to propose specific dosage recommendations. Patients changing from the twice daily dosing regimen to the once daily dosing regimen should take the recommended once daily dose approximately 12 hours after the last twice daily dose, and then continue to take the recommended once daily dose approximately every 24 hours. Older people, no specific data are available; Renal impairment, lamivudine concentrations are increased in patients with moderate - severe renal impairment due to decreased clearance. The dose should therefore be adjusted, using oral solution presentation of 3TC for patients whose creatinine clearance falls below 30 ml/min. Hepatic impairment, data obtained in patients with moderate to severe hepatic impairment shows that lamivudine pharmacokinetics are not significantly affected by hepatic dysfunction. Based on these data, no dose adjustment is necessary in patients with moderate or severe hepatic impairment unless accompanied by renal impairment. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Not recommend the combination of lamivudine with cladribine. **Warnings & precautions:** 3TC is not recommended for use as monotherapy. Renal impairment: In patients with moderate to severe renal impairment, the dose should be adjusted. Pancreatitis: Pancreatitis has been observed in some patients receiving lamivudine. Treatment with 3TC should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur until pancreatitis excluded. Lactic acidosis/severe hepatomegaly with steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues either alone or in combination, including lamivudine. A majority of these cases have been in women. Caution should be exercised when administering lamivudine, particularly to those with known risk factors for liver disease. Treatment with lamivudine should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis with or without hepatitis (which may include hepatomegaly and steatosis in even in the absence of marked transaminase elevations). Serum lipids and blood glucose: Serum lipid and blood glucose levels may increase during antiretroviral therapy. Immune Reconstitution Syndrome: In HIV-infected patients with severe immune deficiency at the time of initiation of anti-retroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of ART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and Pneumocystis jiroveci (P. carinii) pneumonia. Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary. Autoimmune disorders (such as Graves' disease, polymyositis and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution, however the time to onset is more variable, and can occur many months after initiation of treatment and sometimes can be an atypical presentation. Patients co-infected with Hepatitis B virus: Clinical trial and marketed use of lamivudine, have shown that some patients with chronic hepatitis B virus (HBV) disease may experience clinical or laboratory evidence of recurrent hepatitis upon discontinuation of lamivudine, which may have more severe consequences in patients with decompensated liver disease. If lamivudine is discontinued in a patient with HIV and HBV coinfection, periodic monitoring of both liver function tests and markers of HBV replication should be considered. Oral solution: Diabetic patients should be advised that an adult dose contains 3 g of sucrose. Children: Children who at anytime received lamivudine oral solution concomitantly with other antiretroviral oral solutions in clinical trials experienced lower rates of virological suppression, had lower plasma lamivudine exposure and developed viral resistance more frequently than children receiving tablets. **Interactions:** Lamivudine is predominantly eliminated by active organic cationic secretion. The possibility of interactions with other medicinal products administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system e.g. trimethoprim. Other active substances (e.g. ranitidine, cimetidine) are eliminated only in part by this mechanism and were shown not to interact with lamivudine. Zidovudine: A modest increase in Cmax (28%) was observed for zidovudine when administered with lamivudine, however overall exposure (AUC) was not significantly altered. Zidovudine had no effect on the pharmacokinetics of lamivudine (see Pharmacokinetics). Trimethoprim/sulphamethoxazole: Administration of trimethoprim/sulphamethoxazole 160 mg/800 mg (co-trimoxazole) causes a 40% increase in lamivudine exposure because of the trimethoprim component. However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary (see Dosage and Administration). Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulphamethoxazole. The effect of co-administration of lamivudine with higher doses of co-trimoxazole for the treatment of Pneumocystis carinii pneumonia and toxoplasmosis has not been studied. Zalcitabine: Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently. Lamivudine is therefore not recommended to be used in combination with zalcitabine. Emtricitabine: Lamivudine may inhibit the intracellular phosphorylation of emtricitabine when the two medicinal products are used concurrently. Additionally, the mechanism of viral resistance for both lamivudine and emtricitabine is mediated via mutation of the same viral reverse transcriptase gene (M184V) and therefore the therapeutic efficacy of these drugs in combination therapy may be limited. Lamivudine is not recommended for use in combination with emtricitabine or emtricitabine-containing fixed dose combinations. **Pregnancy & lactation:** Lamivudine has been evaluated in the Antiretroviral Pregnancy Registry in over 11,000 women during pregnancy and postpartum. Available human data from the Antiretroviral Pregnancy Registry do not show an increased risk of major birth defects for lamivudine compared to the background rate. However, there are no adequate and well-controlled trials in pregnant women and the safe use of lamivudine in human pregnancy has not been established. Studies in humans have confirmed that lamivudine crosses the placenta. Use in pregnancy should be considered only if the benefit outweighs the risk. Although the results of animal studies (see Non-Clinical Information) are not always predictive of human response, the findings in the rabbit suggest a potential risk of early embryonic loss. Health experts recommend that where possible women infected with HIV do not breast feed their infants in order to avoid the transmission of HIV. In settings where formula feeding is not feasible, local official lactation and treatment guidelines should be followed when considering breast feeding during antiretroviral therapy. In a study following repeat oral dose of either 150 mg lamivudine twice daily (given in combination with 300 mg zidovudine twice daily) or 300 mg lamivudine twice daily, lamivudine was excreted in human breast milk (0.5 to 8.2 micrograms/ml) at similar concentrations to those found in serum. In other studies following repeat oral dose of 150 mg lamivudine twice daily (given either in combination with 300 mg zidovudine or as Combivir or Trizivir) the breast milk:maternal plasma ratio ranged between 0.6 and 3.3. Lamivudine median infant serum concentrations ranged between 18 and 28 ng/mL and were not detectable in one of the studies (assay sensitivity 7 ng/mL). Intracellular lamivudine triphosphate (active metabolite of lamivudine) levels in the breastfed infants were not measured therefore the clinical relevance of the serum concentrations of the parent compound measured is unknown. **Adverse reactions:** Common: Headache, insomnia, cough, nasal symptoms, nausea, vomiting, abdominal pain or cramps, diarrhea, rash, alopecia, arthralgia, muscle disorders, fatigue, malaise, fever. **Overdose:** No additional safety issues have been identified in paediatric subjects receiving either once or twice daily dosing compared to adults. Limited data are available on the consequences of ingestion of acute overdoses in humans. If overdosage occurs the patient should be monitored, and standard supportive treatment applied as required. Abbreviated Prescribing Information based on PI version: HK012017(GDS22/eMC20160714).

Important Safety Information:

· The recommended dose of dolutegravir is 50 mg (one tablet) twice daily for patient with resistance to integrase class (documented or clinically suspected)
· 3TC is not recommended for use as monotherapy.
· Precautions on occurrence of pancreatitis and Immune Reconstitution Syndrome and increased serum lipids, blood glucose.

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. For adverse events report, please call GlaxoSmithKline Limited at (852) 9046 2498. This material is for the reference and use by healthcare professionals only.

References: 1. Cahn P et al. Presented at: International AIDS Conference; July 23-27, 2018; Amsterdam, Netherlands. **2.** Tivicay Hong Kong Prescribing Information 2017. **3.** 3TC Hong Kong Prescribing Information 2017.

ARV, antiretroviral; DTG, dolutegravir

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