Returning Aircrew with Chronic Hepatitis B Back to Flying While on Nucleos(t)ide Analogues

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BACKGROUND: Chronic Hepatitis B (CHB) remains a major cause of morbidity in several parts of the world. Aircrew with immune-active hepatitis are unfit for flying duties due to the risk of acute hepatic decompensation; those who have begun on treatment are generally also disqualified from flying duties due to the potential side effects of antiviral treatment. As treatment endpoints for nucleos(t)ide analogues (NUC) are typically achieved after prolonged therapy, aircrew treated for CHB may be subjected to an extended period of flying restriction.

METHODS: We present a retrospective case series of seven aircrew who were returned to flying duties while on varying combinations of NUC for the treatment of CHB. All seven aircrew were comanaged by the flight surgeon and hepatologist, reviewed by a panel of flight surgeons, and had achieved normalized liver function tests prior to resumption of flying duties; two out of the seven aircrew had detectable serum Hepatitis B virus (HBV) DNA when reinstated back to flying duties. Only one aircrew member experienced side effects from the NUC treatment. This was promptly evaluated and managed prior to resumption of flying duties to ensure flight safety.

DISCUSSION: Aircrew with CHB infection can be safely allowed back to flying duties, especially when their conditions have been well controlled via treatment with any of the NUC regimes. While there are limited studies evaluating the use of NUC in aircrew performing flight duties, our study has shown that NUC are generally well tolerated and have a good safety profile which is compatible with flying duties.

KEYWORDS: flight safety, aeromedical fitness assessment, anti-viral treatment.

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Chronic Hepatitis B (CHB) is known to cause an increased risk of liver-related complications for those affected by the disease. This condition is not uncommon, affecting over 240 million individuals worldwide, with its prevalence highest in the sub-Saharan Africa and East Asia regions.[18] It is, therefore, not uncommon to encounter aircrew with CHB in South-East Asia.

Currently, treatment options for CHB include pegylated interferon α (PEG-IFN α) or nucleos(t)ide analogues (NUC). The main goal of therapy is to prevent disease progression, and consequently development of hepatocellular carcinoma. Recommendations for CHB treatment endpoints can include any of the following: 1) long-term viral suppression; 2) HBeAg clearance, with or without anti-HBe seroconversion (for HBeAg positive patients); or 3) HBsAg clearance, with or without anti-HBs seroconversion.[7] Patients who have achieved these serologic endpoints may be continued on a period of consolidation therapy of at least 12 mo prior to treatment cessation.[15,16]

The rate of seroconversion with NUC treatment is typically low. For example, a 12-mo course of lamivudine would likely achieve HBeAg seroconversion in approximately 16% of HBeAg-positive individuals on treatment.[4] Studies have shown that the sustained viral suppression rates after NUC discontinuation are less than ideal and long-term NUC treatment may be necessary.[12]

While it is widely accepted that aircrew with acute hepatitis will be considered unfit to perform flying duties due to symptoms such as abdominal pain and fatigue, the aeromedical

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concerns for aircrew with CHB are less concrete. CHB is frequently asymptomatic and individuals are very often well and fully functional without any impairment. While CHB can cause incapacitation from decompensated liver function, resulting in fatigue, malaise, nausea, or even hepatic encephalopathy, the progression of liver decompensation leading to symptoms is unlikely to be sudden in nature. Given the gradual nature of symptom onset, the likelihood of incapacitating symptoms occurring in-flight is low. This risk is further mitigated through the regular 6-mo follow-ups which patients with CHB have to undergo.

Current waiver guidelines consider chronic active hepatitis (demonstrated by deranged liver function tests) and requirement for treatment, e.g., NUC, to be disqualifying. The potential side effects of NUC are wide ranging and include headache, nausea, vomiting, dizziness, and rash. Due to these side effects, waiver guidelines in general regard the use of NUC to be incompatible with flying duties.

This retrospective case series focuses on the aeromedical disposition of seven military aircrew with CHB who were successfully returned to active flying duties while on NUC treatment. Through the entire process of determining their flying status, we remained cognizant of the potential adverse events that may arise from the use of NUC. All seven aircrew were assessed individually by a panel of Aviation Medicine specialists to ensure that they had tolerated and responded to treatment well before waiver was granted. Extensive literature review on NUC was also conducted to identify potential adverse events that may be acutely incapacitating. It was only after careful and deliberate consideration that the aircrew were returned back to flying duties, albeit under close supervision.

It should, however, be noted that some of the aircrew presented in this case series were managed with older NUC regimes as they had presented to us from 2006 to 2014. With the emergence of new treatment drugs for CHB, some of the NUC mentioned here may no longer be the first line treatment for CHB. Nonetheless, these NUC are still generally prescribed worldwide in the treatment of CHB and other viral infections, and this paper serves to highlight their suitability for flying duties, as supported by their favorable side effect and safety profiles.

METHODS

Between 2006 and 2014, seven aircrew operating multicrew platforms were returned to flying duties. At the time of resumption of flying duties, all seven aircrew were still receiving treatment with varying combinations of NUC. The seven aircrew are presented here in chronological order, with Subject 1 being the first subject returned to military flying duties while on NUC treatment. Institutional Review Board approval was not required for this review.

Subject 1

A 41-yr-old transport aircraft pilot was diagnosed with CHB following evaluation of abnormal liver function tests. He subsequently developed multiple flares of hepatitis with HBsAg and HBeAg positivity and deranged liver enzymes, for which he was treated and restricted from flying duties. He was initially treated with lamivudine (100 mg OM) and successfully achieved HBeAg seroconversion. He subsequently developed a virological breakthrough and was then started on adefovir (10 mg OM) due to drug resistance. He was restricted from flying duties for 18 mo for observation and monitoring. While Subject 1 had demonstrated good response and tolerance to NUC treatment with normalization of liver enzymes, he was only allowed to resume restricted flying duties as-or-with qualified copilot while on adefovir as it was a relatively new drug at the time of the decision.

Subject 2

A 41-yr-old transport aircraft pilot was diagnosed with CHB following the evaluation of his deranged liver enzymes during the annual medical examination. He was treated with lamivudine (100 mg OM) and adefovir (10 mg OM), before lamivudine was replaced with entecavir (0.5mg OM) due to suboptimal virological suppression. While on lamivudine and adefovir, this pilot was restricted from flying duties for 15 mo to allow the normalization of liver enzymes. Following replacement of lamivudine with entecavir, he was monitored and restricted from flying duties for a further 24 mo due to persistently detectable HBV DNA.

Subject 2 demonstrated good tolerance to NUC treatment and did not report any side effects from the treatment. His HBV DNA levels also demonstrated good response to treatment, diminishing to undetectable levels. However, as entecavir was a relatively new drug at the point of decision, and in view of the risk of virological breakthroughs and subsequent disease flares, he was restricted to flying duties as-or-with a qualified copilot while on NUC treatment.

Subject 3

A 39-yr-old transport aircraft pilot was incidentally diagnosed with CHB following a routine medical examination. His disease had remained quiescent for 4 yr before he developed symptomatic transaminitis. He was initially treated with lamivudine (100 mg OM) and adefovir (10 mg OM), with lamivudine subsequently switched to entecavir (0.5 mg OM) due to suboptimal virological suppression. He was restricted from flying duties for 10 mo while on adefovir and entecavir.

During treatment with adefovir and entecavir, the pilot did not report any side effects of treatment and demonstrated significant decline in serum HBV DNA titers. Similarly, he was allowed to resume restricted flying duties as-or-with qualified copilot due to entecavir being a relatively new drug and that the HBV DNA titers had persisted in remaining detectable (albeit at extremely low levels).

Subject 4

A 42-yr-old helicopter pilot was incidentally diagnosed with CHB following a routine annual medical examination. At the time of diagnosis, he was noted to be HBeAg positive with elevated liver enzymes but was otherwise asymptomatic. He was

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initially started on lamivudine (100 mg OM), with adefovir (10 mg OM) added after a virological breakthrough. He was restricted from flying duties for 3 mo upon commencement of NUC. As Subject 4 tolerated NUC treatment well with no report of side effects and demonstrated normalization of liver enzymes with complete viral suppression, he was returned to unrestricted flying duties while still on lamivudine and adefovir.

Subject 5

A 37-yr-old helicopter pilot was diagnosed with CHB following a routine medical examination. He was started on a combination of lamivudine (100 mg OM) and adefovir (10 mg OM) by his hepatologist as part of an interventional study. The treatment resulted in frequent headaches initially, which was mitigated by having the adefovir and lamivudine taken only at night, minimizing daytime symptoms. In total, he was restricted from flying duties for 6 mo following the commencement of adefovir and lamivudine.

Although it was noted that Subject 5 suffered from headaches, which may pose a significant distraction in flight, he reported that his headache had a very characteristic and consistent nature; it invariably started off with a very mild headache which was nondistracting for hours. As the headache progressed, it would be associated with warning symptoms, such as increased sweating and lethargy, before evolving into a full-blown headache. The very gradual onset of headache over hours would give him ample time to remove himself from any scheduled flights and special arrangements with his squadron were possible in mitigating this inconvenience. Noting how he had meticulously observed and documented his symptoms, and that the onset of his headache was very gradual, Subject 5 was allowed to resume restricted flying duties as-or-with a qualified copilot while on adefovir and lamivudine, and under close and continued medical surveillance.

Subject 6

A 41-yr-old helicopter pilot was diagnosed with CHB following a routine medical examination. He had been asymptomatic and clinically well for approximately 12 yr before a routine medical surveillance revealed elevated liver enzymes, HBeAg positivity, and elevated HBV DNA levels. He was started on entecavir (0.5 mg OM) and restricted from flying duties for 6 mo to monitor for disease control and side effects from CHB treatment.

Subject 6 did not report any side effects from CHB treatment 6 mo after the commencement of entecavir, and demonstrated significant decline in serum HBV DNA titers. In view of the limited literature on the safety of entecavir use in an aeromedical context and the persistence of detectable (albeit very low) serum HBV DNA titers, he was only allowed to resume restricted flying duties as-or-with a qualified copilot while on entecavir, and remained on close monitoring of his disease and treatment outcomes.

Subject 7

A 36-yr-old helicopter pilot with known CHB was found to have deranged liver enzymes and increasing serum HBV DNA titers during the routine surveillance follow-ups with his hepatologist. Prior to this, his disease had been quiescent for approximately 10 yr and no treatment was required.

Following detection of transaminitis and elevated HBV DNA levels, he was started on entecavir (0.5 mg OM) by his hepatologist. He demonstrated good tolerance to the therapy and his liver function tests soon normalized. However, in view of the limited literature on the safety of entecavir use in an aeromedical context, he was restricted from flying duties for a total of 12 mo for observation before being returned to restricted flying duties as-or-with a copilot.

RESULTS

Table I presents a summary of the aircrew details. As highlighted earlier, each of these aircrew was assessed and evaluated on a case-by-case basis by a panel of Aviation Medicine specialists as they had unique disease patterns and career/organizational plans and roles. As some of the NUC used were relatively new at the point of decision, especially for the earlier aircrew, we adopted a more considered approach and opted to err on the side of caution, observing the aircrew for a longer period of time before reinstating their flying duties. All aircrew were made aware of the potential complications from their condition and treatment and were instructed to report any complications to their attending Aviation Medical Officer promptly. When deciding on the duration of observation, we also considered other nonmedical factors, including the aircrew's current role within the organization. For aircrew who were performing staff functions or were attending courses, there was no urgent requirement for them to resume flying duties and, hence, we were able to monitor them over a longer period of time before reinstating their flying duties. Through this holistic approach, we were able to ensure flight safety, which is of utmost importance, and fulfill organizational demands.

Table I. Summary of Case Details.

SUBJECT NUMBER	AIRCRAFT TYPE	DRUG COMBINATION	ALANINE AMINOTRANSFERASE	ASPARTATE TRANSAMINASE	HBV DNA
1	Transport	Adefovir	Normal	Normal	Not Detected
2	Transport	Adefovir + Entecavir	Normal	Normal	Not Detected
3	Transport	Adefovir + Entecavir	Normal	Normal	Detected
4	Rotary	Adefovir + Lamivudine	Normal	Normal	Not Detected
5	Rotary	Adefovir + Lamivudine	Normal	Normal	Not Detected
6	Rotary	Entecavir	Normal	Normal	Detected
7	Rotary	Entecavir	Normal	Normal	Not Detected

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DISCUSSION

HBV is a DNA virus that belongs to the Hepadnaviridae family. The HBV structure consists of: 1) a surface envelope that includes proteins S (HBsAg), pre-S1, and pre-S2; 2) nucleocapsid which contains the core protein (HBcAg); 3) viral polymerase; and 4) viral genome. There are numerous serologic markers associated with hepatitis B infection and CHB is defined as a persistence of HBsAg for more than 6 mo. The presence of HBeAg typically indicates HBV replication and infectivity and is usually associated with high levels of HBV DNA. Clinically, persistently high HBV DNA levels could represent an increased risk for cirrhosis and hepatocellular carcinoma,[6] and could also be used as an indication for treatment initiation.

CHB is generally asymptomatic. Nonetheless, it can be broadly divided into two categories: 1) immune-active chronic hepatitis (deranged liver function tests); and 2) immune-quiescent chronic hepatitis (persistently normal liver function tests, typically over 1 yr of monitoring). Individuals with immune-active chronic hepatitis should always be offered treatment as there is a higher risk of hepatitis flares and progression to cirrhosis. Aircrew with CHB may experience constitutional symptoms, jaundice, and right upper quadrant discomfort during flares, and it is imperative that aircrew with untreated CHB be restricted from all flying duties.

Treatment options for CHB typically include: 1) PEG-IFN α; and/or 2) NUC. The advantages of PEG-IFN α are its finite duration of treatment, more sustained response, and efficacy against resistant variants. However, the side effects from PEG-IFN α treatment can be severe and is generally not compatible with flying. There are a number of NUC for the treatment of CHB, ranging from older options such as lamivudine to newer options such as entecavir. The choice of NUC depends on considerations such as the presence of cirrhosis and concurrent medical conditions, such as impaired renal function.

NUC act by inhibiting HBV DNA polymerase or HBV reverse transcriptase activity, thus decreasing viral replication. Some analogues may act against human mitochondrial DNA, leading to mitochondrial dysfunction. This may manifest in the form of myopathy, neuropathy, or lactic acidosis, although occurrences are uncommon. There is substantive evidence[10] which demonstrate the safety and efficacy of NUC, and that adverse events which are acute and incapacitating in nature are very rare (**Table II**).

Lamivudine was the first NUC approved by the U.S. Food and Drug Administration for use in patients with chronic hepatitis B in 1998. The side effect profile of lamivudine is similar to adefovir, with headache and fatigue being the most commonly reported adverse events. Patients on lamivudine may also experience gastrointestinal reactions such as abdominal pain and diarrhea. Postmarketing and/or case reports of lactic acidosis, myasthenia, peripheral neuropathy, and rhabdomyolysis have also been documented.

In a 1-yr trial of lamivudine for CHB conducted by Lai et al.,[11] it was noted that the rate of adverse events was comparable to the placebo group, with the most common adverse events being headache, cough, and abdominal discomfort. Five patients in the study discontinued therapy but none were thought to be treatment related.[11] A 2-yr follow-up of HBeAg positive patients on lamivudine conducted by Chang et al. found that the most common adverse events were headache (10%) and fatigue (6%), both of which are not acutely incapacitating in nature.[3]

Lamivudine has been used in the treatment of CHB since 1998. While we note that there have been case reports of serious adverse events, these are rare, and lamivudine has proven its safety profile through numerous studies. As with most new NUC, most of the common adverse events caused by lamivudine are neither incapacitating nor acute in nature. Nonetheless, as with all diseases and medications, due diligence must be done to ensure that aircrew are free from debilitating symptoms which could impair their performance in flight.

Adefovir was approved by the U.S. Food and Drug Administration in 2002. The main concern with adefovir is the risk of nephrotoxicity, but the mechanism is not entirely clear. The most commonly reported adverse events include headache and abdominal discomfort, while rare cases of Fanconi's syndrome, myopathy, and osteomalacia have also been reported. In a prospective, double-blinded study by Hadziyannis et al.,[8] the rate of clinical adverse events was similar between the adefovir group and the placebo group (76% vs. 74%). However, no patients discontinued treatment as a result of adverse events attributed to adefovir. Of the 76%, more than 50% were for minor symptoms such as headache, pharyngitis, and abdominal pain, all of which were classified as mild or moderate. There were also no significant differences in serum creatinine changes between the two groups. Additionally, in a study conducted by Benhamou et al.[2] over a 144-wk follow-up, asthenia was found to be the most frequent adverse event. There were no severe or life-threatening adverse events.

The safety of adefovir has been well evaluated and numerous studies have shown that it is generally well tolerated. The majority of adverse events caused by adefovir are also usually grade 1 or 2 adverse events, which are unlikely to result in sudden

Table II. Side Effects of Nucleos(t)ide Analogues.

	ADEFOVIR	LAMIVUDINE	ENTECAVIR
Mechanism of Action	Inhibits HBV reverse transcriptase	Inhibits HBV reverse transcriptase	Inhibits HBV reverse transcriptase
Most Commonly Reported Side Effects	Headache, cough, fatigue, nephrotoxicity	Headache, dizziness and gastrointestinal symptoms; rare cases of neuropathy and pancreatitis have been reported	Fatigue, headache, dizziness

HBV: Hepatitis B virus.

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incapacitation. Although nephrotoxicity caused by adefovir is a key concern for patients on treatment, it similarly does not result in sudden incapacitation and can be monitored through regular renal function tests. Aircrew on adefovir can, therefore, be considered for the reinstatement of flying duties if they have shown good tolerability to the drug.

Entecavir was approved by the U.S. Food and Drug Administration in 2005 and is one of the newer NUC. Since its introduction, entecavir has demonstrated a good safety profile and clinical superiority over other NUC.[4] The adverse events reported from the use of entecavir include headache, fatigue, and dizziness. In patients with decompensated liver disease, adverse events such as peripheral edema, hepatitis flares, and fever appear to be more common.

In a 5-yr follow up study on entecavir treatment in hepatitis B e-antigen positive patients conducted by Chang et al.,[5] 90% of patients reported adverse events. However, the most common adverse events, i.e., occurring in $\geq$10% of patients, were all unlikely to cause incapacitating effects on the patient and no patients discontinued treatment due to adverse events. These adverse events included upper respiratory tract infection, headache, and cough.[4,5] In a study comparing entecavir and adefovir conducted by Leung at al.,[13] it was noted that the frequency of adverse events was similar between the two groups. The most common adverse events were headache and upper respiratory tract infections. There were no treatment discontinuations in the entecavir group.

When compared with lamivudine, several prospective studies have demonstrated that entecavir has a comparable safety profile to lamivudine. In a randomized, double-blind trial by Sherman et al.,[17] the rates of adverse events were 85% and 81% in the entecavir and lamivudine groups, respectively. Only 1% of entecavir patients discontinued the drug due to adverse events. Similar results were achieved by Chang et al.,[4] who demonstrated comparable rates of adverse events between the entecavir and lamivudine group. The most frequent adverse events were also not of an incapacitating nature, and these included headache, cough, and upper respiratory tract infection. Finally, a meta-analysis by Huang et al. showed comparable adverse events rate between patients treated with entecavir and patients treated with a combination of lamivudine and adefovir.[9]

Entecavir has proven efficacy against CHB and has also demonstrated a good safety profile. Most of the adverse events caused by entecavir are of mild-moderate severity and the use of entecavir is unlikely to result in acute, incapacitating effects based on literature review. While we acknowledge that the use of entecavir is unlikely to result in sudden incapacitating events, we need to ensure close medical supervision should we decide to return aircrew on entecavir back to flying.

Of note, none of the aircrew were on tenofovir, which is one of the newer NUC used in the treatment of CHB. Tenofovir can be used in treatment-naïve patients or those who have developed resistance against other NUC. However, there is a risk of renal and bone toxicity with tenofovir which will require close monitoring. Allowing aircrew to fly while on tenofovir will require further evaluation and should also be considered on a case-by-case basis.

There remains the theoretical risk that NUC, which acts against the human mitochondria, can result in subclinical symptoms such as myopathy, affecting aircrew's peak performance. For aircrew flying high performance aircraft, this peak performance impairment could translate into lowered G tolerance, increasing the risk of G-induced loss of consciousness in high G maneuvers. Hence, a functional evaluation may be undertaken in the consideration for any waivers for aircrew on CHB treatment flying high performance aircraft; this could take the form of an assessment on G performance in the human centrifuge. Notwithstanding, waiver for aircrew flying high performance aircraft will need to be carefully evaluated on a case-by-case basis; to date, there have been no Republic of Singapore Air Force aircrew flying high performance aircraft who require a waiver back to flying duties while receiving NUC treatment for CHB.

Moving forward, it is predicted that we would be unlikely to encounter many more new cases of aircrew with CHB. Since 1987, Hepatitis B immunization has been included as part of the Singapore National Childhood Immunization Program. Between 2007 and 2016, Hepatitis B immunization coverage rates have been consistently greater than 95%.[14] A review of the seroepidemiology of Hepatitis B virus infection among adults in Singapore demonstrated an HBsAg prevalence of 1.1% among adults less than 30 yr of age. The same study also demonstrated an increase in the prevalence of Hepatitis B immunity from 27.9% in 1998 to 43.3% in 2010.[1] These results demonstrate the efficacy and impact of the national childhood Hepatitis B immunization program in reducing Hepatitis B infection. Hepatitis B antigen and antibody levels are also screened for all aircrew at entry and booster shots of vaccines are provided when required.

From our experience, military pilots and aircrew with CHB can be safely returned to flying duties following adequate viral suppression, normalization of liver function tests, and the absence of significant side effects following 3–6 mo of CHB treatment with NUC. In this case series, all seven pilots had been aeromedically restricted from flying duties for variable periods of time, ranging from 3 to 39 mo. The duration of treatment depended on the control of their CHB and response to NUC treatment. However, we did not have any further side effects developing beyond 6 mo upon commencement of NUC treatment. Out of seven aircrew, only one developed side effects, i.e., headaches from NUC treatment. Headaches can impair judgement and performance, and it was only after careful consideration of the potential risks did we allow the pilot to return to flying duties. While we could have simply restricted him from flying duties permanently, the evaluating aeromedical board felt that his headaches had been adequately managed, and that the pilot had demonstrated discipline during the course of management of his medical condition. It should also be noted that this retrospective case series comprised a small sample size of only seven aircrew, although our findings in NUC treatment for aircrew support the favorable safety profile reported within the medical literature. Nonetheless, a prudent

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approach must be taken and complications from both the treatment and disease must be taken into consideration when assessing suitability for flying duties.

Good treatment outcomes without further liver inflammation, lower relapse rates, and the favorable side effect profile of NUCs provide sufficient justification for us to review the return of aircrew back to flying duties while on NUC. While we take reference from published waiver guidelines for guidance on the determination of the flying disposition of aircrew, we also recognize the evolving nature of medicine and the need to balance medical treatment with the aircrews' flying careers and cost of training. Notwithstanding, sound clinical judgment and close observation should be exercised when managing aircrew starting on a new course of NUC despite their reported good safety profiles. A variable period of observation (of at least 3–6 mo) is still advisable for aircrew starting NUC to watch for development of treatment-related side effects.

In returning aircrew on CHB treatment back to flying duties, the close and coordinated medical management involving the medical specialist (i.e., hepatologist) and flight surgeon is of paramount importance. Although current waiver guidelines stipulate the need for aircrew to be taken off NUC prior to returning to flying duties, this case series has demonstrated that resumption of flying duties while on NUC is feasible under close medical supervision. Nonetheless, it must be noted that this case series was based on pilots treated with older NUC treatment regimes and newer treatment options, such as tenofovir, must be evaluated further for their flight safety profile.

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