GUIDANCE MATERIAL TO SUPPORT THE PROPOSED CHANGES TO THE MEDICAL PROVISIONS CONTAINED IN ANNEX 1 — *PERSONNEL LICENSING*

March 2008

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1. Background

Class 1 applicants are required to have an annual medical assessment from the time they commence flying until they reach 60 years of age, when the frequency becomes 6-monthly. The exception to this is for the passenger-carrying single pilot operator, who requires a medical assessment every six months after age 40 years. The medical assessment varies little during a pilot's career, although after the initial electrocardiogram (ECG) at the first Class 1 examination the frequency for ECGs increases with increasing age, initially as a Recommendation (two-yearly from age 30-50 years) and then as a Standard (annually from age 50 years). ICAO therefore recognizes the increase in cardiovascular risk with increasing age, which is an observation in all Contracting States. There are, however, differences between States regarding the rate of increase in risk with increasing age.

In most Western States, the annual cardiovascular mortality for males reaches around 1 per cent per annum at age 70 years, which is about 100 times greater than at age 30. Further, the risk of developing other physical diseases such as cancer, diabetes and epilepsy is very low in young adults, but increases with increasing age. On the other hand, mental health illness and behavioural problems, including those related to drug and alcohol use, do not demonstrate such a steep gradient, and in the general population these categories are usually more frequent than physical disease in younger age groups. It therefore seems appropriate to consider the likely prevalence of different diseases in the pilot population when considering the type of routine periodic examination they should undergo.

The annual Class 1 medical examination is unlikely to reveal any significant physical problem in pilots under age 40 years. Some items of the physical assessment could therefore be omitted in alternate years without detriment to flight safety. This would permit additional time to be used to focus on mental health aspects, and on preventative aspects of health. It is widely accepted that illness in later life, both physical and mental, can be prevented or delayed by lifestyle interventions and treatment, if necessary, at an early stage, and professional pilots represent a group of motivated individuals who have a keen interest in health maintenance. Such a change of emphasis in the younger pilot should encourage health and, therefore, flight safety benefits later on in a pilot's career.

The proposed ICAO Standards and Recommended Practices (SARPs) for a Class 1 assessment are being adjusted to permit a licensing authority, in alternate years, to omit certain items from the physical examination in applicants under 40 years of age, thereby enabling a medical examiner to spend more time discussing medical issues, from an educational viewpoint, with an applicant in this age group. However, a licensing authority may wish, for example, to undertake some assessment of the vision every year in order to ascertain those applicants who would benefit from correcting lenses, or a change in prescription, since refractive error can change over time in the younger age group.

It is felt that an examination of, for example, the heart and lungs, and checking the blood pressure and urine in all pilots under 40 years, on an annual basis, is unnecessary – a two yearly examination should be adequate. This does not preclude the licensing authority from requiring more frequent checks in those who are known to have an increased risk. If the content of the physical examination is reduced in alternate years, this releases some time for discussing aspects of health that may, in the longer term (with a timescale greater than that of the validity of the medical assessment/certificate) improve the pilot's health, and as a consequence, improve flight safety.

Two aspects are particularly worthy of consideration. The first concerns the preservation of physical health. The factors for this are well known. Aspects of diet, exercise, smoking, body weight, etc. and their effect on health are familiar to all medical examiners and these can be discussed with the individual applicant in light of the particular circumstances of the individual, such as family history of illness, body weight, exercise habits, etc. Licensing authorities are encouraged to provide guidance to designated medical examiners regarding these aspects of health maintenance.

The second aspect concerns mental health and use of psychoactive substances. Guidance on this area is not so readily available, and at the request of ICAO a small group of experts has reviewed the evidence of benefit in discussing certain topics with applicants, by means of asking specific questions. This review has demonstrated from general population studies that some mental illnesses and misuse of psychoactive substances can be prevented by early intervention, before the situation has deteriorated to an extent where the health, or medical fitness for flying of a licence holder, has been adversely affected. A separate section on this topic with draft guidance material has been provided below.

Historically, the focus of the periodic medical examination has been to detect medical conditions, almost exclusively physical medical conditions, that may pose a threat to flight safety during the forthcoming period of validity of the medical assessment/certificate. The medical examiner's primary role has therefore been to detect significant conditions that may cause incapacitation in the relatively short term. The role of the medical examiner as educator has not played a formal part in the process, although many examiners take on this task as a natural part of the role of any doctor. Whilst the role of the medical examiner in determining the physical fitness of the pilot will continue, because of the low level of physical pathology encountered in the lower age group, an opportunity to improve the health of the applicant, as well as improve flight safety, presents itself. One view is that this is not the role of the regulatory medical examiner, but in reality the examiner is in an excellent position to provide this service to flight safety and to the applicant (who, experience has shown, is unlikely to seek such advice elsewhere).

By reducing the emphasis on the physical examination in those Class 1 applicants less than 40 years of age, time is made available to focus on the non-physical aspects of health, in a non-threatening manner, and at no additional cost to the applicant.

2. Development of questions for use by medical examiners

As there is evidence that several fatal aviation accidents have been caused by psychiatric disorders or use of psychoactive substances, it is reasonable that as part of the periodic aviation medical examination there should be questions that pertain to these issues. Little guidance has been provided concerning how such aspects could be addressed in the periodic medical examination, although experienced medical examiners have often informally and spontaneously included it in assessment of the applicant. Further, the number of non-physical conditions that can affect the health of pilots and which can lead to long term unfitness in those of middle age appears to be increasing. The conditions addressed by the proposed questions that medical examiners could use have been shown to be amenable to preventive action, before they develop into significant health problems, and before there is an impact on the pilot's medical status for flying.

There are various questionnaires available for assessing mental health and behavioural aspects of an individual's health, having a variety of lengths and complexity. However, the main purpose of recommending the questions below is intended to be educational, with the questions serving to promote discussion between the medical examiner and the pilot. To encourage dialogue, it is recommended that no

written record of the conversation is retained concerning these questions and that this should be made clear to the pilot at the outset, thus increasing the likelihood of developing a frank exchange. Further, it is to be expected that only rarely will any formal action need to be considered by the medical examiner to protect flight safety in the light of response to these questions.

The questions suggested address those conditions that are most common in the age range of professional pilots and those which are most likely to affect performance on the flight deck. Statistics show that the main psychiatric conditions that meet these criteria are mood disorders and certain anxiety disorders, especially panic episodes. Additionally, in many Contracting States, excessive alcohol intake and use of illicit drugs in the general population is occurring with increasing frequency and pilots are not immune from these social pressures. Questions have been developed to address these issues as well.

In developing the questions, a review of the literature was undertaken by specialists in the field with the aim of choosing simple questions that can be completed quite quickly. The majority of pilots will answer all questions in the negative, and it is unnecessary to request pilots without any relevant problems to undertake a prolonged screening questionnaire. Those who answer positively, or with uncertainty can be engaged with further dialogue by the medical examiner. The main aim is to encourage the pilot to consider his lifestyle and improve, where necessary, his or her likelihood of maintaining good mental health, including the avoidance of problems linked to the use of psychoactive substances, during his/her career. Occasionally, the medical examiner may find conditions that are amenable to medical support or even treatment, and the goal is to detect these at an early stage, before they become significant problems and before they impact on the pilot's medical fitness and on flight safety.

Not all medical departments will find the questions relevant to their particular pilot population. Therefore, the questions may not represent the best questions for all States, but they offer guidance, a starting point, for States that wish to develop such an approach.

3. Recommended questions concerning mental health and use of psychoactive substances

Questions for Depression:

1) During the past three months, have you often been bothered by feeling down, depressed or hopeless?

2) During the past three months, have you often been bothered by having little interest or pleasure in doing things?

3) During the past three months, have you been bothered by having problems falling asleep, staying asleep, or sleeping too much, that is unrelated to sleep disruption from night flying or transmeridian operations?

4) In the past three months, has there been a marked elevation in your mood lasting for more than one week?

Questions for anxiety/panic attack:

1) In the past three months, have you had an episode of feeling sudden anxiety, fearfulness, or uneasiness?

2) In the past three months, did you experience sensations of shortness of breath, palpitations (racing heart beat) or shaking while at rest without reasonable cause?

3) In the past year have you needed to seek urgent medical advice because of anxiety?

Questions concerning alcohol use:

1) Have you ever felt that you should cut down on your drinking?

2) Have people annoyed you by criticizing your drinking?

3) Have you ever felt guilty about your drinking?

4) Have you ever needed a drink first thing in the morning?

5) How many alcoholic drinks would you have in a typical week?

6) How many alcoholic drinks would you have on a typical day when you are drinking?

Questions concerning drug use:

1) Have you used drugs other than those required for medical reasons?

2) Which non-prescription drugs have you used? When did you last use this drug(s)?

References for those who wish to consider the literature themselves are as follows:

1) Alcohol Alert NIAAA Apr 2002 http://pubs.niaaa.nih.gov/publications/aa56.htm
2) Screening for Alcohol Problems in Primary Care: Fiellen, Reid, et al, Arch Intern Med Vol. 160 July 2000.
3) Case-finding Instruments for Depression. two questions as good as many. Whooley, Avins et al J Gen Intern Med. 1997; 12: 439-445.
4) Using five questions to screen for five common mental disorders in primary care. A.J. Means-Christensen et al; General Hospital Psychiatry 28 (2006) 108-118.
5) Counselling Resource Welcome to the Drug Abuse Screening Test (DAST). http://counsellingresource.com/quizzes/drug-abuse/index.html.
6) Manual on prevention of problematic use of substances in the aviation workplace, Document 9654; International Civil Aviation Organization, Montreal, Canada, 1995

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TREATMENT OF DEPRESSION

1. Introduction

A new Recommendation and a Note is proposed concerning licence holders who have depression and are in need of treatment with antidepressants:

> 6.3.2.2.1 (and 6.4.2.2.1, 6.5.2.2.1) ***Recommendation***.— *An applicant with depression, being treated with antidepressant medication, should be assessed as unfit unless the medical assessor, having access to the details of the case concerned, considers the applicant's condition as unlikely to interfere with the safe exercise of the applicant's licence and rating privileges.*
>
> *Note 1.— Guidance on assessment of applicants treated with antidepressant medication is contained in the* Manual of Civil Aviation Medicine *(Doc 8984).*

2. Background

The use of antidepressant medication in aircrew and air traffic controllers (ATC) has traditionally been disqualifying for medical certification due to the underlying medical condition and the potential safety relevant side-effects of the available medications to treat it [1, 2]. In the United States, in accordance with Federal Aviation Administration (FAA) rules, antidepressant usage must have ceased for at least three months [3], while in Europe the Joint Aviation Authorities' policy is that no certification can be considered whilst using psychoactive medication[4,5].

Depression is a common worldwide disorder in the adult population, although reported prevalence varies quite widely [6]. In the United States the lifetime prevalence of major depressive disorder was found to be 16.2 per cent, which would involve almost 34 million US adults, and for a twelve-month period the figure was 6.6 per cent [7].Whilst there is no evidence that selective serotonin reuptake inhibitors (SSRI) medications are more efficacious than older antidepressant medications, this new generation of antidepressants is better tolerated by patients and has an improved side effect profile [8, 9, 10].

Many patients require long term treatment with antidepressants to reduce the risk of recurrence. One systematic review [11] found that continuing antidepressant medication treatment after recovery dramatically reduced the proportion of patients who relapsed over one to three years, compared with placebo. The average rate of relapse on placebo was 41 per cent, compared with 18 per cent on active treatment.

There is emerging evidence in the literature that suggests that policies which disqualify pilots from flying whilst on antidepressant medications may lead to pilots flying when depressed and untreated, or flying on antidepressant medication but not reporting it to the regulatory authority [12, 13, 14]. An Aerospace Medical Association position paper [12] stated that, according to the Aviation Medicine Advisory Service database of pilots' telephone inquiries, approximately 15 per cent of pilots who had been advised by their physicians to take antidepressant medications showed an intention to take the medications and continue flying without informing the Federal Aviation Administration.

Canfield et al. [13] reported on post-mortem toxicological evaluations performed on 4 143 pilots. Psychotropic medications were found in 223 pilots but only fourteen of these pilots had reported a

psychological condition to the FAA and only one of the fourteen pilots had reported the psychotropic medication.

In Australia in 1987, the Civil Aviation Safety Authority (CASA) began allowing aviation personnel who had been depressed to operate once they had been effectively treated and had become stable with the use of antidepressant medications. The policy had become somewhat liberal with the allowance of use of most medication groups including monoamine oxidase inhibitors (MAOI) and tricyclic antidepressants (TCA). There were no reported adverse outcomes related to this policy but in 2003 a more restrictive approach was introduced with increased surveillance and limitation to specific medications (17). A study published in August 2007 looking at safety outcomes such as accidents and incidents in 481 certificate holders over a ten year period found no evidence of adverse outcomes related to allowing pilots to fly on antidepressant medication provided specific criteria were met (14).

In Canada, pilots on maintenance therapy are allowed to fly "with or as co-pilots" under an aeromedically supervised treatment protocol in which pilots are followed prospectively (18).

The AsMA position paper (12) points out that several factors must be considered in relation to safety should certificate holders be allowed to operate whilst using antidepressant medications. Firstly, it is important to establish the diagnosis. SSRIs are used to treat not just depression, but some other aeromedically significant illnesses such as obsessive compulsive disorder and panic disorder. Second, patients generally have their adverse reactions to SSRIs early in treatment; these side effects usually diminish as the patient becomes physiologically accustomed to the medication. Third, the newer SSRIs have fewer side effects than the older antidepressants because the pharmaceutical industry is designing them to act only on receptors in specific areas of the brain.

Some of these medications are sedating and some are not, thus offering a therapeutic choice in treating depressed patients who show psychomotor agitation or retardation. Fewer side effects generally result in improved aeromedical safety. However, successful treatment of depression is a dynamic and complex process involving more than just writing a prescription and the SSRIs can have some aeromedically significant side effects and withdrawal effects that are of little importance in ordinary clinical practice (12).

Finally, an important aspect to consider is that a diagnosis of depression often carries with it significant social stigma and in many societies it is common that symptoms of depression are not discussed openly with either colleagues or the medical profession. Aeromedical policies that place an absolute prohibition on operating after a diagnosis of depression may also make it less likely that an aviator or air traffic controller will seek treatment or declare their illness to the licensing authority.

3. **Draft guidance**

3.1 *The assessment of pilot and ATC applicants with depression*

Depressive mood disorders (ICD-10: Depressive episode; DSM-IV-TR: Major Depressive Disorder) are common disorders which present with depressed mood, reduced energy, impaired concentration and memory, loss of interest in surroundings, slowed cerebration, difficulty in making decisions, alteration of appetite and sleep, guilt feelings, and low self esteem. Suicide is common; the incidence varies with cultural background, but may approach 20 per cent per depressive episode.

The illness is usually of insidious onset and persists for many months when not treated adequately. Depression may be accompanied by a number of somatic symptoms. There may be diurnal variation in

the symptoms, and many persons with depression may have some good days in between. It is not unusual for sufferers to try to modify their symptoms (especially the dysphoria and insomnia) by the use of alcohol and prescribed medications or illicit drugs.

Depression leads to subtle (and sometimes overt) incapacitation, mainly due to the decreased ability to concentrate, as well as to distractibility and indecision, which are frequent features of the illness. It is these symptoms, along with the risk of suicide, which make a depressed individual unsuitable to work in the aviation environment. Because the symptoms wax and wane during a depressive episode, there may be days when the individual is relatively well and may appear to be fit to fly. However, impaired concentration and lack of cognitive agility are always more or less present and may interfere with the ability to integrate the multiple sensory inputs required to make decisions in an emergency.

Depression is by nature a recurrent disorder and although single episodes do occur, the history of a depressive episode should alert the medical examiner to ask specific questions to ensure that the applicant does not currently have the illness. Those persons who have had one serious depressive episode have approximately a 50 per cent risk of experiencing a second episode. Because depressive mood disorders are recurring disorders, it is imperative that the “recovered” patient be monitored closely for signs of recurrence for a period of time following recovery. There is evidence that recurrence is most likely to happen during the first two years. An educative approach may help the individual recognize the earliest signs and thus facilitate early intervention.

Historically, pilots have not been allowed to return to flying unless they have ceased taking medication for at least some months after having returned to their euthymic state of health. In recent years, the use of SSRIs has become widespread in the general population and there is reason to believe that such treatment may be compatible with flying duties in carefully selected and monitored cases. This may be in a situation of an initial successful response to treatment of acute depressive episode, or where treatment is aimed at the prevention of recurrences.

It should be noted that even with good responses, there may be the potential for impairment of cognition and decision making ability from either an incomplete response to treatment or from safety relevant side effects of medications. From the patient’s perspective, the pronouncement of “being well” may refer only to relative improvement in comparison with the untreated state. Applicants therefore need to be carefully assessed for the presence of any residual symptoms and any performance relevant side effects of the medication.

3.2 *The assessment of pilot and air traffic controller applicants treated with antidepressants*

States may, on a case-by-case basis certificate applicants who are prescribed (and are taking) an approved SSRI antidepressant medication for an established diagnosis of depression which is in remission. Conditions necessary for air safety may be imposed on the certificate as appropriate, for example "holder to fly as or with co-pilot", thus limiting operations to multi-crew aircraft. Pilots and ATCs taking other types of anti-depressants will not usually be considered for certification.

States’ certification of pilots and ATCs taking medications accepted by the Licensing Authority should be conditional on the following:

a) The applicant should be under the care of a medical practitioner experienced in the management of depression

b) The applicant should:

1) be stable on an established and appropriate dose of medication for at least four weeks before returning to flying/ATC duties and exhibiting:

i) minimal acceptable side-effects
ii) no medication interactions or allergic response

2) be subject to regular clinical review by the medical practitioner with progress reports provided to the medical department of the Licensing Authority. The applicant may be involved in other concurrent treatment (e.g. psychotherapy).

3) have an absence of other significant psychiatric co-morbidities

4) require no other psychoactive medications

c) Symptoms of depression being well controlled, without evidence of psychomotor retardation

d) An absence of suicidal ideation or intent

e) No history of psychotic symptoms

f) An absence of features of arousal (e.g. irritability or anger)

g) The presence of a normal sleep pattern

h) Resolution of any significant precipitating factors of the depression

Ongoing cognitive-behavioural, rational-emotive or similar therapy is desirable, but not necessarily required for certification.

Pilots or ATCs authorized to fly or perform duties when taking SSRIs or related antidepressant medications must cease exercising the privileges of their licences if their antidepressant medication is altered or if the dose changed. Their supervising medical practitioner may return them to duty when they are assessed as stable and without unacceptable side effects.

Pilots and ATCs whose medication is being reduced with a view to cessation should stop exercising the privileges of their licences for the entire period during which they are weaned off medication, plus an additional period of two weeks. Their supervising medical practitioner may return them to duty when they are assessed as stable and without unacceptable side effects or evidence of withdrawal syndrome.

The use of objective assessment tools in the monitoring of these certificate holders is encouraged. The Hamilton ratings scale is one such tool and formal neuropsychological testing is another option. Simulator or other functional based testing can also be utilized to assess performance. States should provide guidance on preferred medications with lower side effect profiles such as sertraline, citalopram, and escitalopram.

Outcome criteria/data on the cohort returned to work should be established prospectively and captured for review of the programme.

4. References

1. International Civil Aviation Organization. International standards and recommended practices. Personnel licensing. Chapter 6. Medical provisions for licensing. Montreal: ICAO; 2005.
2. *Manual of Civil Aviation Medicine* (Doc 8984-AN/895), Second Edition, 1985. ICAO publication.
3. Federal Aviation Authority Guide for Aviation Medical Examiners. Accessed 18 December 2005 http://www.faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide/media/amd47psych.pdf
4. Joint Aviation Authorities' Policy. JAR-FCL 3 Appendix 10, paragraph 2.
5. Joint Aviation Authorities (Europe) Manual of Civil Aviation Medicine. Accessed 18 December 2005 http://www.jaa.nl/licensing/manual/11%20-%20Psychiatry.pdf
6. Prevalence, Severity, and Unmet Need for Treatment of Mental Disorders in the World Health Organization World Mental Health Surveys. The WHO World Mental Health Survey Consortium JAMA. 2004; 291:2581-2590.
7. Ronald C. Kessler; Patricia Berglund; Olga Demler; Robert Jin; Doreen Koretz; Kathleen R. Merikangas; A. John Rush; Ellen E. Walters; Philip S. Wang The Epidemiology of Major Depressive Disorder: Results From the National Comorbidity Survey Replication (NCS-R) JAMA 2003 289: 3095-3105
8. Westenberg HG, Sandner C. Tolerability and safety of fluvoxamine and other antidepressants. Int J Clin Pract. 2006 Apr;60(4):482-91. http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=16620364
9. Arroll B, MacGillivray S, Ogston S, et al. Efficacy and tolerability of tricyclic antidepressants and SSRIs compared with placebo for treatment of depression in primary care: a metaanalysis. Ann Fam Med. 2005;3(5):449– 456.
10. Cipriani A, Geddes JR, Furukawa TA, Barbui, C. Metareview on short-term effectiveness and safety of antidepressants for depression: an evidence-based approach to inform clinical practice. Can J Psychiatry. 2007 Sep;52(9):553-62
11. Geddes JR, Carney SM, Davies C, et al. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. Lancet. 2003;361(9358):653–661.
12. Jones DR, Ireland RR. Aeromedical regulation of aviators using selective serotonin reuptake inhibitors for depressive disorders. Aviat Space Environ Med 2004; 75:461–70.
13. Canfield DV, Salazar GJ, Lewis RJ, Whinnery JE. Pilot medical history and medications found in post mortem specimens from aviation accidents. Aviat Space Environ Med. 2006 Nov;77(11):1171-3.
14. Ross J, Griffiths K, Dear K, Emonson D, Lambeth L. Antidepressant use and safety in civil aviation: a case-control study of 10 years of Australian data. Aviat Space Environ Med. 2007 Aug;78(8):749-55.
15. Hudson DE Jr. SSRI use in professional aircrew. [abstract]. Aviat Space Environ Med 2002; 73:244–5.
16. Hudson DE Jr. SSRI use in professional aircrew. Panel presentation. Aerospace Medical Association annual meeting. 9 May 2002, Montreal, Canada.

17. Civil Aviation Safety Authority (CASA) (2003). Use of antidepressant medication by depressed pilots and air traffic controllers. Designated Aviation Medical Examiners handbook. Australia: Civil Aviation Safety Authority.

18. Lange M. Maintenance SRI use in professional pilots: the Canadian experience [Abstract]. Aviat Space Environ Med 2002; 73:244.

19. Ahmet Sen, Ahmet Akin Gülhane Dennis V. Canfield Arvind K. Chaturvedi. Selective Serotonin Reuptake Inhibitors:Medical History of Fatally Injured Aviation Accident Pilots DOT/FAA/AM-07/19 Office of Aerospace Medicine

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REPORTING OF MEDICAL CONDITIONS

In previous editions of Annex 1, it was a Recommendation that licence holders should inform the Licensing Authority of pregnancy, decrease in medical fitness for more than 20 days, or the continued use of prescribed medication. However, experience has shown that Licensing Authorities have interpreted this in different ways and, following discussion with States it has been revised to the following:

> 1.2.6.1.1 **Recommendation**.— *States should ensure that licence holders are aware of physical and mental conditions and treatments that are relevant to flight safety. They should provide guidance concerning those circumstances when medically related information should be forwarded to the Licensing Authority*

It is clearly important that licence holders are aware of those medical conditions that are relevant to flight safety, so that, when they have developed a medical condition, they know when to seek medical help, and when to cease flying. For example, cardiac disease is an important flight safety risk for all Licensing Authorities, although the degree of risk is likely to vary from State to State, depending on the prevalence of such disease in different States. States should inform applicants of this potential risk to their medical fitness and to their health and Licensing Authorities may wish to place more or less emphasis on this aspect of fitness for holders of licences issued by their State. The same principle applies to certain infections, depending on the prevalence of such infections in different parts of the world.

States can provide information concerning relevant physical and mental conditions in many ways. Examples include: internet website; information circular; medical examiner briefing. The most effective way(s) is likely to differ from State to State. A medical examiner briefing may be effective and for Class 1 applicants under 40 years of age it is suggested that this could be formally included in the preventative and educative part of the medical assessment, as discussed in other parts of the proposed amendment to Annex 1.

For many conditions, modern medical practice has changed the length of time required in hospital, and some conditions that, in the past, involved a lengthy hospital stay, can now be dealt with very quickly, even as an outpatient. One State lists the following conditions (which are not exhaustive) as requiring advice from a designated medical examiner before a return to operations can be considered:

a) any surgical operation
b) any medical investigation with abnormal results
c) any regular use of medication
d) any loss of consciousness
e) kidney stone treatment by lithotripsy
f) coronary angiography
g) transient ischaemic attack
h) abnormal heart rhythms including atrial fibrillation/flutter

In many instances of ill-health, a medical practitioner without any training in aviation medicine may be unable to provide appropriate advice to a licence holder regarding fitness to fly. Any licence holder should be aware of the action to take in the event of suffering a common cold, without having to seek advice from a designated medical examiner unless there are complicating factors, but for more serious conditions advice concerning fitness to operate should be readily available from those with specialist knowledge, e.g. a designated medical examiner or the Licensing Authority headquarters. If a “temporarily unfit” assessment is made, the method for regaining fitness should be clear and, when fitness is regained, return to operations should not be unduly delayed. If a licence holder is affected by the circumstances

such as those listed above, it is considered that they should be aware of the need to seek aviation medicine advice before exercising licence privileges.

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HUMAN IMMUNODEFICIENCY VIRUS (HIV)

SUGGESTED PROTOCOL FOR ASSESSMENT OF HIV DISEASE

1. **Following an initial diagnosis of HIV seropositivity**

Assess temporarily unfit, pending submission of reports.

a) HIV Specialist Review

- History of infection
- Current and previous symptoms
- Stability of condition
- History of opportunistic infections or associated illnesses
- History of CD4+ T cell counts
- History of Viral Load measurements
- Medication history (including 'over the counter' medications and alternative medicines)
- Report concerning side effects of medications
- Laboratory testing to include:

  – Hepatitis B & C, Cytomegalovirus, toxoplasma, tuberculosis.
  – Full Blood Count, urea, creatinine and electrolytes, liver function tests, fasting glucose, lipids.

b) Neurology Review – can be undertaken by HIV specialist, or neurologist

Assessment for neurological sequelae. Include assessment of primitive reflexes (because of their association with cognitive decline)

c) Neuropsychological Review

- Baseline neuropsychological assessment.
- Tests should include timed psychomotor tasks and memory tasks requiring attention, learning, active monitoring and retrieval of information.

d) Psychiatry Review

Assessment for psychiatric sequelae related to HIV seropositivity and antiretroviral treatment.

e) Cardiology Review (only if indicated)

Cardiological review is recommended if the following exist:

- Lipodystrophy or metabolic syndrome (dyslipidaemia — raised total cholesterol, low high density lipoprotein cholesterol and raised triglycerides or insulin resistance with hyperglycaemia);

- Cardiac risk factors are present, including:

  – hypertension, evidence of left ventricular hypertrophy, smoking, raised lipids, diabetes, age over 40 years.

2. **Aeromedical Certificatory Assessment**

On receipt of satisfactory reports, applicants who are asymptomatic, stable, without significant opportunistic infection may be considered for certification, if their CD4* count is above the minima stated below. Once diagnosed HIV positive, solo operation as a pilot should not be accepted for Class 1 or Class 2 applicants.

a) Table 1 — Applicants not established on combined antiretroviral therapy (cART)

Age (yr)	**Minimum CD4+ count**
20 – 39	350
40 – 59	400
60 +	500

Applicants over 40 years of age with CD4+ counts below these levels but above 350/mm^3 may be considered for certification on an individual basis.

b) Table 2 Applicants established on combined antiretroviral therapy (cART)

CD4 Count	> 350 = 0	201 − 350 = +0.62	51 − 200 = +1.46	≤50 = +2.44
BMI	≤ 18 = +0.80	18.1 − 25 = 0	> 25 = −0.29	
Viral Load	< 500 = 0	≥ 500 = +0.18		
CD4 slope (3 month)	< −25/mm^3 = +0.49	−25 to +25/mm^3 = 0	> 25/mm^3 = +0.18	
Anaemia	No = 0 Hb > 14.0g/dl male Hb > 12.0g/dl female	Mild = +0.68 Hb 8.01 − 14.0g/dl male Hb 8.01 − 12.0g/dl female	Severe = +1.02 Hb ≤ 8.0g/dl	
ART experience prior to cART	Yes = 0	No = −0.39		
Taking antiretrovirals	Yes = 0	No = +1.24		
Age	Age × 0.027			
Infected with HIV	Via intravenous drug use = +0.25		Via any other route = 0	
Prior diagnosis of AIDS at starting cART	No = 0	Yes = +0.19		
Score	**% Risk of clinical progression in following twelve months**			
<1.5	0.5			
1.5 – 2.99	1.4			
3.0 – 4.49	6.25			
≥4.5	>20			

Table 2 enables a risk assessment to be undertaken. The figures are summated to reach a score that allows a prediction of risk of progression during the next 12 months.

Notes:

Acceptable medications include: abacavir, didanosine, emtricitabine, lamivudine, tenofovir, zidovudine, atazanavir, fosamprenavir, lopinavir/ ritonavir, nelfinavir, saquinavir, nevirapine and efavirenz

Unacceptable medications include enfuvirtide, zalcitabine, indinavir and stavudine.

Recently available medication, e.g. tipranavir, darunavir, raltegravir and maraviroc, may be acceptable on an individual basis. Particular attention needs to be given to the toxicity and side-effect profile of such medications.

A "temporary unfit" assessment should be made when initiating, modifying or discontinuing ART. When stable, recertification after 3 months of monitoring may be permitted providing that there has been an acceptable serological response, no ongoing side-effects and FBC, LFTs, lipids and fasting glucose are acceptable.

Those commencing or modifying efavirenz treatment require a psychiatric and neurological examination at initial certification or within 6 months after initiating therapy.

Reviews should take account of any over the counter medications and alternative therapies being taken

3. **Follow-up**

Regular follow-up is required, to include:

- 3 monthly CD4[*] and viral load measurements
- 6 monthly neurology assessment (by HIV specialist or neurologist including consideration of the need for psychiatric evaluation)
- if taking ART: 6-monthly LFTs, FBC, lipids and fasting glucose.
- Annual cognitive function assessment

  – Evidence of having passed a Licence Proficiency Check (LPC) or the report from a medical flight test (MFT) with a Flight Instructor Examiner (FIE) may be considered in lieu of this where disease stability and the risk of disease progression is acceptable. Impaired performance will require further neuropsychological assessment to be compared with baseline testing and any deficits will require that the pilot is declared temporarily unfit. Neuropsychological assessment should be undertaken if there are any clinical concerns about cognitive impairment.

Further co-infection testing should be undertaken where clinically indicated and those with new positive tests must be deferred for further assessment.

If an applicant develops new symptoms and/or fails to achieve the nominal levels listed above[*] he must be declared temporarily unfit and referred to the Licensing Authority.

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[*] CD4+ T cell counts are subject to substantial variability due to both biological and laboratory methodologies and can vary up to 30 per cent on repeated measures in the absence of a change in clinical status. Therefore it is important to monitor trends over time rather than take a decision on one specific determination. Sudden changes in the count need to be confirmed by a second determination.

References:

1. Table 1 is derived from Phillips A. CASCADE Collaboration. Short-term risk of AIDS according to current CD4 cell count and viral load in antiretroviral drug-naive individuals and those treated in the monotherapy era. AIDS 2004 Jan 2. 18(1):51-8 and from the WHO guidelines on initiating ART.

2. Table 2 is derived from Mocroft A, Ledergerber B, Zilmer K, Kirk O, Hirschel B, Viard J-P, Reiss P, Francioli P, Lazzarin A, Machala L, Phillips A, Lundgren J; for the EuroSIDA study group and the Swiss HIV Cohort Study Short-term clinical disease progression in HIV-1-positive patients taking combination antiretroviral therapy: the EuroSIDA risk-score. AIDS. 21(14):1867-1875, September 2007.

II. REVISED DRAFT OF CHAPTER ON HIV CONTAINED IN DOC 8984

(Note.— This is a revised draft of the current chapter on HIV, part of Doc 8984 (Manual of Civil Aviation Medicine)*, that is currently available in draft form on the ICAO public website)*

1. Introduction

In the introductory chapters of this manual the basic principles for the assessment of an applicant's medical fitness for aviation duties are outlined.
In the general medical provisions of Annex 1 the SARPs related to Human Immunodeficiency Virus (HIV) are the same for all three classes of medical assessment (medical certification) – commercial pilots, private pilots, and air traffic controllers – and state that:

> 6.3.2.20.1 Applicants who are seropositive for human immunodeficiency virus (HIV) shall be assessed as unfit unless full investigation provides no evidence of HIV-associated disease that might give rise to incapacitating symptoms.
>
> *Note 1.— Early diagnosis and active management of HIV disease with antiretroviral therapy reduces morbidity and improves prognosis and thus increases the likelihood of a fit assessment.*

The main purpose of the guidance material contained in this section is assist with determining the requirements for a full investigation and risk assessment for disease that might lead to incapacitation in HIV-seropositive applicants.

2. Background

HIV infection is pandemic with cases reported from virtually every country. Untreated the infection usually leads to Acquired Immunodeficiency Syndrome (AIDS) with AIDS-defining opportunistic infections or associated illnesses. A 2007 report from UNAIDS/WHO estimated that 33.2 million people are living with HIV. There were 2.5 million new infections in 2007 with 1.7 million (68 per cent) of these occurring in sub-Saharan Africa and important increases in Eastern Europe and Central Asia, where there are some indications that infection rates have risen by more than 50 per cent since 2004. In 2006, 2.1 million people died of AIDS defining illnesses. The prevalence of HIV infection in pilots and air traffic controllers is unknown.

3. Causative agent

In 1984, the human immunodeficiency virus type 1 (HIV-1) was discovered as the primary causative agent. In 1986, a second type of HIV, called HIV-2, was isolated from AIDS patients from West Africa. Both HIV-1 and HIV-2 have the same modes of transmission and are associated with similar opportunistic infections and AIDS. In persons infected with HIV-2, immunodeficiency seems to develop more slowly and to be milder. HIV-2 infection is predominantly found in West Africa and there is less known about managing infection and predicting outcomes, than for HIV-1. Care is required therefore, with interpreting the information provided in this chapter to determine fitness for certification of persons with HIV-2 infection.

The etiological agent is a retrovirus and the CD4+ T-lymphocyte is the primary target for HIV infection. The CD4+ T-lymphocyte coordinates a number of important immunological functions, and a loss of these functions results in progressive impairment of the immune response. Studies of the natural history of HIV infection have documented a wide spectrum of disease manifestations, ranging from asymptomatic infection to life-threatening conditions characterized by severe immunodeficiency, serious opportunistic infections, and cancers. Other studies have shown a strong association between a decrease of the number of CD4+ T-lymphocytes and an increase of the risk and severity of opportunistic illnesses.

4. Transmission

HIV is transmitted by sexual contact (both homosexual and heterosexual), by blood and blood products, and by infected mothers to infants either intrapartum, perinatally, or via breast milk. There is no evidence that HIV is transmitted by casual contact or by insects, such as mosquito bites. HIV has been demonstrated in seminal fluid, cervical smears, and vaginal fluid. In these it appears to concentrate where there are increased numbers of lymphocytes and monocytes in the fluid, as in genital inflammatory conditions. There are strong associations of HIV transmission with a history of sexually transmitted diseases (STDs) and of HIV transmission with anal intercourse. Although the virus can be identified from virtually any body fluid, there is no evidence that transmission can occur via exposure to tears, sweat, and urine. There is no convincing evidence that saliva can easily transmit HIV infection, although occasional cases have been reported in which the victim was bitten by someone infected with HIV.

5. Course of HIV infection

The typical course of the HIV-infection in *untreated* patients is presented in Figure 1. After entrance of the virus in the host system, the CD4+ T cells (and to lesser extent cells of monocyte lineage) are the major targets of HIV infection.

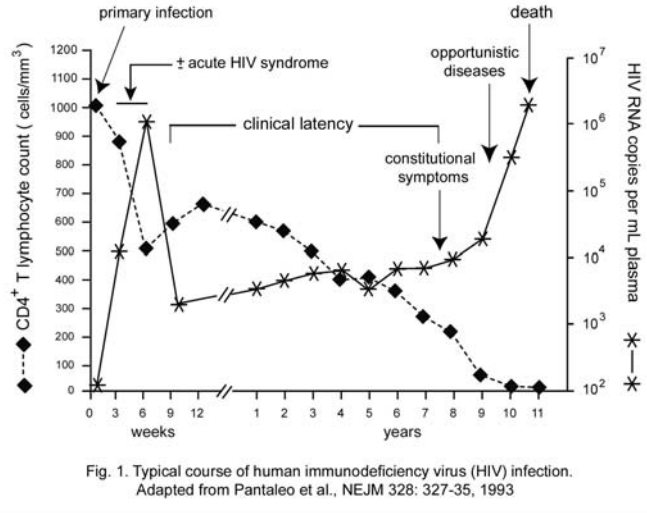

Fig. 1. Typical course of human immunodeficiency virus (HIV) infection.
Adapted from Pantaleo et al., NEJM 328: 327-35, 1993

In primary HIV infection, virus replication in CD4+ T cells intensifies prior to the initiation of an HIV-specific immune response, leading to a burst of viraemia and to rapid dissemination of virus to other lymphoid organs, brain, and other tissues. At that stage, 3-6 weeks after primary infection, 50-70 per cent of the patients experience an "acute retroviral syndrome" (acute HIV infection). The hallmark of acute infection is a high level HIV ribonucleic acid (RNA) or viral p24 antigen in conjunction with a negative HIV enzyme-linked immunosorbent assay (ELISA) test, negative or evolving Western blot test, and subsequent demonstration of full antibody seroconversion. Seroconversion typically occurs within 21-28 days after exposure (range 7 days to 12 months). The classic presentation of acute retroviral syndrome resembles a mononucleosis-like illness, which is often mistaken for malaria in tropical settings. The most common symptoms include fever, fatigue, myalgia/arthralgia, pharyngitis, lymphadenopathy, rash, anorexia, non-specific gastrointestinal complaints, and sometimes neurological symptoms. Symptoms spontaneously resolve in most patients.

There is evidence that the persistence of the acute retroviral syndrome beyond 14 days, as well as a shorter incubation than 21 days, are predictors of a more rapid progression to AIDS. Significant viraemia persists for several weeks, and subsides after 9-12 weeks to much lower levels, while at the same time the level of CD4+ T cells increases after having reached its trough at about 6 weeks after infection (Fig. 1). During the period of peak viraemia, it is believed that HIV-specific immune responses begin to drive down the viral load until a "set point" between viral replication and immune pressure is reached. This occurs within the first 6-12 months following infection, and most HIV-researchers assume that the level of this set point is highly prognostic of the patient's rate of progression to AIDS.

Once the infection has been established, the virus is never cleared completely from the body. A chronic infection develops that persists with varying degrees of virus replication. For adults in developed countries, the average time of progression to the clinical signs and symptoms of AIDS is approximately 10 years in the absence of antiretroviral therapy. Progression is markedly age-related, with older patients doing much worse than younger patients. Although the patients are asymptomatic during this period, in the majority of untreated cases viral load gradually increases and CD4+ T cells gradually decrease, patients become symptomatic and clinically ill finally developing severe opportunistic infections. Some (20 per cent) untreated persons develop AIDS defining illnesses within 5 years of infection, whereas others (<5 per cent) have sustained long-term (>10 years) asymptomatic HIV infection without decline of CD4+ T cell counts to <500/μL. Perhaps 2 per cent of untreated infected persons – often called "long-term non-progressors" – seem to be able to contain HIV replication to extremely low levels and maintain stable CD4+ T cell counts within normal range for lengthy periods (>12 years). The appearance of effective antiretroviral therapy, resulting in near-complete suppression of viral replication, has brought long-term delay of progression to AIDS defining illnesses and prevention of related conditions for many HIV-seropositive subjects in the developed world. These drugs also appear to significantly reduce the rate of sexual and vertical transmission of the virus and are of importance in a population such as aircrew, who are highly mobile.

6. Clinical manifestations of HIV infection

The latency period (clinical latency period; Fig. 1) is characterized by large inter-individual variability in duration. Initial symptoms of HIV-related immunosuppression (Stage 2, mild symptom, in the WHO clinical staging classification) include herpes zoster, recurrent UTRIs and seborrhoeic dermatitis. Stage 3 denotes more advances symptoms and includes persistent oral candidiasis, oral hairy leukoplakia, severe weight loss or fever or chronic diarrhoea and severe bacterial infections or pulmonary tuberculosis.

After a latency period, untreated HIV-positive individuals will develop WHO Stage 4 disease or an AIDS defining illnesses, which may be characterized by neuropsychiatric symptoms including dementia, cognitive or other psychological changes associated with HIV encephalopathy, opportunistic respiratory and central nervous system (CNS) infections, and diseases of the cardiovascular, gastrointestinal, hepatobiliary, kidney and genitourinary, and endocrine system. The majority of neurological disorders will be HIV-associated dementia complex (HAD). Other neurological involvement includes myelopathies, peripheral neuropathies and myopathies, opportunistic infections, primary central nervous system lymphoma, and cerebrovascular diseases. Moreover, cognitive and psychiatric symptoms, visual changes, headache, seizures, dizziness, involuntary movements, gait disturbances, cranial neuropathies and focal deficits can impair safe functioning of HIV-positive personnel engaged in aviation duties. Conditions included in the 1993 AIDS surveillance case definition are shown in Table 1.

Along with the four-level WHO clinical staging system for HIV disease, the Centers for Disease Control and Prevention (CDC) in the United States have also devised a classification system for HIV disease

progression. This was linked with AIDS case definition (which was as initially intended for epidemiological use as a surveillance tool) and allows only for a unidirectional progression through the categories from asymptomatic (Category A) to having an AIDS indicator condition (Category C). It is recognized now that some people can make a significant recovery from AIDS defining illnesses and so the development of these illnesses is not necessarily an indicator of long-term unfitness for aeromedical certification. The WHO has recently modified the clinical staging system to recognize that antiretroviral therapy will reverse disease progression and that subsequent HIV-related events and clinical staging events can be used to guide decision making on when to switch to second-line ART.

Table 1. — AIDS defining illnesses

Candidiasis of oesophagus, bronchi, trachea or lungs
Cervical cancer, invasive
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (greater than 1 month duration)
Cytomegalovirus disease (other than liver, spleen or nodes)
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy (Dementia), HIV related
Herpes simplex: chronic ulcer(s) (greater than 1 month duration); or bronchitis, pneumonitis or oesophagitis
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (greater than 1 month duration)
Kaposi's sarcoma
Lymphoma, Burkitt's (or equivalent term)
Lymphoma, immunoblastic (or equivalent term)
Lymphoma, primary, of brain
Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary
Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary)
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
Pneumocystis carinii pneumonia
Pneumonia, recurrent
Progressive multifocal leukoencephalopathy
Salmonella septicaemia, recurrent
Toxoplasmosis of brain
Wasting syndrome due to HIV

7. **Assessment of HIV and disease that might give rise to incapacitating symptoms**

7.1 *Current health*

General examination

Besides specific screening for progression of the disease and CNS involvement (described separately), HIV-positive applicants should be thoroughly screened to exclude any disqualifying condition. HIV and/or antiretroviral medication may also affect heart, respiratory system, liver, and metabolic functions and so the assessment should include haematological, cardiovascular, and pulmonary evaluation, liver and kidney function, and metabolic tests. Opportunistic infections generally occur with advanced or severe disease and the physician should always pay attention to signs and symptoms of Stage 3 or Stage 4 disease, such as oral or oesophageal candida, pneumocystis carinii pneumonia, toxoplasmosis,

cytomegaly, progressive multifocal leukoencephalopathy, tuberculosis, and fungal infections. This especially applies for candida infections, which can be seen early in the course of HIV infection, heralding the onset of clinical immunodeficiency.

The following specific assessments are recommended:

a) Immunological status

Two laboratory tests are routinely used as surrogate markers of HIV disease progression to determine indications for treatment and to monitor the efficacy of therapy. These are the CD4+ T cell count and plasma HIV RNA (or viral load).

CD4+ T cell count.— The extent of immune system damage is indicated by the CD4+T cell count, which is a measure for disease status and can enhance the assessment of the risk of developing opportunistic infections and other sequelae of HIV infection when used together with viral load determinations. CD4+ T cell counts are subject to substantial variability due to both biological and laboratory methodologies and can vary up to 30 per cent on repeated measures in the absence of a change in clinical status. Therefore it is important to monitor trends over time and to repeat a test to confirm a value rather than take a decision on one specific determination. Sudden changes in the count need to be confirmed by a second determination. The number of CD4+ cells varies diurnally, being higher in the morning, increasing slightly with smoking and decreasing acutely with stress and with intercurrent infection. A significant change between two tests (two standard deviations) is defined approximately as more than a 30 per cent change of the count. For practical use, a decline in CD4+ T cells by 75/year is considered to indicate a higher risk for progression to AIDS, when the reference CD4+ T cell count is <500/μL. A CD4+ T cell count of <200/μL is AIDS-defining even in the absence of any signs and symptoms of HIV disease.

Viral load.— The rate of progression of HIV disease is predicted by the magnitude of active HIV replication, which is reflected by the viral load. Measurement of the viral load through the use of quantitative plasma HIV RNA assays permits assessment of the relative risk of disease progression and time to death. However, plasma HIV RNA levels obtained within the first six months of HIV infection do not accurately predict disease progression. In contrast, plasma HIV RNA levels stabilize after approximately six to nine months of initial HIV infection and the viral set point is considered predictive of subsequent disease progression. Immunizations and intercurrent infections can lead to transient elevations of plasma HIV RNA levels. Values obtained within 4 weeks of such episodes may not accurately reflect the actual plasma HIV RNA level. Two specimens should be obtained within one to two weeks of each other and analyzed by the same quantitative method (either Branched DNA=bDNA, or Reverse Transcriptase Polymerase Chain Reaction=RT-PCR). Plasma HIV RNA assays are also used as the best measure of the activity of antiretroviral therapy. A viral load of <5000 copies/ml is considered low and provides evidence for non-progression of the disease. The minimal change in viral load considered to be statistically significant (2 standard deviations) is a threefold or a 0.5 $\log_{10}$ copies/ml change. For practical use, an increase by >20,000 copies/year is considered to indicate a higher risk of progression to AIDS.

b) Assessing co-infection

Hepatitis B and C are frequent co-infections in HIV-infected individuals. They can cause progressive liver disease especially in those receiving anti-retroviral therapy. The progression of HIV infection appears to be slowed in people co-infected with Hepatitis G virus. Other sexually

transmitted diseases such as syphilis should also be considered. Tuberculosis is the most common HIV associated opportunistic infection in developing countries, compared to pneumocystis pneumonia in industrialised countries. Cytomegalovirus is the most frequent cause of retinitis in advanced HIV infection. Other associated co-infections include Epstein-Barr virus, toxoplasma gondii (associated with multiple CNS lesions) and JC virus (named after the initials of the patient in whom it was first discovered) that cause progressive multifocal leukoencephalopathy, and cryptococcal meningitis, particularly in tropical countries.

c) Neurological assessment

The spread of HIV-1 into the CNS is known to occur early in the course of the infection. However, except for early HIV-associated meningitis (as part of an acute HIV seroconversion illness), the majority of nervous system complications of HIV in the CNS take years to appear. HIV-related neurological disorders may arise from infection, neoplasm, systemic metabolic derangement, antiretroviral therapy, or direct HIV effects on the nervous system.

Several large-scale studies have shown that HIV-associated cognitive dysfunction is antedated by immunological (CD4+ T cell) decline. This finding is important when considering aeromedical fitness.

During neurological examination, specific attention should be paid to extra-pyramidal signs, and ocular disorders such as dissociated nystagmus, gaze-evoked nystagmus, impaired saccadic function, and smooth pursuit. Testing of primitive reflexes (glabellar, snout, Rossolimo, digital signs) should be part of the examination because they are associated with cognitive decline in HIV patients without overt neurological disease.

Most studies demonstrate that the risk of new-onset seizures in asymptomatic individuals is low. In the majority of cases, seizures in HIV-positive individuals are caused by disorders that generally occur in late stages of HIV-infection, such as encephalopathy, neoplasm, or opportunistic infections.

d) Cognitive function testing

HIV associated dementia (HAD), also known as AIDS dementia complex and HIV encephalopathy is a late complication of HIV disease that occurs in those with very low CD4+ cell counts. Fortunately, HAD is very responsive to anti-retroviral therapy and has become uncommon in the developed world. In the developing world, more studies are required to enable conclusions to be made on HAD. Since the introduction of Highly Active Anti-Retroviral Therapy (HAART) in 1996 the incidence of HAD has declined significantly by about 50 per cent compared to the early 1990s. Studies conducted in the pre-HAART era found that HAD was associated with increasing age, a diagnosis of AIDS and injection drug use. The majority of cases have presented with advanced immunosuppression with CD4+ counts <200. However more cases are presenting at higher CD4+ counts since the advent of HAART.

The clinical presentation in adults includes prominent psychomotor slowing, deficits in learning, attention/working memory, speeded information processing, mental flexibility, and motor control. Neuropsychological testing can demonstrate deficits in these areas. Typically, HAD progresses slowly over several months, rather than being sudden in onset, and those affected or their families describe a slowing of thought with loss of interest in activities previously enjoyed and a tendency to forget details. Less commonly, psychotic behaviour may be quite florid. Diagnosis of HAD can be made clinically, but MRI imaging or CT scanning should be considered to exclude

opportunistic lesions. The scans may be normal in the presence of HAD but generally cerebral atrophy is present.

e) Mild neurocognitive impairment

It is difficult to come to a clear conclusion on the absolute risk and significance of mild neurocognitive impairment in asymptomatic HIV infected individuals. Whilst some studies comparing cognitive function in asymptomatic HIV positive persons and HIV negative persons find no difference others have detected a higher frequency of cross-sectional neuropsychological test abnormalities than in seronegative controls. However, few have shown that these cognitive impairments are progressive, or predictive of later development of dementia. The clinical significance of new cognitive symptoms or test impairment in asymptomatic HIV infection is uncertain because the reported neuropsychological abnormalities do not necessarily affect every day function, may not progress, and in some individuals may improve on retesting.

Where abnormalities have been detected they relate to timed psychomotor tasks and memory tasks, which require attention, learning and active monitoring or retrieval of information. These may be assessed using trail making, digit symbol substitution, grooved pegboard and computerized reaction time tests. The development of sensitive and reliable neuropsychological test batteries now means that evolving neurocognitive impairment may be detected at a relatively early stage in individuals at risk of HIV dementia.

Under ideal circumstances every patient should receive baseline neuropsychological assessment when first diagnosed with HIV but there is no perfect approach. Tests vary in their sensitivity and specificity, as well as the degree to which they are affected by other general factors such as age, education and cultural background, premorbid neurological disease, and alcohol and drug use, fatigue and constitutional symptoms, and mood. This is a reason for assessing cognitive ability domains utilizing more than one test of each domain.

Overall neuropsychological assessment may be enhanced by the results of functional assessment such as the Proficiency Checks that commercial pilots undertake in a flight simulator. This may be particularly useful where cognitive function testing has detected mild impairments of uncertain significance or instead of cognitive function testing in asymptomatic individuals who are at low risk of disease progression (see Risk of Progression).

f) Simulator checks

In general, simulator checks test two main abilities, which are: learned skills, e.g. controlling an aircraft after engine failure, flying an instrument approach with engine(s) failed, and decision making, e.g. choosing an appropriate course of action given more than one alternative, determining the cause of a malfunction from a given set of data. Most, if not all, of the identified types of neurocognitive deterioration can be identified by a well-designed simulator check. Controlling a twin-engine aircraft after an engine failure, following take-off and when flying an approach and go-around is a demanding psychomotor task and should be part of any routine simulator test. Memory tasks are also necessary as a routine, but can be emphasized by the airline medical officer in discussion with the training captain. Tasks such as recall of six digits when changing frequencies can be required of the affected pilot, delegation to the second pilot should not be permitted, and conditional clearances (“after waypoint X, descend to flight level 120” can test longer term memory.

It is vital to involve the operator's training department when assessing a pilot who is returning to line flying after the diagnosis of HIV infection. Good communications should be established and the airline's medical adviser should ensure that he or she is very familiar with the simulator environment and with the tasks required of pilots in routine checks. It is only if the medical adviser is knowledgeable of simulator tests, and mutual trust is established between the medical adviser and training department that the most benefit can be obtained from simulator checks. Any performance that is regarded as below average for that individual pilot should be seen as a cause for concern, and should require further assessment.

g) Psychiatric assessment

Although it is assumed to be uncommon that psychiatric symptoms are the first manifestations of CNS involvement, the psychiatric examination should address the potentially serious complications of infection with HIV. There is evidence that the average HIV infected person experiences at least transient difficulties following notification of HIV seropositivity. A study (in the pre-HAART era) among HIV-infected US military personnel in 1993 showed that 17 per cent of the subjects had experienced serious suicidal ideation or behaviours since notification of seropositivity. Ten percent had a major mood disorder and 5 per cent a psychoactive substance disorder. The knowledge of being seropositive *per se* may be a reason for (temporary) disqualification. The examiner should focus on signs of depression, other mood disorders and use of psychoactive substance. A similar study of military personnel does not appear to have been undertaken since the introduction of HAART, but there is evidence of a lower prevalence of mood disorders amongst those attending HIV outpatient clinics compared to the pre-HAART era.

Psychiatric symptoms may also be associated with medication, e.g. Efavirenz and assessment should be made after commencing this treatment and before considering a return to certification. Consideration should be given to psychiatric assessment, particularly at the first assessment after seroconversion, with subsequent review associated with clinical indication and the introduction of efavirenz in any HAART regimen.

h) Cardiological assessment

Lipodystrophy and a metabolic syndrome may arise as an interaction between HIV disease and/or immune recovery and antiretroviral medication. This may manifest as dyslipidaemia with raised total cholesterol, low HDL cholesterol and raised triglycerides or insulin resistance with hyperglycaemia. Cardiology review may be required in the presence of these or other significant cardiac risk factors, e.g. hypertension, smoking, raised lipids, diabetes, age and evidence of left ventricular hypertrophy. Some antiretroviral medicines are more likely to cause these side effects and expert consultation with a view to changing ART regimen is indicated.

i) Medication

The clinical effectiveness and tolerability of antiretroviral therapy has improved markedly over the last few years. Most regimens are patient-friendly with low pill burden and few dietary restrictions. Since 1996, there have been dramatic falls in the incidence of new AIDS cases and AIDS associated deaths in the developed world. Many (highly active) antiretroviral therapy regimens (HAART or ART) result in near-complete suppression of HIV-1 replication. For HIV-2 the picture is not quite so clear, as it is far less prevalent and there is limited clinical experience. Both the nucleoside reverse transcriptase inhibitors (NRTI) and protease inhibitors (PI) classes of ARV medicines are active but neither efavirenz nor nevirapine as, non-nucleoside reverse transcriptase inhibitors (NNRTI) are active against HIV-2.

HAART does not cure HIV infection so once started life-long therapy is always necessary. Although complete eradication of the infection cannot be achieved, sustained inhibition of viral replication results in partial and often substantial reconstitution of the immune system in most patients, greatly reducing the risk of clinical disease progression.

Combination ART usually starts with 2 NRTI together with a NNRTI as the first-line therapy. The PI class is usually reserved for second-line therapy. Some drugs are so similar or have synergistic toxic effects and so should not be combined. Expert opinion should always be sought. Adequate viral suppression for most patients on therapy is defined as a reduction in viral load to undetectable levels. There are cases in which adequate viral suppression may not be achieved despite appreciable increases in CD4 cell count. Increases in CD4 cell count in people with good virological control show an average increase of approximately 100 cells/mm^3 per year for subsequent few years until a threshold is reached, which in many patients may be within the normal range. However, successful outcomes have not been observed across all patients.

Problems encountered with HAART are drug resistant virus, poor patient adherence, drug-drug interactions when treating co-infections like tuberculosis, and drug toxicity. In the beginning of the HAART era it was hoped that all HIV-seropositive persons would benefit from antiretroviral therapy. Nowadays, clinicians have considerable reservations about treating asymptomatic immunocompetent cases, because of the risk of adverse drug effects, the challenge of long-term adherence and development of virus resistance.

In asymptomatic patients with HIV, decisions on when to start treatment are based on an assessment of the risk of disease progression over the medium term if treatment is not started (e.g. using data from the CASCADE collaboration – see section on “Risk of Progression”) versus the potential risks of starting treatment earlier (toxicity and resistance), and in any case always before the CD4+ lymphocyte count has fallen to below 200 cells/mm^3.

In 2004 the Panel on Clinical Practices for Treatment of HIV Infection (convened by the Department of Health and Human Services, USA) published revised indications for antiretroviral therapy, which are shown in table 2. Similar cut-off values are used in guidelines in other industrialized countries. WHO recommendations, adopted by many low and middle-income countries are slightly more conservative and the debate about early treatment with HAART vs. deferring until lower CD4+ counts are reached goes on.

When assessing aeromedical certification of persons on HAART, consideration must be given to aeromedically relevant adverse effects and clinicians treating aviation personnel should be asked to carefully design treatment regimens to minimise these. Drugs that are likely to interfere with flight safety should be avoided e.g. indinavir, which causes nephrolithiasis (with radiolucent stones), and with others specialist assessment may be required before deciding on certification, e.g. efavirenz, which may cause psychiatric symptoms.

Table 2.— Indications for antiretroviral therapy (Panel on Clinical Practices for Treatment of HIV Infection, 2004, USA)	
1	Antiretroviral therapy is recommended for all patients with history of an AIDS-defining illness or severe symptoms of HIV infection regardless of CD4+ T cell count.
2	Antiretroviral therapy is also recommended for asymptomatic patients with < 200 CD4+ T cells/ μL.
3	Asymptomatic patients with CD4+ T cell counts of 201-350 cell/ μL should be offered treatment.
4	For asymptomatic patients with CD4+ T cell of >350/ μL and plasma HIV RNA >100.000 copies/mL most experienced clinicians defer therapy but some clinicians may consider initiating treatment.
5	Therapy should be deferred for patients with CD4+ T cell counts of >350 cells/ μL and plasma HIV RNA < 100.000 copies/mL.

Only drugs that are licensed by national authorities will be acceptable. During the initiation of therapy and when adjustments are made to the regimen used, applicants should be assessed as temporarily unfit. Further assessment should then be made for side effects that are likely to be disabling after treatment is stable for a period of months, before any decision on certification is made. Adverse effects of HAART include GI intolerability, drug hypersensitivity, Stevens-Johnston syndrome, cytochrome P450 interactions, CNS effects, myopathy, neuropathy, bone marrow depression, nausea, diarrhoea, fatigue, headache, hepatitis, hepatic steatosis, lactic acidosis, pancreatitis, dilated cardiomyopathy, renal colic, nephrolithiasis, haematuria, abdominal pain, metabolic syndrome and lipodystrophy. There is considerable variability in the occurrence of adverse effects between drugs and between individuals. Noteworthy is the occurrence of a lipodystrophy syndrome, characterized by a “buffalo hump” fat distribution, in 50 per cent of the cases. This syndrome is associated with aeromedical risk factors, such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, and Type 2 diabetes mellitus. Possible cognitive effects of HAART, relevant for flight safety, may be assessed with validated neuropsychological test batteries or a functional evaluation, e.g. simulator check. A 1997 study showed no impairment of cognitive processes in patients treated with the NRTIs didanosine, or zidovudine (monotherapy). Regular follow up is required to monitor treatment efficacy, ARV adherence, toxic side effects or evidence of drug resistance.

j) Other issues

Magnetic Resonance Imaging (MRI) can detect white matter abnormalities, high signal abnormalities in gray matter structures, and/or cerebral atrophy of HIV encephalopathy. However, such changes are relatively non-specific and the differentiation of different causes for the abnormalities is difficult with conventional MRI. Significant improvements may come as functional imaging methods, such as perfusion imaging, magnetic resonance spectroscopy (MRS) and brain mapping with functional MRI become more widespread in clinical practice.

Cerebrospinal Fluid (CSF) - Abnormalities of the CSF in HIV-associated dementia are generally non-specific, with mild elevations in protein and pleocytosis. It appears that HIV RNA levels in CSF correlate with the presence of cognitive impairment, although the precise relationship of HIV-1 RNA values in CSF and the risk of development or progression of neurological disease has not yet been determined. Even in patients with neurological disease, CSF RNA levels are relatively low. The false-negative rate of CSF RNA values is high, and minor neurological dysfunction is often not associated with high CSF HIV RNA levels. CNS syphilis screening should be routinely performed with any CSF sample.

7.2 *Risk of progression*

In HIV-seropositive persons, the average latency period to developing AIDS is 10 years and without any therapy, survival of about 12 years. Treatment significantly extends survival and near normal life expectancy may even be possible with relatively non-toxic and highly effective combination ART. During the latency period most HIV infected persons are asymptomatic and those engaged in aviation duties would be able to continue their careers for several years (if the HIV diagnosis is made early on after infection) until therapy is started and for many years once HAART has been successfully commenced. However, some patients may present relatively late in the course of their infection and there is inter-individual variability in the rate of progression to symptomatic disease and then AIDS as well as in the occurrence of adverse effects of HAART. As symptomatic HIV-related disease including (subtle) cognitive impairment, AIDS-defining illnesses and several adverse effects of HAART are incompatible with aviation duties, prediction and early detection of cognitive involvement and/or AIDS-related symptoms and long-term monitoring for the adverse effects of treatment are essential for the aeromedical assessment of a HIV-seropositive applicant. In the absence of HIV-related symptoms (including cognitive decline), aeromedical considerations could be aided by risk assessment methods that use CD4+ T cell counts, viral load, and age.

Several large study groups have published data that can be used in the assessment of the risk of disease progression for those who are treatment naïve and those who commenced therapy.

The Concerted Action on SeroConversion to AIDS and Death in Europe collaboration (CASCADE) have produced a Poisson regression model based on data of 5126 person-years of 3226 asymptomatic seropositive subjects who either had no treatment or monotherapy, to predict the 6-month risk of developing AIDS. This can be modified to give a 12-month risk (see Table 3).

For the assessment of individual cases, adverse trends in CD4+ and viral load levels and the applicant’s age should be taken into account.

For those who have already commenced HAART data from EuroSIDA or the Antiretroviral Therapy (ART) Cohort Collaboration can provide a basis for assessing the risk of disease progression. The former reports on the risk of clinical progression (diagnosis of a new AIDS defining illnesses or death). The scoring system is shown in Table 4. The ART Cohort Collaboration found that 6 months after starting ART, the current CD4 count and viral load, but not the baseline values, are strongly associated with subsequent disease progression. The data presented by the collaboration is limited by its broad categories (although recent updates on their original publication have improved this). The CDC category A and B (both asymptomatic individuals and those who have had symptoms of conditions attributed to or complicated by HIV infection) are included in one group and the age ranges divided into 4 groups. Their most recent study reports that the annual risk of developing a new AIDS defining illnesses during the first year after commencing HAART is around 1 per cent per annum for those whose 6 month CD4+ count is >=350, viral load is <500 and where HIV transmission was not by intravenous drug use, the person meets

the criteria for CDC category A or B and aged 16-29yr and gradually decreases over the subsequent four years. A calculator can be found on their web site at **http://www.art-cohort-collaboration.org/6mhiv_form.html**

Table 3.— Risk of developing AIDS in those who have had no treatment or monotherapy
Rate = exp{-3.55 + [-0.21 √(CD4 cell count)] + 0.71 (log viral load) + 0.024(Age)} 12-month percentage risk of developing AIDS = [1 – exp(-1Rate)] x 100% exp = exponential function CD4 cell count = count x 10^6 cells/l log = logarithm viral load = copies/ml Age = age in years
Example: A 25 year old pilot with CD4+ cell count of 450 and viral load of 5000 will have a 12-month risk of developing AIDS of 0.84 per cent. Rate = exp {-3.55 + [-0.21 x √450] + [0.71 x log5000]+ [0.024 x 25]} = 0.008 12-month percentage risk of developing AIDS = [1 – exp(-1 x 0.008)] x 100% = 0.84% A pilot aged 50yr with the same serological measurements would have a 12-month risk of developing AIDS of 1.52 per cent. Derived from Phillips A. CASCADE Collaboration**. Short-term risk of AIDS according to current CD4 cell count and viral load in antiretroviral drug-naive individuals and those treated in the monotherapy era.** AIDS 2004 Jan 2. 18(1):51-8.

Table 4.— Risk of Clinical Progression in those being treated with combination Anti-Retroviral Therapy (cART)				
CD4 Count (/mm^3)	>350 = 0	201−350 = +0.62	51−200 = +1.46	≤50 = +2.44
Body Mass Index	≤18 = +0.80	18.1−25 = 0	>25 = −0.29	
Viral Load (copies/ml)	<500 = 0	≥500 = +0.18		
CD4 slope (3 month)	< −25/mm^3 = +0.49	−25 to +25/mm^3 = 0	>25/mm^3 = +0.18	
Anaemia	No = 0 Hb >14.0g/dl male Hb >12.0g/dl female	Mild = +0.68 Hb 8.01−14.0g/dl male Hb 8.01−12.0g/dl female	Severe = +1.02 Hb ≤8.0g/dl	
Retroviral treatment prior to cART	Yes = 0	No = −0.39		

Currently taking antiretrovirals	Yes = 0	No = +1.24		
Age	Age × 0.024			
Total Score	**% Risk of Clinical Progression in following 12 months (95% CI)**			
<1.5	0.50			
1.5−2.99	1.40			
3.0−4.49	6.25			
≥4.5	≥20.00			

Example: 30yr old who has had no previous anti-retroviral therapy prior to cART, whose current CD4 count is 400, viral load 50, BMI 22 and no anaemia. Their CD4 slope increased by 15/mm^3 in the last three months and they are currently taking cART. Total score is 0.38 and therefore their risk of progression for next 12 months is 0.66 per cent.

(Data from *Mocroft A, Ledergerber B, Zilmer K, Kirk O, Hirschel B, Viard J-P, Reiss P, Francioli P, Lazzarin A, Machala L, Phillips A, Lundgren J; for the EuroSIDA study group and the Swiss HIV Cohort Study* **Short-term clinical disease progression in HIV-1-positive patients taking combination antiretroviral therapy: the EuroSIDA risk-score.** AIDS. 21(14):1867-1875, September 2007)

Both these studies indicate that the lowest risk of progression in the most favourable groups is about 0.7 to 1.0 per cent per annum (but not significantly less than 1 per cent) after commencing HAART. The populations used in these studies are predominantly Western European, Israeli and Australian and so caution may be required when applying the data to pilots from out with these regions. In addition the socioeconomic groups of pilots and air traffic controllers may differ from the study populations.

It is recommended that CD4+ T cell count and viral load levels should be determined every three to four months and that clinical condition, including general, neurological and, if indicated, psychiatric examinations should be assessed every six months. A neuropsychological evaluation may be considered every twelve months. Regular assessment of cockpit performance may be considered in lieu of this or to enhance assessment in asymptomatic, stable applicants with very low risk of progression. Further co-infection testing will be required where clinically indicated and those with new positive tests may require specialist evaluation prior to further certificatory assessment.

Clearly not every individual with HIV infection will be fit for certification. However, some applicants may be fit and remain so for a prolonged period and it is to assist in the identification of such individuals that the information in this chapter is written. The assessment of HIV-positive applicants requires specialist expertise and careful consideration of all the points mentioned in this chapter and applicants need to be advised at the outset that continued certification will require ongoing medical scrutiny and prolonged follow-up.

8. Asymptomatic HIV positive cases and travel vaccination

Vaccinations can temporarily increase the viral load for approximately four weeks. As a rule, immune-compromised people should not receive vaccines based on live-attenuated organisms, such as measles and yellow fever. However, risk is not increased in true asymptomatic and immuno-competent cases, confirmed by a sufficient CD4+ T cell level (> 350/ μL) and these cases will have a normal response of the immunological system to these vaccinations.

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INSULIN-TREATED DIABETES
GUIDANCE FOR CERTIFICATION OF AIRCREW WITH INSULIN TREATED DIABETES MELLITUS

This guidance should be used in conjunction with the *Manual of Civil Aviation Medicine* (Doc 8984, Chapter 4) and Annex 1 (below) — Risk Analysis and Literature Review.

1. Introduction

Several Contracting States permit applicants having insulin treated diabetes to exercise the privileges of their licence. The purpose of this guidance material is to provide a protocol that will enable other States to consider such applicants under the flexibility Standard in Annex 1 — *Personnel Licensing*, paragraph 1.2.4.8. The key areas of concern in certificating aircrew with insulin treated diabetes mellitus are hypoglycaemia and the enhanced risks of micro and macrovascular disease. In the paragraphs that follow, the focus will be on the risks of hypoglycaemia, but the protocol at the end of the section will include an assessment of cardiovascular risk.

2. Hypoglycaemia

Achieving and sustaining near normal glycaemia is a central target in the management of patients with both Type 1 and Type 2 diabetes mellitus whose microvascular complications are then reduced 1, 2. However, the clinical consequence of improving glycaemic control is an increase in the frequency of hypoglycaemia 2, 3 which is a concern in the risk assessment of diabetic aircrew. The relative risk of severe hypoglycaemia (requiring the assistance of another) is greater for intensively treated (to achieve lower HbA1C levels) patients with Type 1 diabetes (about 27 per cent per year according to the Disease Control and Complications Trial [DCCT]) 3 than for those with Type 2 (2 per cent per year according to the UK Prospective Diabetes Study [UKPDS]) 2 despite similar glycaemic control.

Several factors may explain why patients with Type 2 diabetes are less prone to severe hypoglycaemia. Normally, as plasma glucose concentrations fall, there is a hierarchy of defense responses. The first is an increase in the release of counter-regulatory hormones as plasma glucose falls to approximately 3.8 mmol/L which is designed to prevent glucose concentrations from falling further. The second is an awareness of warning symptoms, predominantly autonomic (sweating, hunger, anxiety, tachycardia, etc.), which begin as plasma concentration decreases to approximately 3.4 mmol/L. In patients well educated in diabetic management, such symptoms will prompt preventative steps, i.e. ingestion of carbohydrate, which will prevent neuroglycopaenia, which commences at approximately 3.0 mmol/L.

In people who have had Type 1 diabetes for over five years, counter-regulatory hormone responses to hypoglycaemia are generally impaired. Initially, most patients lose their glucagon response to hypoglycaemia, thereby becoming dependent on catecholamine responses to prevent or reverse hypoglycaemia. Sometimes even that response becomes impaired and the risk of severe hypoglycaemia increases several fold. Additionally, episodes of mild hypoglycaemia, even if symptomless, can further impair glucose counter regulation and may reduce ß-adrenergic sensitivity leading to a situation of "hypoglycaemic unawareness". In this situation, patients may not recognize impending hypoglycaemia until it is too late to institute preventative measures (Gerich J F) 4. The situation is somewhat different in Type 2 diabetes; firstly, although glucagon responses are commonly impaired, catecholamine responses are usually normal or increased. Secondly, the patients are insulin resistant and thirdly, they have persistent ß-cell function. The ability to modulate insulin secretion can act as a buffer, since endogenous insulin secretion will decrease as plasma glucose falls. This opportunity is not available in Type 1 patients

whose insulin availability is pre-determined by the amount already injected. Fourthly, most Type 2 patients are not on intensive insulin regimes so they are less at risk of hypoglycaemic unawareness as a result of insulin induced hypoglycaemia.

This differing rate of hypoglycaemia has been confirmed recently by Heller et. al.(5) who found no differences in the rate of severe hypoglycaemia in Type 2 diabetic patients treated with sulfonylureas or insulin for less than 2 years (0.1 and 0.2 episodes per subject – year) and this frequency was far less than that encountered in Type 1 diabetes (< 5 years 1.1; > 15 years 3.2 episodes per subject – year).

From a number of studies including Akram et. al.(6), the risk factors for severe hypoglycaemia include previous hypoglycaemia, long duration of diabetes and impaired hypoglycaemic awareness.

3. **Protocol**

From the literature review, the risk of hypoglycaemia in Type 1 diabetes is outside that which would be acceptable in terms of the "1 per cent rule". States using different risk criteria should make their own assessment of risk.

For aircrew with Type 2 diabetes, whether taking insulin or not, individuals should be at low risk of hypoglycaemia. What follows is a cautious protocol that may assist States to determine fitness in applicants who present with Type 2 diabetes. It provides guidance and may be adjusted by individual States to suit their own requirements.

4. **Initial assessment**

- Stimulated C-peptide levels* > 25 per cent of normal;
- No previous hypoglycaemic episodes requiring the intervention of another person;
- Stable blood glucose control: satisfactory HbA1C ~ 7 – 8 per cent;
- Adequate self-monitoring with a memory chip glucose meter;
- No evidence of hypoglycaemic unawareness;
- Good diabetes education and understanding;
- Positive attitude to monitoring and self-care.

An annual assessment may include:

- Review of adequate self-monitoring with a glucose meter;
- Review of blood glucose control with satisfactory, stable HbA1C;
- Report from the treating physician to confirm no complications of diabetes, including renal and visual complications;

* C-peptide is an indicator of beta cell activity. Most Type 1 diabetics are C-peptide negative.

- Annual cardiovascular assessment such as a symptom limited exercise ECG and clinical review by a cardiologist.

Follow-up should be agreed jointly between the treating physician and the medical assessor.

This approach could be extended to encompass pilots and air traffic control officers with Type 2 diabetes on sulphonylureas as well as those on insulin. This would avoid any period of unfitness on sulphonylureas with the resultant potential degradation in training.

5. References

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus. N Engl J Med 1993; 329: 977-86.

2. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352: 837-53.

3. The DCCT Research Group. Hypoglycaemia in the diabetes control and complications trial. Diabetes 1997; 46: 271-86.

4. Gerich J F. Hypoglycaemia and counter regulation in type 2 diabetes. Lancet 2000; 356: 1946-47.

5. Heller S. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia 2007; 50(6): 1140-7.

6. Akram K, Pedersen-Bjergaard U, Carstensen B et al. Frequency and risk factors of severe hypoglycaemia in insulin-treated Type 2 diabetes: a cross-sectional survey. Diabetic Medicine 2006; 23: 750-6.

ANNEX 1

INSULIN TREATED DIABETIC AIRCREW

1. Risk analysis and literature review

Any risk assessment requires a review of the literature looking at the prevalence of hypoglycaemia in insulin treated diabetes mellitus and the application of clinical judgement as to whether one can extrapolate population data to individual cases. It is proposed to discuss the rate of hypoglycaemia firstly in Type 1 diabetes and secondly review the differing rates in Type 2.

It is very difficult to assess the frequency of hypoglycaemia in insulin treated diabetic populations because of the wide variation of severity and outcome. For example, the common occurrence of asymptomatic biochemical hypoglycaemia that is only evident if blood glucose is measured frequently and the failure to recognize or record many mild episodes including those occurring during sleep. However, a critical review of the medical literature on the subject provides some data on which to base a risk assessment. Since the publication of the Diabetes Control and Complication Trial {DCCT} (1993) in Type 1 diabetes which showed that tight diabetic control could assist in the prevention of complications, diabetic physicians have striven to improve overall control. However, this study showed an approximate three-fold increase in prevalence of severe hypoglycaemia in the intensively treated group compared to that of the conventionally treated (0.54 v 0.17 episodes/patient/year). An analysis of the cumulative incidence of successive episodes indicated that intensive treatment was also associated with an increased risk of multiple episodes within the same patient (e.g. 22 per cent experienced five or more episodes of severe hypoglycaemia within five years of follow-up v 4 per cent in the conventional group). Several sub-groups defined by baseline characteristics, including males, adolescents and subjects with no C-peptide or with a prior history of hypoglycaemia had a particularly high risk of severe hypoglycaemia in both treatment groups. Ward and colleagues (1990) found in an out-patient study of 158 patients in Auckland that almost all, 98 per cent, had experienced hypoglycaemic episodes and for 30 per cent these were a major problem. These symptoms of hypoglycaemia, which represent a combination of neuroglycopaenia and autonomic neural stimulation, would be likely to degrade pilot performance. In theory this may be modulated by good hypoglycaemic awareness and adequate early correction. The adverse effects of hypoglycaemia on cognitive function, in Type 1 diabetes, have been studied by Holmes (1983, 1986), Pramming (1986) and Herold (1985). Cox and colleagues (1993) studied this problem in a driving simulator and found that the degradation in performance was not reliably recognized by subjects, none of whom had lost hypoglycaemic awareness. In practice, therefore, it would be unacceptable for a pilot to experience a hypoglycaemic episode in flight where a lack of hypocglycaemic awareness would present a risk to the safety of the flight.

The risk of severe hypoglycaemia with intensive insulin therapy was further explored in a study by Bott and colleagues (1997) in 636 insulin dependent diabetics. The incidences of severe hypoglycaemia between participants in the study varied between 0.05 and 0.27 cases per patient per year. In particular, the authors sought to find a relationship between a level of haemoglobin A1 which could predict severe hypoglycaemia but there was no linear or exponential relationship.

More recently Egger and colleagues (1997) performed a meta-analysis of 14 trials which contributed to 16 comparisons of 1028 patients with Type 1 diabetes allocated to intensive insulin treatment and 1039 allocated to conventional treatment. The authors found a substantial risk of adverse effects associated with intensive insulin treatment which included an excess of severe hypoglycaemia confirming that the

findings noted in the DCCT (1991) were not exceptional, but commented that multiple daily injection schemes may be safer than treatment with insulin pumps.

Having accepted that there is evidence in the literature that intensive insulin regimens increase the rate of hypoglycaemia, it is logical to postulate how one might predict the frequency of such hypoglycaemic episodes and perhaps prevent them.

Cox and colleagues (1994) studied 78 insulin dependent subjects with diabetes mellitus from two different sites performing self-monitoring of blood glucose. Over the following six-month period these subjects recorded their severe hypoglycaemic episodes (stupor or unconsciousness). There was no difference in the number of severe hypoglycaemic episodes between the subjects in good versus poor metabolic control. The higher frequency of severe hypoglycaemia during the subsequent six months of follow-up was predicted by frequent and extreme low self-monitoring blood glucose readings and the variability in the day-to-day readings of the blood glucose. Regression analysis indicated that 44 per cent of the variance in severe hypoglycaemic episodes could be accounted for by initial measures of blood glucose variance and the extent of low blood glucose readings. Individuals who had lower haemoglobin A1 levels were not at a higher risk of severe hypoglycaemic episodes and thus blood glucose variability and low blood glucose readings were good predictors of severe hypoglycaemia.

Casparie (1985) found that one of the causes of hypoglycaemia in a study of 32 severe hypoglycaemic episodes in 26 patients (a patient per year incidence of 8 per cent) was often a lack of alertness or carelessness in calculating the insulin dose. The author felt that by teaching patients to respond more adequately to changing circumstances in daily life and to react to warning signs by appropriate action would also reduce the incidence of hypoglycaemia. The difficulty in predicting hypoglycaemic episodes in an individual patient was highlighted by Goldgewitch and colleagues (1983) when they found that emotional factors were often given as a cause of hypoglycaemia but in 11 per cent of cases there were no obvious reasons for the hypoglycaemic attacks in spite of the appropriate management of their diabetic control.

Ter Braak and colleagues (2000) carried out a retrospective study of 195 consecutive cases with Type 1 diabetes to ascertain frequency of severe hypoglycaemia and found this to be 150 episodes per 100 patient years and occurred in 40.5 per cent of the study population. The clinical characteristics which predisposed to hypoglycaemic coma were the presence of neuropathy, coincident treatment with beta blocking agents and the use of alcohol. These three observations were controlled to adjust for duration of diabetes, which is also a significant predictor of hypoglycaemia.

The data on mild hypoglycaemia are more variable and it is difficult to obtain accurate estimates. However, Pramming (1991) studied the frequency of the symptomatic hypoglycaemic episodes in 411 randomly selected Type 1 diabetic outpatients. From questionnaire analysis the retrospective frequencies of mild and severe hypoglycaemia were 1.6 and 0.029 episodes per patient per week. From the patient diaries prospective frequencies of mild and severe hypoglycaemic episodes were 1.8 and 0.027 episodes per patient per week. Interestingly, symptomatic hypoglycaemia was more frequent on working days than during weekends (1.8:1) and more frequent in the morning than during the afternoon, evening and night (4.5: 2.2: 1.4:1). Importantly, the symptoms of hypoglycaemia were somewhat non-specific, heterogeneous, and weakened with increasing duration of diabetes. These data are congruent with other data in the literature suggesting that hypoglycaemic unawareness increases with duration of diabetes and, of course, the duration of diabetes is also a predictor of hypoglycaemia.

The basic pathology in Type I diabetes is islet cell failure and that of Type 2 diabetes is of insulin resistance. It is, therefore, inappropriate to transpose hypoglycaemic frequency data from Type 1 individuals to Type 2.

MacLeod and colleagues (1992) studied the frequency of severe hypoglycaemia in 600 randomly selected patients with insulin treated diabetes attending a large diabetic outpatient clinic. 175 (29.2 per cent) of the 600 patients reported a total 964 episodes of severe hypoglycaemia in the preceding year giving an overall frequency of the group of 1.6 episodes per patient per year. Interestingly, the frequency of severe hypoglycaemia in Type 1 diabetics was almost double that of Type 2 diabetics being treated with insulin (1.7 v 0.73 episodes per patient per year).

This differing rate of hypoglycaemia has been confirmed recently by Heller et al (2007) who found no differences in the rate of severe hypoglycaemia in Type 2 diabetic patients treated with sulfonylureas or insulin for less than 2 years (0.1 and 0.2 episodes per subject – year) and this frequency is far less than that encountered in Type 1 diabetes (< 5 years 1.1; > 15 years 3.2 episodes per subject – year).

This finding of a lower average rate of hypoglycaemia in Type 2 diabetes was noted by Wright and colleagues (2002) in the United Kingdom Prospective Diabetic Study (UK PDS 57) who found the rate of severe hypoglycaemia in Type 2 diabetics treated with insulin alone was 3.2 per cent per annum and 1.6 per cent per annum in those who were treated with clorpropramide or glycazide with or without insulin. Cryer (2002) in a review of the literature also suggested that the risk of serious hypoglycaemia is much less in Type 2 diabetes, even in patients treated intensively as judged by HbA1c levels.

2. **Estimation of incapacitation risk**

Using the data from this literature review, the rate of severe hypoglycaemia, i.e. hypoglycaemia requiring the help of another in Type 2 diabetes treated with insulin, is of the order of 3 per cent per annum. These data, however, do come from hospital populations and the pilot group are highly selected, well motivated and meticulous in managing their diabetes. By selecting those with Type 2 diabetes who have a low risk of hypoglycaemia the figure may be less. Using this extrapolation one may estimate the rate to be between 1 and 2 per cent per annum.

4. **Risk of subtle impairment of performance**

Data to estimate this prevalence are rather difficult to obtain and frequently not robust but from the study of Pramming (1991) one may postulate using the work of McLeod (1992) that the rate of mild hypoglycaemia may be 50 per cent less in Type 2 diabetics than Type 1, giving a figure of approximately 0.85 episodes/patient/week. This may be due in part to the preservation of the glucose counter regulation mechanism which may protect against progression to severe hypoglycaemia.

5. **Selection criteria**

On the basis of the literature review it would be appropriate in the first instance to look at Type 2 diabetes which would appear to have a lower prevalence of hypoglycaemia. For Class 1 professional pilots the certification category should be limited to a multicrew operation. What follows are the selection criteria used by one Contracting State.

- No hypoglycaemic episodes requiring the intervention of another party during the previous five years. In Type 2 diabetes it is reasonable to reduce this period to six months

- Stability of blood glucose control in the year prior to certification as measured by glycosylated haemoglobin which should be less than twice the upper limit of normal for the laboratory assay. 90 per cent of blood glucose levels should be greater than 5.5 mmol/L. The individual should have good diabetic education and be well motivated to achieve good

control. There should be no evidence of hypoglycaemic unawareness and the individual should fall into the "low risk group of hypoglycaemia" shown in Table 1. In addition they should be regularly monitored by their diabetic specialist to exclude any complications. Specifically, with the increased incidence of coronary heart disease in Type 2 diabetics, there should be a cardiovascular assessment to include, for example, an annual exercise ECG to mitigate against the cardiovascular risk.

Table 1

Hypoglycaemia Risk Among Insulin users

Low Risk

- Stimulated C-Peptide levels > 25% of normal
- No previous hypoglycaemic reactions requiring the intervention of another person.
- Stable blood glucose control as measured by:
  (a) Glycated Hb (Patient /upper lab normal ratio <2.0.
  (b) 90% of blood glucose measurements >5.5 mmol.L.
- Adequate self monitoring with a memory chip glucose meter.
- Good diabetes education and understanding.
- No evidence of hypoglycaemia unawareness
- Positive attitude to monitoring and self care.

C-peptide is an indicator of beta cell activity
Most Type 1 diabetics are C-peptide negative

6. Risk benefit analysis

The benefit to aviation of introducing this protocol would be to maintain individuals in the flight deck environment who have a wealth of experience as the majority of Type 2 diabetics present with oral hypoglycaemic failure between 40 and 50 years. Individuals in this age group have excellent flying experience and arguably may be safer than those more junior individuals without such. By selecting Type 2 diabetics who are already professional pilots and returning them to the flight deck with a multicrew limitation the risk is further reduced due to the incapacitation training that commercial pilots are required to undertake when operating on two-pilot flight decks. This risk can be further mitigated by a stipulation that the pilot must inform their colleagues on the flight deck of the nature of their multicrew endorsement and instruct them in actions should mild or severe hypoglycaemic events occur. In any long haul operation there is ample time to check blood sugar levels at regular intervals and the availability of carbohydrate is not a problem. In a short haul operation it is unlikely that the blood sugar will change dramatically over a one to two hour period but at the midpoint of the flight monitoring should be carried out. Using these interventions this approach has potential benefit to the aviation industry.

7. Monitoring procedures

It is essential that individuals who are accepted for this approach use a glucometer which is regularly calibrated and has a memory chip. The individual must carry a supply of 10 g portions of readily absorbable carbohydrate to cover the duration of the flight. Prior to the flight the blood glucose must be greater than 6.0 mmol/L. During the flight the blood glucose should be monitored every 30-60 minutes, and if the blood glucose falls below 6.0 mmol/L then a 10 g carbohydrate portion should be ingested. If, for operational reasons, the inflight blood glucose measurement cannot be done then 10 g of carbohydrate should be ingested. The frequency of monitoring on flights/duty periods over two hours may be reduced depending on individual circumstances, in consultation with the diabetologist and aviation medicine specialist.

Blood glucose should be measured approximately 30-45 minutes prior to landing and if the blood glucose has fallen below 6.0 mmol/L, 10 g of carbohydrate should be consumed. With modern diabetic management involving prandial bolus injections of insulin, it is reasonable on long haul flights to have the diabetic pilot inject at appropriate times. In flights over 8 hours it is likely that the aircraft will carry "heavy crew" and thus this should not present a significant problem. If, despite this approach, the blood glucose exceeds 15 mmol/L then the individual should arrange for medical advice in order that corrective therapeutic measures may occur.

8. End points for terminating

This approach balances risk and benefit, but should event rates exceed those experienced in the literature and stated above, consideration should be given to discontinuing it. Any significant hypoglycaemia, i.e. requiring the help of another, which has caused any potential impact on flight safety would again result in close scrutiny with a view to terminating this approach.

The approach is highly specific and an estimate of the numbers likely to be included is difficult. However, in the UK approximately 1-2 professional pilots/20,000 per annum show oral hypoglycaemic failure and it is likely that similar numbers may occur within the jurisdiction of other Authorities. This is similar to the rate experienced by another Contracting State which permits pilots on insulin to fly.

9. Acknowledgements

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Dr. Warren Silberman, FAA.

10. References

Berger M, Mühlhauser I. Implementation of Intensified insulin therapy: a European perspective. Diabetic Medicine 1995; 12: 201 – 8.

Björk E, Palmer M, Schwarcz E et al. Incidence of severe hypoglycaemia in an unselected population of patients with insulin-treated diabetes mellitus, with special reference to autonomic neuropathy. Diabetes Nutrition and Metabolism 1990; 4:
303 – 9.

Bott S, Bott U, Berger M et al. Intensified insulin therapy and the risk of severe hypoglycaemia. Diabetologia 1997; 40: 926 –32.

Casparie AE, Elving LD. Severe hypoglycaemia in diabetic patients: Frequency, causes, prevention. Diabetes Care 1985; 8: 141 – 5.

Cox DL, Kovatchev BP, Julian DM et al. Frequency of severe hypoglycaemia in insulin-dependent diabetes mellitus can be predicted from self-monitoring blood glucose data. Journal of Clinical Endocrinology and Metabolism 1994; 79(6):
1659 – 1662.

Cryer PE, Hypoglycaemia: the limiting factor in the glycaemic management of Type I and Type 2 diabetes. Diabetologia 2002; 45: 937– 48.

Egger M, Davy Smith G, Stettler C et al. Risk of adverse effects of intensified treatment in insulin-dependent Diabetes Mellitus. Diabetic Medicine 1997; 14:
919 - 28.

Gold AE, MacLeod KM, Frier BM. Frequency of severe hypoglycaemia in patients with type 1 diabetes with impaired awareness of hypoglycaemia. Diabetes Care 1994; 17(7): 697 – 703.

Goldgewitch C, Slama G, Papoz L et al. Hypoglycaemic reactions in 172 type 1 (Insulin-dependent) diabetic patients. Diabetologia 1983; 24: 95 – 9.

Heller S. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia 2007; 50(6): 1140-7(8).

Herold K C, Polonsky K S, Cohen R M et al. Variable deterioration in cortical function during insulin-induced hypoglycaemia. Diabetes 1985;34:677-8S.

Holmes C S, Hayford J T, Gonsalez J L et al. A survey of cognitive functioning at different glucose levels in diabetic persons. Diagetes Care 1983; 6(2):180-5.

Holmes C S, Koepke K M, Thompson R G. Simple versus complex impairments at three blood glucose levels. Psychoneuroendocrinology 1986; 11:353-7.

Jörgens V, Grüβer M, Bott U et al. Effective and safe translation of intensified insulin therapy to general internal medicine departments. Diabetologia 1993; 36:
99 – 105.

Kovatchev BP, Cox DJ, Gonder-Frederick LA et al. Assessment of risk for severe hypoglycaemia among adults with IDDM. Diabetes Care 1998; 21(11): 1870 – 75.

MacLeod KM, Hepburn DA, Frier BM. Frequency and morbidity of severe hypoglycaemia in insulin treated diabetic patients. Diabetic Medicine 1993; 10:
238 – 45.

Mühlhauser I, Bruckner I, Berger M et al. Evaluation of an intensified insulin treatment and teaching programme as routine management of Type 1(insulin-dependent) diabetes. Daibetologia 1987; 30: 681 – 91.

Mühlhauser I, Overmann H, Bender R et al. Risk factors of severe hypoglycaemia in adult patients with type 1 diabetes – a prospective population based study. Diabetologia 1998; 4:1274 – 82

Mühlhauser I, Santaigo JV, Bolli GB. The frequency of severe hypoglycaemia during intensive insulin therapy. Diabetes Nutrition and Metabolism 1988; 1: 77 – 82.

Nilsson A, Tideholm BO, Kalen J et al. Incidence of severe hypoglycaemia and its causes in insulin-treated Diabetics. Acta Medica Scandinavica 1998; 224: 257 – 62.

Pramming S, Thorsteinsson B, Bendtson I et al. Symptomatic hypoglycaemia in 411 type 1 diabetic patients. Diabetic Medicine 1991; 8: 217 – 22.

Ter Braak EWMT, Appelman AMMF, Van de Lak ME et al. Clinical characteristics of type 1 diabetic patients with and without severe hypoglycaemia. Diabetes Care 2000; 23: 1467 – 71.

The DCCT Research Group. Epidemiology of severe hypoglycaemia in the Diabetes Control and Complications Trial. The American Journal of Medicine1991; 90:
450 – 9.

The Diabetes Control and Complications Trial Research Group. Hypoglycaemia in the Diabetes Control and Complications trial. Diabetes 1997; 46: 271 – 286.

Thorsteinsson B, Pramming S, Lauritzen T et al. Frequency of daytime biochemical hypoglycaemia in insulin-treated diabetic patients: Relation to daily median blood glucose concentrations. Diabetic Medicine 1986; 3: 147 – 51.

Ward CM, Stewart AW, Cutfield RG. Hypoglycaemia in insulin dependent patients attending an outpatients' clinic. New Zealand Medical Journal 1990; 103: 339 – 41.

Wright et al, 2002, UK Pds 57. www.dtu.ox.ac.uk.

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