Australian Government
Department of Home Affairs

Notes for guidance for Human Immunodeficiency Virus (HIV) / Acquired Immune Deficiency Syndrome (AIDS)

Deals with financial implications and consideration of prejudice of access to services associated with Human Immunodeficiency Virus (HIV) / Acquired Immune Deficiency Syndrome (AIDS)

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Table of Contents

Tables

Figures

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Information provided in this document, including the estimated financial considerations within a specified framework for treatment, are based on accurate, available resources at the time of development/review. It is the end user's responsibility to re-confirm the details before using the information for any binding purposes.

Human Immunodeficiency Virus (HIV)/ Acquired Immune Deficiency Syndrome (AIDS)

Definition and brief description of HIV/AIDS

HIV is the human immunodeficiency virus. AIDS is the acquired immune deficiency syndrome that is caused by HIV. A person is described as having AIDS when they experience at least one of several defined opportunistic infections and cancers that can occur after being infected with HIV. Sometimes, the public will use the terms “HIV” and “AIDS” synonymously however, while all persons with AIDS have HIV infection, not all those with HIV infection will go on to develop AIDS. The distinction has less prognostic significance than it had in the past and is not particularly helpful from a costing point of view.

Since the introduction of effective antiretroviral treatments, the accumulated evidence strongly suggests that HIV/AIDS in high-income countries has changed from a fatal illness to a chronic, manageable condition. Most people who receive combination active antiretroviral therapy (ART), and who adhere to their prescribed therapy, maintain an undetectable viral load, experience immune reconstitution and therefore might be expected to live a normal or near normal lifespan.

In recent years, ART combinations have become better tolerated by patients, with fewer side effects, and they require fewer tablets to be taken less frequently. While there are now more than 20 different antiretroviral agents available for prescription, some have been superseded and others are rarely used due to intolerable adverse effects. The continued development of better-tolerated combinations is likely to lead to further improvement in prognoses. In addition, clinicians may switch medications to avoid toxicities in individual patients.

A recent study found the life expectancy of recently diagnosed asymptomatic HIV-positive patients now approaches that of the general population. Patients who start ART before becoming severely immunodeficient, and achieve restoration of normal CD4+ T-cell counts can expect good longevity.[23]

Globally, access to ART is improving, although it continues to vary within and between countries and regions.[34] In Australia, the number of people diagnosed with HIV has been stable for the last five years and the main route of HIV transmission in 2015 was sexual contact between men.[12, 32] The pattern of the epidemic varies worldwide, including high income countries. In some countries, the number of cases related to the use of injected drugs is high; the sexual pattern of disease transmission also varies, for example in sub-Saharan Africa HIV is predominantly spread through heterosexual contact.

Prognosis, factors affecting progression, including rate of progression

A 2017 publication of a study compared the life expectancy of patients starting ART between 1996 and 2013, and found patients who started ART during 2008-2010 whose CD4 counts exceeded 350 cells per µL one year after ART initiation, have a life expectancy (78 years) approaching that of the general population.[1] However, among people who inject drugs, there was little evidence to indicate mortality rates have improved.

All coinfections may have an impact on outcomes in HIV infection, although chronic coinfections with hepatitis viruses are generally associated with worse overall outcomes. It should be noted that some treatments for HIV (e.g. lamivudine, tenofovir and emtricitabine) also are used in the treatment of infection with hepatitis B virus leading to potential cost savings.

Resistance to antiretroviral drugs can be acquired at the infection stage, or may be secondary to inadequate adherence to ART. Resistance to antiretroviral agents depends on changes in the ribonucleic acid (RNA) of HIV, which allows the virus to replicate in the presence of particular antiretroviral drugs.

The prevalence of primary or transmitted resistance to one or more antiretroviral agents has been reported to be as low as 4% of newly diagnosed Australian patients,[3] except up to 20% of newly diagnosed patients in the US.[26] Primary resistance varies worldwide depending on the availability of different medications in the HIV infected population.

Resistance does not develop in the presence of fully suppressive combination ART that is taken regularly, without missed doses. The likelihood of developing resistance depends on the combination. World Health Organisation (WHO) data suggests most (~84%) patients who commence therapy with one of the current first-line drug regimens will achieve and maintain viral suppression.[24] In patients in low-income and middle-income countries, factors associated with resistance have included the need to pay for medications and employment status.

Most clinicians order a genotyping test to look for resistance at the time of diagnosis and in instances of the setting of virological treatment failure. This assists in the choice of a new antiretroviral combination. Genotyping may not be possible if the viral load is <1000 copies per mL as the amplification success rate is low. Resistance testing is now funded by the Medicare Benefits Schedule (MBS) under Item 69380.[13]

It is unlikely that people living with HIV will require admission to hospital for treatment. Admission would generally only be necessary for the management of AIDS defining illnesses, including opportunistic infections and HIV-related cancers, in addition to comorbidities including liver disease and substance dependency.[30] The rate of disease progression is highly variable between individuals, ranging from six months to more than 20 years.[25] In the absence of treatment, the median survival following AIDS in the absence of ART is dependent on CD4+ T cell count at AIDS diagnosis: 3.7 years if the CD4+ T cell is less than 200 cells/μL and 1.3 years if the CD4+ T cell count is less than 70 cells/μL.[16]

Information required for diagnosis

Screening for HIV is usually undertaken with an enzyme-linked immunosorbent (ELISA) antibody test. The 4th generation test is now routine in Australia as a highly specific and sensitive combined HIV antibody-antigen ELISA.

If the ELISA result is seropositive or close to the positive cut-off value, this is confirmed by a Western blot test (another, more specific antibody test). A seropositive western blot test result is analogous to infection with HIV. An indeterminate Western blot test result may imply infection with HIV (particularly if around the time of HIV seroconversion), or may be a false-positive result. An indeterminate test result should generally be repeated after two weeks and then again after three months. In some countries, two positive test results with two different enzyme immunoassays (EIA) or rapid test kits on the same sample of blood will be considered to represent HIV seropositivity without a further Western blot test.

Testing for HIV is indicated for all permanent visa applicants of more than 15 years of age; all applicants who will be working or training in Australia as a doctor, dentist, nurse or paramedic; temporary applicants with clinical indications of AIDS (recurrent, severe, and occasionally life-threatening infections and/or opportunistic malignancies); all children for adoption; children of fewer than 15 years of age who are suspected of having HIV infection.

For children <18 months of age: HIV serology is not the recommended test and a virological assay (PCR) is needed (see Appendix B: algorithm for early infant diagnosis). In the case of “needlephobia”, alternative testing may be provided. Finger prick samples rather than venepuncture is permissible, and salivary-based tests are currently being trialled. A positive test result should be confirmed through repeat testing, on at least one occasion. RNA or DNA tests may be confirmatory but do not make good screening tests.

The presumptive exclusion of HIV infection in non-breastfed infants is based on:

- Two negative virologic tests (one obtained at age ≥14 days and one at age ≥4 weeks), OR
- One negative virologic test at age ≥8 weeks

Definitive exclusion of HIV infection in non-breastfed infants is based on:

- Two or more negative virologic tests (one obtained at ≥1 month of age and one at ≥4 months of age), OR
- Two negative antibody tests from separate specimens obtained at ≥6 months of age.

Previous testing overseas may not be reliable for a variety of reasons, so it may be difficult to determine whether someone has seroconverted recently. Recent seroconversion often is associated with a glandular fever type illness and may be associated with changing test results, especially a negative to positive ELISA test result and a negative or indeterminate western blot test result that becomes seropositive. Risk factors for HIV may be useful in specific national or regional settings; however, in most countries with a high prevalence of HIV infection, the most common source of acquisition is heterosexual intercourse. There are few, if any, situations in which risk factor data would alter the understanding of an HIV test result.

In general, most practitioners would repeat HIV RNA testing every 6 months and the CD4+ T-cell count every 12 months. The exception is when CD4+ <200 cells/µL, in which case it should be repeated at every visit, so that antimicrobial prophylaxis can be stopped once the CD4+ is stable at a particular threshold (for example ≥200 cells/µL for at least 6 months). Together, the viral load test and CD4+ T-cell count determine:

- the level of activity of the virus in the bloodstream
- the level of damage to the immune system
- if the current antiviral treatments are working and whether it may be necessary to change treatments
- when to take preventative drugs (prophylaxis) to decrease the chances of acquiring some of the more common opportunistic illnesses that are associated with AIDS.

Tests for coinfections/complications which usually are performed at diagnosis may include:

- hepatitis B serology
- hepatitis C serology
- syphilis serology (Venereal Disease Research Laboratory [VDRL] or rapid plasma reagin tests [RPR])
- cytomegalovirus antibody
- toxoplasma antibody
- Mantoux test or Quantiferon Gold assay
- chest x-rays image
- HIV genotype resistance assay (if available).

The CD4+ count is a measure of the current degree of immunodeficiency. The viral load is a measure of the risk of future damage to the immune system. Caution must be used in considering an individual CD4+ T-cell count. Factors which may impact on a CD4+ T-cell count include the individual assay, diurnal variation and acute illness.

Usually, patients require three to six monthly medical reviews, with clinical assessment and monitoring of the CD4+ T-cell numbers and HIV viral load. In addition, a full blood examination, and renal and liver function tests are performed in all patients. Additional tests would be undertaken only if another condition, or new symptoms, are present. These reviews can be carried out by a specialist in infectious diseases, or a general practitioner with a special interest in HIV, who has section 100 prescribing rights for ART.

It is important to note that considerable individual variation occurs in the rate of decline of CD4+ T- cell counts, therefore a series of readings over time is required to assess the future antiretroviral needs of a person living with HIV infection. A small but significant number of individuals (approximately 3-5%) may be long term non-progressors.[5] Generally, in untreated HIV, the CD4 cell count declines gradually as the illness progresses, and this fall accelerates over time.[15]

In those who are receiving ART therapy, responses to antiretroviral treatment generally are good.[36]

While concerns have been expressed about the long-term toxicities of some antiretroviral drugs, the clear over all clinical benefits can be seen in the decline in the frequency of deaths of all causes.

Currently accepted treatments

The recommended treatment guidelines in Australia are updated regularly in conjunction with international guidelines.[6] Since April 2014, all HIV positive people in Australia are eligible under the Pharmaceutical Benefit Scheme (PBS) to receive subsidised ART. Patients no longer need to wait for their CD4 counts to fall, or for clinical symptoms to emerge, before they can be prescribed PBS subsidised treatments.[14] The Strategic Timing of Antiretroviral Therapy (START) trial definitively showed that all people with HIV should be treated for HIV-infection regardless of CD4 count at diagnosis and that ART should start as soon as possible after diagnosis.[20]

The Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) Sub-Committee for Guidance on HIV Management Committee, strongly recommends ART be initiated in all people with HIV, wherever possible, irrespective of CD4 count, to reduce the risk of disease progression and transmission.[9, 10]

ART has significantly improved the prognosis of individuals who are infected with HIV. Although some types of antiretroviral drugs have been associated with various toxicities, these can usually be minimised with substitution of therapy. In some people 'nucleoside-sparing' ART combination regimens may be preferred, although at this stage none are recommended and preferred treatment options. Factors included in the choice of a regimen include:

- co-morbidities, for example liver disease, tuberculosis (TB), mental illness, diabetes, osteoporosis
- cardiovascular risk
- chemical dependency
- pregnancy or pregnancy potential
- likely adherence
- dosing convenience
- possible adverse effects
- drug-drug interactions
- pre-treatment CD4+ T-cell counts
- sex and genotyping results (if available).

Since the last revision of the ASHM ARV Adult and Adolescent Guidelines in 2016, new data from clinical trials and cohort studies, as well as experience in clinical practice, have prompted several changes to preferred regimens for treatment-naive patients.[6] Listed below in Table 1 are preferred antiretroviral component options for constructing a regimen for a treatment-naïve patient. The most commonly prescribed regimens are currently:

- Triumeq (dolutegravir + abacavir + lamivudine)/DTG+ABC+3TC
- Tivicay (dolutegravir) and Descovy (emtricitabine + tenofovir alafenamide)/DTG+TAF/FTC or TDF/FTC
- Genvoya (tenofovir alafenamide + emtricitabine + elvitegravir + cobicistat)/EVG+cobi+TAF+FTC.

The selection of a regimen should be individualised based on virologic efficacy, toxicities, pill burden, dosing frequency, drug interaction potential and comorbid conditions. Components are designated as preferred when clinical trial data suggests optimal and durable efficacy, with acceptable tolerability and ease of use. Alternative components are those in clinical trial data showing efficacy, however have disadvantages, such as antiviral activity or toxicities, when compared with the preferred agent. In some cases, for an individual

patient, a component listed as alternative may actually be the preferred component. When there is more than one component for a preferred or alternative option, the components are listed in alphabetical order.

Table 1: *Regimens for Antiretroviral Therapy-Naive Patients*

Regimens	Comments
An antiretroviral (ARV) regimen for a treatment-naive patient generally consists of two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with a third active ARV drug from one of three drug classes: an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI) with a pharmacokinetic (PK) enhancer (booster) (cobicistat or ritonavir). **The preferred regimens are arranged first by evidence rating and when ratings are equal, in alphabetical order.**	
INSTI-Based Regimen • Dolutegravir/abacavir/lamivudine—only for patients who are HLA-B*5701 negative (AI) • Dolutegravir plus either tenofovir disoproxil fumarate/emtricitabine (AI) or tenofovir alafenamide/emtricitabine (AII) • Elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine (AI) • Elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine (AI) • Raltegravir plus either tenofovir disoproxil fumarate/emtricitabine (AI) or tenofovir alafenamide/emtricitabine (AII)	Protease Inhibitor-Based Regimens: • Darunavir/ritonavir plus either tenofovir disoproxil fumarate/emtricitabine (AI) or tenofovir alafenamide/emtricitabine (AII)
For more detailed information, refer to the ASHM's Sub-Committee for Guidance on HIV Management Committee Antiretroviral Guidance available at: http://arv.ashm.org.au/arv-guidelines [8] **Key abbreviations**: 3TC = lamivudine, ABC = abacavir, ART = antiretroviral therapy, ARV = antiretroviral, ATV/c = atazanavir/cobicist, ATV/r = atazanavir/ritonavir, AV = atrioventricular, CVD = cardiovascular disease, DRV/c = darunavir/cobicist, DRV/r = darunavir/ritonavir, DTG = dolutegravir, ECG = electrocardiogram, EFV = efavirenz, EVG = elvitegravir, FDA = Food and Drug Administration, FPV/r = fosamprenavir/ ritonavir, FTC = emtricitabine, HSR = hypersensitivity reaction, INSTI = integrase strand transfer inhibitor, LPV/r = lopinavir/ritonavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleos(t)ide reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, PPI = proton pump inhibitor, RAL = raltegravir, RPV = rilpivirine, RTV = ritonavir, SQV/r = saquinavir/ritonavir, TAF = tenofovir alafenamide, TDF = tenofovir, ZDV = zidovudine **Rating of Recommendations**: A = Strong; B = Moderate; C = Optional **Rating of Evidence**: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion	
Source: US DHHS Antiretroviral guidelines with Australian commentary (http://arv.ashm.org.au/component/content/article/11-arv-guidelines/56-considerations-when-selecting-a-first-antiretroviral-regimen-for-treatment-naive-patients)[2] http://arv.ashm.org.au/arv-guidelines/what-to-start#Table6[9]	

The pattern of switching between regimens would depend on the reason; whether because of adverse effects or because of a failure to control the virus, as a result of resistance. Current guidelines suggest all patients complete baseline resistance testing before commencing treatment. Resistance testing should be repeated if the viral load becomes detectable, that is, in the advent of virological failure. Since a certain amount of virus is required for amplification, this usually means the viral load needs to be ≥1000 copies/mL. Viral replication in most patients initially is suppressed successfully with therapy and such suppression can be maintained over many years. Therefore, resistance testing is unlikely to be a significant cost in the management of individual patients who are newly commencing therapy, but may be more important in those who are receiving third or fourth line treatment.

Treatment of pregnant women infected with HIV

Treatment recommendations listed in this document are based on the principle that therapies of known benefit to women should not be withheld during pregnancy – unless there are known adverse effects on the mother, foetus or infant, and these adverse effects outweigh the benefit to the pregnant woman. Thus, pregnancy should not preclude the use of optimal drug regimens.[11, 28]

All pregnant and breastfeeding women with HIV should initiate a recommended ART regimen, and continue lifelong with ART. HIV infected pregnant women should receive regular monitoring for complications of pregnancy and for potential toxicities.

WHO guidelines on ART, recommend that efavirenz can be included as part of first-line therapy in adults regardless of gender, and that it can be used throughout pregnancy, including during the first trimester.[17, 39]

Prevention of mother to child transmission of HIV

If a pregnant woman does not commence an ART regimen, the rate of perinatal transmission is approximately 25-30%. This can be reduced to as low as 1-2% with appropriate management and prevention strategies. Risk factors that increase the likelihood of perinatal transmission include:

- acute stage of the mother's illness;
- high maternal viral load;
- low CD4 (T cell) count;
- prolonged rupture of the membranes;
- vaginal birth;
- premature birth; and
- breastfeeding.[29]

Perinatal strategies for the prevention of mother to child transmission of HIV require that an HIV infected woman’s status is known during pregnancy, whether by testing before becoming pregnant or during the antenatal period.

Effective preventive strategies now include:

- Highly active ART (HAART) use during pregnancy;
- Six weeks of ART (usually zidovudine alone) postnatally for the newborn child;
- Elective Caesarean section, particularly if HIV viral suppression has not been achieved with HAART and;
- Formula feeding (refer to the perinatal guidelines available at http://aidsinfo.nih.gov/guidelines[28])

Early infant diagnosis of HIV

Australian recommendations are in line with the current USA DHHS position (refer to Appendix B: algorithm for early infant diagnosis).

In infants and children younger than 18 months with perinatal or postnatal HIV exposure:

Virologic assays (e.g. HIV RNA and HIV DNA nucleic acid tests) that directly detect HIV must be used to diagnose HIV infection in infants and children younger than 18 months with perinatal and postnatal HIV exposure. HIV antibody tests should not be used

RNA or DNA polymerase chain reaction (PCR) testing are recommended equally for most patients; RNA PCR is recommended for known maternal non-subtype B virus

Virologic diagnostic testing is recommended for all infants with perinatal HIV exposure at the following ages:

- 14 to 21 days
- 1 to 2 months
- 4 to 6 months

Additional virologic diagnostic testing at birth should be considered for infants at higher risk of perinatal HIV transmission and at two to four weeks after cessation of antiretroviral prophylaxis

A positive virologic test should be confirmed as soon as possible by a repeat virologic test on a second specimen

For children with non-perinatal exposure only, or children with perinatal exposure aged >24 months:

Diagnostic testing relies primarily on the use of HIV antibody (or antigen/antibody) tests. When acute HIV infection is suspected, additional testing with an HIV nucleic acid test may be necessary to diagnose HIV infection.

Definitive exclusion of HIV infection:

Definitive exclusion in non-breastfed infants is based on two or more negative virologic tests, with one obtained at age ≥1 month and one at age ≥4 months, or two negative HIV antibody tests from separate specimens obtained at age ≥6 months.

Some experts confirm the absence of HIV infection at 12 to 18 months of age in children with prior negative virologic tests by performing an HIV antibody test to document loss of maternal HIV antibodies.

Since children aged 18 to 24 months with perinatal HIV exposure occasionally have residual maternal HIV antibodies, definitive exclusion or confirmation of HIV infection in children in this age group who are HIV antibody-positive should be based on an HIV nucleic acid test.

In summary:

The result of an HIV antibody test at less than 18 months of age is unreliable in infants who were born to HIV infected mothers

An infant with two negative virologic tests (at age ≥ 14 days and at age ≥ 4 weeks) or one negative test at age ≥ 8 weeks can be judged as presumptively uninfected if no evidence of clinical HIV infection

HIV polymerase chain test, whether by HIV proviral DNA or HIV RNA polymerase chain testing, is the best test for children who are aged less than 18 months.

Treatment of HIV infection in paediatric patients

Treating children who are diagnosed HIV-positive with antiretroviral drugs within their first 12 weeks of life reduces mortality by 75%. Without treatment, a third of children living with HIV die before their first birthday and half before their second.[33]

Most children living with HIV become infected through mother-to-child transmission. Children born to mothers living with HIV need to be tested as soon as possible after birth to find out if they are infected with the virus and to commence antiretroviral treatment.

Prophylactic ARV therapy should be given to all exposed infants for the first six weeks of life and if HIV infection is confirmed, then changed to a full regimen of ART.

The WHO 2016 consolidated guidelines state that ART should be initiated in all children living with HIV, regardless of WHO clinical stage or at any CD4 cell count:[38]

- Infants diagnosed in the first year of life; and
- Children living with HIV one year old to less than 10 years old.

Infants aged under three years of age

For infants and children younger than three years of age, the NRTI backbone for an ART regimen should be ABC or AZT + 3TC.

Preferred first-line regimens:

- ABC (or AZT) + 3TC + LPV/r

Alternative first-line regimens

- ABC (or AZT) + 3TC + NVP

Children aged three years to less than 10 years of age

Preferred first-line regimens:

- ABC + 3TC + EFV

Alternative first-line regimens:

- ABC + 3TC + NVP
- AZT + 3TC + EFV (or NVP)
- TDF + 3TC (or FTC) + EFV (or NVP)

For infants and children infected with HIV who are under three years of age, ABC + 3TC + AZT is recommended as an option for children who develop TB while on an ART regimen containing NVP or LPV/r. Once TB therapy has been completed, this regimen should be stopped and the initial regimen should be restarted.

The use of ART has significantly impacted on morbidity and mortality in children with HIV.[37] However, there are unique paediatric challenges with ART therapy. These issues include the limited number of syrup or liquid preparations for the majority of the antiretroviral drugs that are suitable for infants and children who are unable to swallow pills or whose weight precludes the use of fixed tablet/capsule formulations. (see Table 2).

Table 2: *Pharmaceutical costs of antiretroviral drugs commonly prescribed for paediatric patients as at September 2018*

Drug	PBS item number	Usual dosage	PBS price	Estimated annual cost
Nucleoside reverse transcriptase inhibitor drugs				
zidovudine 50 mg/5 mL oral liquid, 200 mL	10361H	10mL tds	$38.41	$2,112
lamivudine 10 mg/mL oral liquid, 240 mL	10320E	6mL bd	$59.13	$1,123
abacavir 20 mg/mL oral liquid, 240 mL	10356C	6mL bd	$70.30	$1,336
Non-nucleoside reverse-transcriptase inhibitor drugs				
nevirapine 10 mg/mL oral liquid, 240 mL	10319D	5ml daily	$139.73	$1,118
efavirenz 30 mg/mL oral liquid, 180 mL	10275T	6.7mL daily	$69.87	$978
Protease-inhibitor drugs				
lopinavir 400 mg/5 mL + ritonavir 100 mg/5 mL oral liquid, 60 mL (Kaletra)	10327M	1.9 mL bd	$130.88	$3,141
Source of unit cost data: Schedule of Pharmaceutical Benefits – Effective 1 – 30 September 2018[14] Available from: www.pbs.gov.au/info/publication/schedule/archive Unit cost of drug = Dispensing Price for Maximum Quantity (DMPQ)/Max qty packs Unit values are presented up to 2 decimal places. Total costs have been computed on these unit values, and rounded to the nearest whole number or to the nearest whole number of full pack size costs.				

Maternal viral load

Infants born to mothers not on ART with detectable viral load and those born to mothers on ART with an undetectable vital load in plasma require different management.

Infants of mothers on suppressive ART:

The risk of HIV infection in infants born to women who had achieved viral suppression on ART or who had been regularly taking ART for more than four weeks by the time of delivery is low. The recommended prophylaxis regimen for such infants is six weeks of daily nevirapine for those who are breastfeeding, and four to six weeks of daily nevirapine or twice-daily zidovudine for those who are receiving replacement feeding.

Infants of mothers with detectable viral load:

For these infants, the recommended prophylaxis regimen is daily nevirapine plus twice-daily zidovudine for the first six weeks of life. Breastfeeding infants should continue an additional six weeks of prophylaxis with the same combination or with nevirapine alone; if the mother cannot tolerate or declines ART, then the infant

should continue nevirapine prophylaxis throughout the duration of breastfeeding, until one week following breastfeeding cessation (if nevirapine is not tolerated, daily lamivudine can be used).

Coinfection with Hepatitis C, Hepatitis B and Tuberculosis

All coinfections can impact outcomes in people with HIV infection, but coinfection with chronic hepatitis generally is associated with worse overall outcomes. Some treatments for HIV are also used in hepatitis B (e.g. lamivudine, emtricitabine and tenofovir) therefore care should be taken to avoid double counting of costs.

Hepatitis C

Approximately 10% of people living with HIV infection in Australia have coinfection with hepatitis C. In other parts of the world, rates depend on the mode of transmission of HIV and hepatitis C. In southern Europe, coinfection rates are as high as 50% as a result of the high prevalence of HIV in injecting drug users, while in northern Europe rates are lower at 10%-37%.[4]

People with HIV and hepatitis C virus (HCV) coinfection show a higher rate of chronic infection with hepatitis C virus, a higher viral load of hepatitis C virus, and accelerated progression of liver disease. Evidence is emerging that immune restoration by means of ART may slow the progression of liver disease in persons with coinfection with HIV and hepatitis C virus. While accelerated progression of HIV disease in persons with coinfection with HIV and hepatitis C virus has been demonstrated in some studies, it has been refuted by others.

Testing for hepatitis C virus usually takes place at the time of diagnosis of HIV. Persons with a positive result for hepatitis C antibody are tested further by means of a hepatitis C virus PCR assay. Persons with HIV, particularly those with advanced immunodeficiency, show lower sensitivity in antibody testing for hepatitis C virus. Hepatitis C virus RNA assessment, by PCR or by an alternative method, is recommended if the result of antibody testing for hepatitis C virus is negative however this method increases the chance of HCV infection. In about 25% of people, HCV infection clears spontaneously.[19]

Baseline testing generally includes viral genotype and a quantitative hepatitis C virus RNA (viral load) test as the efficacy of antiviral therapy against hepatitis C virus is associated with both parameters. Unlike HIV viral load, the hepatitis C viral load has no prognostic value in terms of assessing disease progression and does not require regular monitoring. Newer ‘pangenotypic’ direct acting antiviral (DAA) regimens (e.g. sofosbuvir/velpatasvir) will mean that response to therapy will not necessarily be dependent on HCV genotype.

In persons with coinfection with HIV and hepatitis C, the risk of progressive liver disease is relatively high. A mandatory requirement for a preceding liver biopsy in order to access PBS section 100 treatments for chronic hepatitis C was removed in April 2006. Nonetheless, the staging of liver disease will remain an important tool for the determination of a prognosis and decision-making on treatment. Fibroscanning and elastography has taken over from biopsy as a way to identify the stage of liver diseases.[22] In addition, the AST to Platelet Ratio Index (APRI) score is used to exclude cirrhosis, particularly where elastography is unavailable or not readily available.

Treatment of HCV

In the current environment of rapidly evolving antiviral therapy against HIV and hepatitis C virus infections, and expanding knowledge regarding coinfection with HIV and hepatitis C, the therapeutic decision making process for persons with coinfection with HIV and hepatitis C and their clinicians is complex.

Several factors contribute to the complexity:

- hepatitis C infection in the setting of HIV has a faster progression to complications, both cirrhosis and hepatocellular carcinoma
- declining morbidity and mortality from HIV related opportunistic disease has increased the proportion of non-HIV related morbidity and mortality, including those as a result of advanced liver disease
- hepatitis C virus infection may impair immune responsiveness after the introduction of cART in persons with coinfection with HIV and hepatitis C

Direct acting antiviral treatment regimens for co-infected patients are same as those used for hepatitis C mono-infections, with due consideration to potential drug-drug interactions.

In ART-naive patients: HIV infection should be controlled and HIV-related opportunistic infections should be treated before initiation of hepatitis C treatment, particularly in those with advanced HIV immunosuppression (CD4+ count, <200 cells/mm^3). Treatment of people with a CD4+ cell count greater than 500 cells/mm^3 may be deferred until hepatitis C treatment is completed, to avoid drug–drug interactions. Tipranavir, in particular, should be avoided in concurrent ART-DAA therapy. However, it is recommended that ART be initiated as soon as reasonable.

An ART regimen without DAA drug-drug interactions should be chosen if DAA therapy is planned.

ART should not be switched for people who are on a stable regimen unless an unavoidable and unmanageable drug–drug interaction is identified, because switching ART in HIV virologically suppressed patients has a risk of HIV virological failure.

An important resource for assessing potential drug-drug interactions is the University of Liverpool's Hepatitis Drug Interactions website.[35] Available from: www.hep-druginteractions.org

Monitoring of hepatitis C viral load at 12 weeks after the commencement of HCV treatment allows an assessment of response and a decision to be made whether to persist with treatment.

For DAA treatment regimens, see http://arv.ashm.org.au/arv-guidelines/considerations-for-antiretroviral-use-in-patients-with-coinfections/hiv-hcv [4]

For further details on management of hepatitis C mono-infection, refer to *Financial Implications and Consideration of Prejudice of Access to Services Associated with Viral Hepatitis*

Hepatitis B

HIV infection modifies the natural history of hepatitis B infection. Higher rates of progression to advanced liver disease occur among persons with coinfection with HIV and hepatitis B. The presence of HIV infection is associated with greater rates of progression to cirrhosis. The impact of hepatitis B infection on the natural history of HIV infection is less certain.

Persistent infection with hepatitis B virus is more common in people with HIV. Studies among men who have sexual intercourse with men exposed to hepatitis B virus show evidence of chronic infection with hepatitis B virus in almost 25% of individuals compared with 3%-5% in those without HIV. Although it is rare, reactivation of hepatitis B virus infection may occur in the setting of advanced immunodeficiency, in spite of seroconversion to hepatitis B surface antibody (HBsAb). Furthermore, in persons with coinfection with HIV and hepatitis B virus, hepatitis B DNA levels are substantially higher and rates of seroconversion from HBe antigen (HBeAg) to antiHBe are lower, than in persons with HBV alone.[4]

At diagnosis with hepatitis B infection, people have serology testing, including HBeAg, hepatitis B viral load estimation, ultrasound examination and measurement of alpha-fetoprotein levels. Asymptomatic patients

with coinfection with HIV and hepatitis B require a similar number of routine clinical consultations for monitoring, as mono-infected patients. Monitoring liver enzyme levels occurs as part of HIV care.

It is well established that hepatitis B infection markedly increases the risk of primary hepatocellular carcinoma. Although an increased rate of hepatocellular carcinoma has yet to be described in people with HIV, the known over all increased risk of malignancy in this population suggests a risk that is potentially higher. Screening every 6-12 months with triple phase CT scanning and alpha-fetoprotein protein levels is strongly recommended.

In the case of people with HIV coinfected with HBV, ART should contain the NtRTI tenofovir (either in TDF or TAF forms). In these instances, the use of FTC would also occur as TDF and TAF are co-formulated with FTC. In this instance, the TDF or TAF plus FTC offers excellent HBV suppressive therapy. The use of the ABC/3TC FDC should not be used as this offers only 3TC monotherapy against HBV, which is suboptimal and leads to HBV lamivudine resistance and the risk of liver disease progression. Treatment costs for hepatitis B infection depend on the use of antiretroviral drugs for coinfection with HIV. Refer to Appendix C for the costing of coinfection with HIV and hepatitis C virus.

If it is not possible to obtain TAF/FTC or TDF/FTC then the anti-HBV drug 'entecavir' should be administered to achieve adequate HBV control (as well as ART directed at the HIV-infection of course).

Refer to Co-infection: HIV & Viral Hepatitis a guide for clinical management[4] http://arv.ashm.org.au/arv-guidelines/considerations-for-antiretroviral-use-in-patients-with-coinfections/hiv-hcv

Tuberculosis and HIV

The risk of reactivation of tuberculosis in HIV infected people is approximately 14% during the two years after exposure to *Mycobacterium tuberculosis*, in contrast to the risk in HIV negative persons of 10% in a lifetime. The development of tuberculosis in an HIV infected person may accelerate the progression of HIV disease.

Treatment of latent infection with *Mycobacterium tuberculosis* is important to prevent the development of active disease in HIV infected individuals with latent tuberculosis infection (LTBI). People at risk are those with a positive Mantoux test with a reaction of at least 5 mm in diameter, or known exposure to a person with infectious *Mycobacterium tuberculosis* disease.

The TEMPRANO trial has now shown clinical benefit (reduced mortality) for anergic people as an adjunct to ART initiation in people with HIV.[31] WHO has recommended the use of isoniazid preventive therapy (IPT) regardless of Mantoux test result in people with HIV. Generally, if someone is HIV-positive and from a country endemic for TB then they should be offered IPT (along with ART initiation and other standard prophylaxis as per guidelines).

Interferon gamma release assays (IGRAs) have been available alternatives to Mantoux testing for some years. While the current consensus is that these assays do not offer a clear advantage in terms of assessing LTBI compared to Mantoux testing, they do not require people to return for a reading three days later.[27]

Before instituting prophylaxis for *Mycobacterium tuberculosis*, it is important to exclude tuberculous infection. To reasonably exclude active TB, it is important to consider the presence of a cough of any duration, fever of any duration or night sweats lasting three or more weeks in the preceding four weeks.

Prophylaxis with a single agent during active infection with *Mycobacterium tuberculosis* will lead to drug resistance. Isoniazid given in a daily 300mg dose for nine to 12 months is effective, as is daily rifabutin and pyrazinamide, which are administered for two months.

Both regimens are associated with hepatotoxicity and should be used with caution in people with hepatic disease. Close monitoring of liver function is required during the administration of a rifamycin drug and pyrazinamide combination and as a result of this higher rates of hepatotoxicity is recommended. Isoniazid is the preferred drug in this setting.

The management of *Mycobacterium tuberculosis* infection requires systemic combination antimicrobial therapy. If HAART is used in combination with the standard tuberculosis treatment regimen, then consideration of drug interactions between the antiretroviral agents and the rifamycin drug is paramount.

The timing of antiretroviral and anti-tuberculous therapy is important. The initiation of cART was previously deferred until at least two months after the commencement of treatment for *Mycobacterium tuberculosis* infection, as inflammatory reactions, significant drug-drug interactions and overlapping toxicities occurred during simultaneous therapy against infections with HIV and *Mycobacterium tuberculosis*. However recent data suggests that simultaneous commencement of ARVs and anti-tuberculous therapy may be the safest approach depending on the CD4+ counts.[21]

- If CD4 count <50:
  - Initiate anti-tuberculosis therapy (ATT) first, and then ART two weeks later.
  - EFV can be used as the third drug at doses of 600mg or 400mg in combination with the ATT; the doses of the N(t)RTI backbone do not require adjustment.
  - The dose of TAF (if used) does require adjusting, but the exact dose is not yet known so best to avoid TAF in this situation.
- If CD4>50 but <200: best to initiate ATT and then ART 2 months, at which time the ATT is simplified from four drugs to the maintenance phase of INH and Rifampicin.
- If CD4+ >200: general advice is to start as soon as practicable – likely at two months.

See coinfection with tuberculosis[7] Available from: http://arv.ashm.org.au/arv-guidelines/considerations-for-antiretroviral-use-in-patients-with-coinfections/hiv-tb

Financial considerations

It is unlikely people living with HIV will require admission to hospital for treatment of HIV related morbidities. Most of them require only regular check-ups and monitoring, either in specialised general practices or in hospital outpatient departments, every three to six months. Table 3 provides a summary of the cost of therapies for HIV. Table 4 provides a summary of costings on a broader range of medications commonly used in the management of patients with HIV. Table 5 provides a summary of costings on medical benefits provided to people with HIV.

Table 3: *Pharmaceutical costs of commonly prescribed antiretroviral medications as at September 2018*

Drug	PBS item no.	Usual dose/ frequency	Unit cost	Estimated annual cost
Nucleos(t)ide reverse transcriptase inhibitor drugs (NRTIs)*				
abacavir 300 mg tablet, 60	10294T	300mg bd	$241.86	$3,144
tenofovir disoproxil fumarate 300 mg tablet, 30	10310P	300mg daily	$404.59	$5,260
lamivudine 150 mg tablet, 60	10348P	150mg bd	$71.78	$933
zidovudine 100 mg capsule, 100	10266H	100mg two tds	$175.39	$3,859
emtricitabine 200 mg capsule, 30	10274R	200mg daily	$254.40	$3,307
Non-nucleoside reverse transcriptase inhibitor drugs (NNRTIs)*				

Drug	PBS item no.	Usual dose/ frequency	Unit cost	Estimated annual cost
nevirapine 200 mg tablet, 60	10304H	200mg bd	$167.08	$2,172
rilpivirine 25 mg tablet, 30	10298B	25mg daily	$271.97	$3,536
efavirenz 200 mg tablet, 90	10336B	200mg daily	$233.06	$1,165
etravirine 200 mg tablet, 60†	10301E	200mg bd	$609.33	$7,921
Protease Inhibitors (PIs)*				
atazanavir 150 mg capsule, 60	10276W	150 mg bd	$467.73	$6,080
tipranavir 250 mg capsule, 120† (Co-administered with 200 mg ritonavir twice daily)	10344K	500mg bd	$756.21	$9,831
darunavir 600 mg tablet, 60† (co-administered with 100 mg ritonavir twice daily)	10329P	600mg bd	$920.29	$11,964
fosamprenavir 700 mg tablet, 60	10337C	700mg bd	$340.80	$4,430
indinavir 400 mg capsule, 180	10363K	800mg tds	$388.00	$5,044
saquinavir 500 mg tablet, 120	10335Y	1000mg bd	$430.72	$5,599
ritonavir 100 mg tablet, 30	10273Q	600mg bd	$34.89	$5,094
Combination drugs				
abacavir 300 mg + lamivudine 150 mg + zidovudine 300 mg tablet, 60 (Trizivir)‡	10305J	One bd	$414.97	$5,395
abacavir 600 mg + lamivudine 300 mg tablet, 30 (Kivexa) *‡	10357D	One daily	$305.82	$3,976
tenofovir disoproxil fumarate 300 mg + emtricitabine 200 mg + efavirenz 600 mg tablet, 30 (Atripla)	10297Y	Once daily	$854.79	$11,112
tenofovir disoproxil fumarate 300 mg + emtricitabine 200 mg + elvitegravir 150 mg + cobicistat 150 mg tablet, 30 (Stribild)	10307L	Once daily	$892.20	$11,599
tenofovir disoproxil fumarate 300 mg + emtricitabine 200 mg tablet, 30 (Truvada)*	10347N	Once daily	$232.80	$3,026
lopinavir 200 mg + ritonavir 50 mg tablet, 120 (Kaletra)*	10272P	2 bd	$693.26	$9,012

Drug	PBS item no.	Usual dose/ frequency	Unit cost	Estimated annual cost
lamivudine 150 mg + zidovudine 300 mg tablet, 60 (Combivir)*	10284G	One bd	$185.08	$2,406
dolutegravir 50 mg + abacavir 600 mg + lamivudine 300 mg tablet, 30 (Triumeq)‡	10345L	Once daily	$923.99	$12,012
tenofovir disoproxil fumarate 300 mg + emtricitabine 200 mg + rilpivirine 25 mg tablet, 30 (Eviplera)	10314W	Once daily	$892.20	$11,599
emtricitabine 200 mg + tenofovir alafenamide 25 mg, 30 (Descovy)	11113X	Once daily	$723.71	$9,408
tenofovir alafenamide 10 mg + emtricitabine 200 mg + elvitegravir 150 mg + cobicistat 150 mg tablet, 30	11114Y	Once daily	$981.71	$12,762
Other antivirals				
dolutegravir 50 mg tablet, 30*	10283F	Once daily	$689.20	$8,960
raltegravir 400 mg tablet, 60*	10286J	Twice daily	$655.92	$8,527
maraviroc 150 mg tablet, 60*†‡§	10318C	Twice daily	$895.47	$11,641
enfuvirtide 90 mg injection [60 vials] (&) inert substance diluent [60 x 1.1 mL vials] 1 pack (Fuzeon)*†	10365M	BD injection	$1,915.77	$24,905

* The treatment must be in combination with other antiretroviral agents.

† Patient must have experienced virological failure or clinical failure or genotypic resistance after each of at least three different antiretroviral regimens that have included one drug from at least three different antiretroviral classes. (Virological failure is defined as a viral load greater than 400 copies per mL on two consecutive occasions, while clinical failure is linked to emerging signs and symptoms of progressing HIV infection or treatment-limiting toxicity.)

‡ Patient must be aged 12 years or older; and must weigh 40 kg or more.

§ Patient must be infected with CCR5-tropic HIV-1

Source of unit cost data: Schedule of Pharmaceutical Benefits – Effective 1 – 30 September 2018[14] Available from: www.pbs.gov.au/info/publication/schedule/archive

Unit cost of drug = Dispensing Price for Maximum Quantity (DMPQ)/Max qty packs

Unit values are presented up to 2 decimal places. Total costs have been computed on these unit values, and rounded to the nearest whole number or to the nearest whole number of full pack size costs.

Table 4: *Pharmaceutical costs of commonly prescribed prophylactic medications as at September 2018*

Drug	PBS item no.	Usual dose/ frequency	Unit cost	Estimated annual cost	Usual indications
aciclovir 200 mg tablet, 25	1003T	200mg one tds	$12.49	$549	Herpes simplex virus
famciclovir 500 mg tablet, 56	8896F	500mg bd	$72.19	$1,011	Herpes simplex virus
valaciclovir 500 mg tablet, 42	8064K	One daily	$31.29	$282	Herpes simplex virus
ganciclovir 500 mg injection, 5 vials	5749N	One daily	$223.44	$16,311	Cytomegalovirus
valganciclovir 450 mg tablet, 60	9569P	2 tabs daily (maintenance)	$1,792.15	$23,298	Cytomegalovirus
trimethoprim 160 mg + sulfamethoxazole 800 mg tablet, 10	2951H	Once daily	$13.22	$489	*Pneumocystis carinii* (jerovicii) pneumonia / toxoplasmosis
dapsone 100 mg tablet, 100	1272Y	Once daily	$318.44	$1,274	*Pneumocystis carinii* (jerovicii) pneumonia
trimethoprim 300 mg tablet, 7	2922T	Once daily	$13.03	$691	*Pneumocystis carinii* (jerovicii) pneumonia
itraconazole 100 mg capsule, 60	8196J	Once daily	$128.90	$902	Oral candidiasis; other fungal infections
fluconazole 200 mg capsule, 28	1475P	200mg daily	$51.70	$724	Oral Candidiasis; Cryptococcus
pyrimethamine 25 mg tablet, 50	1966L	2 tabs initially then once daily	$18.36	$147	Toxoplasmosis
clindamycin 150 mg capsule, 24	3138E	1 Cap daily	$12.54	$201	Toxoplasmosis
clarithromycin 500 mg tablet, 100	5624B	500mg bd	$31.33	$251	Mycobacterium avium complex
azithromycin 600 mg tablet, 8	5616N	600mg x 2 once a week	$55.38	$720	Mycobacterium avium complex
rifabutin 150 mg capsule, 30	9541E	2 daily (prophylaxis)	$131.46	$3,287	Mycobacterium avium complex

Drug	PBS item no.	Usual dose/ frequency	Unit cost	Estimated annual cost	Usual indications
Source of unit cost data: Schedule of Pharmaceutical Benefits – Effective 1 – 30 September 2018[14] Available from: www.pbs.gov.au/info/publication/schedule/archive Unit cost of drug = Dispensing Price for Maximum Quantity (DMPQ)/Max qty packs Unit values are presented up to 2 decimal places. Total costs have been computed on these unit values, and rounded to the nearest whole number or to the nearest whole number of full pack size costs.					

Table 5: *Medical Benefits Schedule and other medical-service costs as at September 2018*

Service	MBS item number	Frequency	Unit cost	Estimated annual cost
Medical				
General practitioner consultation	23	3-6 monthly	$37.60	$150
Specialist consultations – initial Treatment and Management Plan	132	Once only	$267.85	$268
Specialist consultations – review of plan	133	Annual	$134.10	$134
Specialist consultations – subsequent	116	6 monthly	$76.65	$153
Nurse support	10956	Monthly	$62.25	$747
Chronic Disease Management Plan	721	Yearly	$144.25	$144
Diagnostics				
Renal function test	12524	3-6 monthly	$158.35	$633
FBE incl. Erythrocyte count, haematocrit, haemoglobin, calculation or measurement of red cell index or indices, platelet count, leucocyte count and manual or instrument generated differential count	65070	3 monthly	$16.95	$68
Liver Function Tests, fasting lipids	66512	3-6 monthly	$17.70	$71
HIV viral load	69378/69381	3-6 monthly	$180.25	$721
Genotypic testing for HIV antiretroviral resistance (in a patient with confirmed HIV infection if the patient's viral load is greater than 1,000 copies per ml)	69380	Maximum two tests in a 12 month period	$770.30	$1,541
CD4 T cell lymphocyte count	71139	3-6 monthly	$104.05	$416

Service	MBS item number	Frequency	Unit cost	Estimated annual cost
Quantitation of 1 antibody to microbial antigens (including CMV)	69384	As required	$15.65	$16
Fasting glucose	66551	Annual	$16.80	$17
Ambulatory ECG (optional)	11710	Annual	$51.90	$52
Chest x-ray (Requested)	58503	Once	$47.15	$47
Mantoux test	73811	Once	$11.20	$11
HIV genotyping	71151	Once	$118.85	$119

Source of unit cost data: Medicare Benefits Schedule operating from 01 September 2018.[13] Available from: www.health.gov.au/internet/mbsonline/publishing.nsf/Content/downloads

Unit values are presented up to 2 decimal places. Total costs have been computed on these unit values, and rounded to the nearest whole number.

Prejudice to access and scarcity of resources

There is no relevant prejudice to access.

Effect on applicant's ability to work

In most people with a CD4 count of greater than 200 cells/mm^3 (that is, greater than the range for the diagnosis of AIDS), HIV infection will not affect an individual's ability to work. If opportunistic infections or cancers occur (in particular, rare AIDS illnesses, such as HIV dementia or wasting), then there may be an impact on an individual's capacity to work.

Many individuals who have been unwell, have returned to work once they have responded to ART. Regarding return to work, factors that may play a role, including sex, age, race/ethnicity, health status and the belief that health will improve if employed, independently were associated with contemplating a return to work.

Very few insurance companies now accept the diagnosis of HIV alone as indicative of total and permanent disability, because of the likelihood of a future return to work. Most breaks from work, as a result of ill health, now are temporary. It would seem reasonable to correlate the probability of disability, and time to disability, with progression to AIDS. There should be awareness that many of those who respond to therapy will return to work once their HIV infection is under control.

Appendices

Appendix A: HIV testing on Australian visa applicants

Venepuncture should be done onsite at the Panel clinic once the applicant's identity has been confirmed

The visa case officer will generate testing requirements for HIV, based on visa class and intended occupation in Australia. A summary is provided below.

Table 6: *HIV testing requirements*

TYPE OF APPLICANT	Test for HIV?
Permanent visa applicants 15 or more years of age	Yes
Children who have been, or are to be, adopted by Australian residents	Yes
Unaccompanied Minor Refugee Children	Yes
Children younger than 15 years of age with clinical suspicion for HIV infection, a history of blood transfusions or haemophilia, or if the mother or father is HIV-seropositive	Yes
Temporary Entry Applicants with clinical signs of AIDS	Yes
All applicants aged 15 years of age and older, who intend to work as, or study to be a physician, nurse, paramedic or dentist*	Yes
Persons known or found to be infected with Hepatitis C	Yes
Persons known to be infected with HIV	Yes
* Other allied health professionals including physiotherapists, occupational and speech therapists, laboratory technicians and veterinarians, do not routinely need HIV, hep B or hep C testing.	

Acceptable screening tests for HIV

There are four categories of HIV tests: simple/rapid anti-HIV tests, Enzyme ImmunoAssays (EIAs), immunoblot tests and nucleic-acid tests. First-line HIV screening should ideally be performed with a fourth generation EIA based kit. Third generation kits are acceptable if fourth generation kits cannot be accessed. Machine-based ELISA assays are acceptable as first-line screen.

Note: For any reactive initial screening test, this should be rechecked on the same blood sample with an alternate HIV test, and if still reactive or indeterminate there is the need for formal confirmatory testing.

Confirmatory and supplementary tests results are as follows:

- Screening test negative – no further action is needed.
- Screening test indeterminate – proceed to confirmatory testing with immunoblot. If this is not available, retesting with a different EIA method to the original test is advised.
- Screening test reactive – a second supplemental test to clarify the status of the sample should be performed with a confirmatory immunoblot assay. If these are not available, retesting with two alternative kits is advised.

Appendix B: Algorithm for early infant diagnosis

Source: WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection[38] Available from: www.who.int/hiv/pub/arv/arv-2016/en/

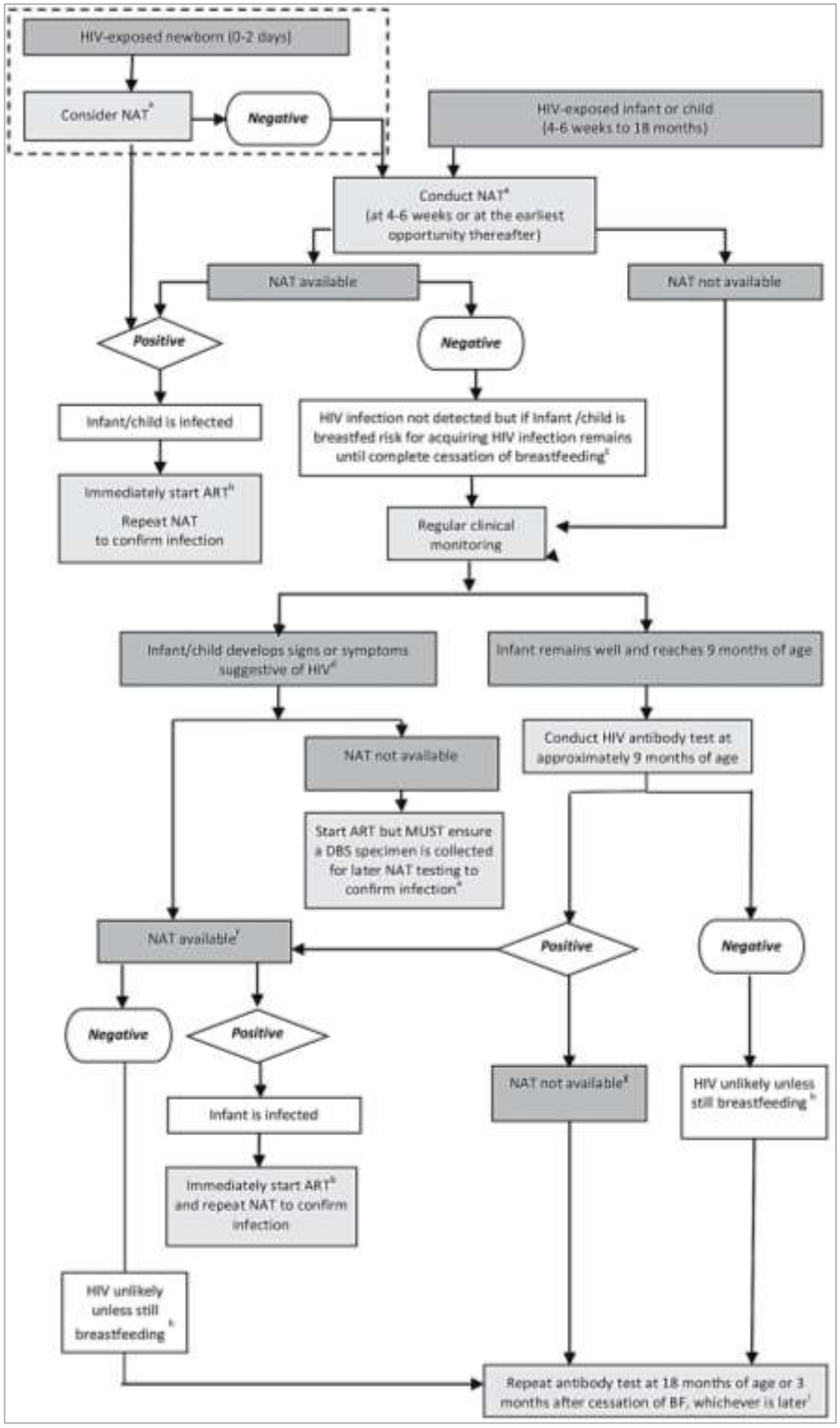

Figure 1: *Algorithm for Early Infant Diagnosis of HIV Infection*

Notes on Figure 1

[a] Based on these revised Guidelines addition of NAT at birth to the existing testing algorithm can be considered. POC NAT can be used to diagnose HIV infection at birth, but positive results should be confirmed using laboratory-based NAT assays, because of limited experience with POC assays close to birth.

[b] Start ART, without delay. At the same time, retest to confirm infection. As maternal treatment is scaled up and MTCT transmission rates decrease, false-positive results are expected to increase and re-testing after a first positive NAT is important to avoid unnecessarily treatment, particularly in settings with lower transmission rates. If the second test is negative, a third NAT should be done before interrupting ART.

[c] For children who were never breastfed additional testing following a negative NAT at 4-6 weeks is included in this algorithm to account for potential false-negative NAT results.

[d] Signs and symptoms suggestive of HIV (oral thrush, recurrent or severe bacterial infections such as pneumonia or sepsis, FTT/wasting or AIDS indicator condition).

[e] If infant presents with signs and symptoms of HIV disease (see footnote d above) but NAT is unavailable, consider starting ART, especially if an antibody test is conducted and result positive at 9 months or later. A DBS specimen must be collected prior to starting treatment for later NAT testing to confirm HIV diagnosis, because subsequent diagnostic testing while already on ART might be difficult to interpret.

[f] If infant presents with signs and symptoms of HIV disease (see footnote d above) consider starting ART while waiting for NAT result. However, another DBS specimen should be collected prior to starting treatment for later NAT testing to confirm HIV diagnosis.

[g] Regular and periodic monitoring should be ensured while waiting for NAT to be available or for antibody testing to be conducted at 18 months. If infant presents with signs and symptoms of HIV disease should be managed as described previously (see footnote e).

[h] The risk of HIV transmission remains as long as breastfeeding continues. If the 9 months antibody testing is conducted earlier than 3 months after cessation of breastfeeding, infections acquired in the last days of breastfeeding may be missed so retesting at 18 months should be ensured for final assessment of HIV status.

[i] If breastfeeding beyond 18 months, final diagnosis of HIV status can only be assessed at the end of breastfeeding. If breastfeeding ends before 18 months, final diagnosis of HIV status with antibody testing can only be assessed at 18 months. Antibody testing should be undertaken at least 3 months after cessation of breastfeeding (to allow for development of HIV antibodies). For infants < 18 months of age positive antibody testing requires NAT to confirm infection. If infant is > 18 months, negative antibody testing confirms infant is uninfected; positive antibody testing confirms infant is infected

Appendix C: Scenarios

Scenario 1 – HIV 1 infection

A Thai man, 22 years of age, currently holds a student visa for a four year stay, has been in Australia for three years and has applied for a permanent visa. The applicant was diagnosed as being HIV antibody seropositive one year after arriving in Australia and is asymptomatic. He denies intravenous drug use and has no coinfection with hepatitis B or C viruses.

His CD4+ T-cell count and HIV viral load were measured in the last 12 months; the results were 600 cells/mm^3 and fewer than 10 000 copies/mL, respectively.

Clinical Opinion

Since the presentation of the START and TEMPRANO trials in mid-2015, the consensus on treatment is everyone should initiate ART as soon as possible after receiving an HIV diagnosis, regardless of their CD4+ T-cell count. The START trial demonstrated that patients who defer ART fare worse than those who started ART immediately – resulting in more HIV-related and non-HIV related adverse events.

Regarding the success of treatment, the most recent trials of first-line ART using InSTI+2N(t)RTI demonstrate approximately 90% of patients have an undetectable viral load (<50 copies/mL) at 48 weeks.[18] Guideline advice regarding preferred initiation ART options is constantly evolving. Table 9 provides the likely regimen for this applicant.

Based on current recommendations, initiation of ART would most commonly be with one of these three regimens:

- Triumeq (dolutegravir + abacavir + lamivudine)/DTG+ABC+3TC
- Tivicay (dolutegravir) and Descovy (emtricitabine + tenofovir alafenamide)/DTG+TAF/FTC or TDF/FTC
- Genvoya (tenofovir alafenamide + emtricitabine + elvitegravir + cobicistat)/EVG+cobi+TAF+FTC

NB: given the rapid advances in the field of HIV and the potential introduction of generic medicines, there is a high likelihood that regimens and costs may change in the medium term.

Table 7: *Scenario 1: Prospective regimen/ service profile and costs involved*

Description	Item reference	Code	Unit cost	Year 1		Year 2 onwards	
				Frequency	Annual cost	Frequency	Annual cost
MEDICAL							
General-practitioner consultations	MBS	23	$37.60	3 monthly	$150	3 monthly	$150
Specialist consultations – initial treatment and management plan	MBS	132	$267.85	once only	$268	-	-
Specialist consultations – review of plan	MBS	133	$134.10	Once	$134	-	-

Description	Item reference	Code	Unit cost	Year 1		Year 2 onwards	
				Frequency	Annual cost	Frequency	Annual cost
Specialist review consultation	MBS	116	$76.65	6 monthly	$153	6 monthly	$153
subtotal					$706		$304
DIAGNOSTICS							
FBE Liver enzymes/renal Glucose/lipids	MBS	65070	$16.95	3 monthly	$68	3 monthly	$68
CD4 T cell lymphocyte count	MBS	71139	$104.05	3 monthly	$416	3 monthly	$416
HIV viral load	MBS	69378	$180.25	3 monthly	$721	3 monthly	$721
Toxoplasma antibody	MBS	71121	$20.80	Once	$21	-	-
CMV antibody							
Mantoux test	MBS	73811	$11.20	Once	$11	-	-
Chest Xray	MBS	58503	$47.15	Once	$47	-	-
subtotal					$1,284		$1,205
PHARMACEUTICAL AGENTS							
Triumeq (dolutegravir 50 mg + abacavir 600 mg + lamivudine 300 mg tablet, 30)	PBS	10345L	$923.99	Once daily	$12,012	Once daily	$12,012
Totals*					**$14,002**		**$13,521**
* Unit values are presented up to 2 decimal places. Total costs have been computed on these unit values, and rounded to the nearest whole number or to the nearest whole number of full pack size costs.							

Total PBS cost (year 2 onwards): $12,012

Total MBS cost (year 2 onwards): $1,509

Scenario 2 – HIV 2 infection

A 28 year old female refugee from Sudan who in applying for a subclass 200 refugee visa was found to be HIV seropositive (HIV-2). HIV-2 circulates in Africa (mainly Western Africa). HIV-2 does not respond to NNRTI class ARVs. She currently is asymptomatic and has a CD4+ T-cell count of 270 cells/mm^3 and a viral load of 50 000 copies/mL.

Clinical Opinion

The predicted risk of progression to AIDS in six months is 2-3% which is moderate. Once the patient commences receiving antiretroviral drugs, her probability of progressing to an AIDS defining illness or death would be around 5% in three years.

Based on current recommendations, initiation of ART would most commonly be with one of the following three regimens:

- Triumeq (dolutegravir + abacavir + lamivudine)/DTG+ABC+3TC
- Tivicay (dolutegravir) and Descovy (emtricitabine + tenofovir alafenamide)/DTG+TAF/FTC or TDF/FTC
- Genvoya (tenofovir alafenamide + emtricitabine + elvitegravir + cobicistat)/EVG+cobi+TAF+FTC

This regimen would be continued indefinitely unless intolerability or adverse effects lead to a switch to an alternative first-line regimen or virological failure leads to a change to a guideline-recommended second-line ART regimen.

If the patient continues to be adherent to ART, the viral load will remain suppressed. The increase in her CD4+ T-cell count is expected to be in the order of 50-100 cells/mm^3 after six months and thereafter should return to a level within the normal range. She would have a likelihood of between 85-90% probability of having a viral load <50 copies/mL after six months of ART, assuming adequate adherence to ART. Once the viraemia is suppressed, it should remain that way for the foreseeable future, again assuming adequate ART adherence.

Table 8: *Scenario 2: Prospective regimen/ service profile and costs involved*

Description	Item reference	Code	Unit cost	Year 1		Year 2 onwards	
				Frequency	Annual cost	Frequency	Annual cost
MEDICAL							
General-practitioner consultations	MBS	23	$37.60	3 monthly	$150	3 monthly	$150
Specialist review consultation	MBS	116	$76.65	6 monthly	$153	6 monthly	$153
subtotal					$304		$304
DIAGNOSTICS							
FBE Liver enzymes/renal Glucose/lipids	MBS	65070	$16.95	3 monthly	$68	3 monthly	$68

Description	Item reference	Code	Unit cost	Year 1		Year 2 onwards	
				Frequency	Annual cost	Frequency	Annual cost
CD4 T cell lymphocyte count	MBS	71139	$104.05	3 monthly	$416	3 monthly	$416
HIV viral load	MBS	69378	$180.25	3 monthly	$721	3 monthly	$721
Toxoplasma antibody	MBS	71121	$20.80	Once	$21	-	-
CMV antibody							
Mantoux test	MBS	73811	$11.20	Once	$11	-	-
Chest X-ray	MBS	58503	$47.15	Once	$47	-	-
subtotal					$1,284		$1,205
PHARMACEUTICAL AGENTS							
Triumeq (dolutegravir 50 mg + abacavir 600 mg + lamivudine 300 mg tablet, 30)	PBS	10345L	$923.99	Once daily	$12,012	Once daily	$12,012
TOTAL*				**$13,600**		**$13,521**	

* Unit values are presented up to 2 decimal places. Total costs have been computed on these unit values, and rounded to the nearest whole number or to the nearest whole number of full pack size costs.

Total PBS cost (year 2 onwards): $12,012

Total MBS cost (year 2 onwards): $1,509

Scenario 3 – HIV infection with first line drug resistance

A 45-year-old US citizen, who is the long-term partner of an Australian citizen resident in the United States, wishes to visit for business reasons. He currently is receiving treatment comprising tenofovir, lamivudine, zidovudine or lopinavir/ritonavir, and raltegravir as a 3rd agent (known as RED in Australia). He has a CD4+ T-cell count of 100 cells/mm^3 and a viral load of greater than 100 000 copies/mL. He has experienced recent hospitalisation for *Pneumocystis jiroecii* pneumonia but is now symptom-free. He tolerates Bactrim for prophylaxis of *Pneumocystis jiroecii* infection (PJP) (this medication would cease after virological control is achieved and maintained at CD4 > 200 for 6 months).

Clinical Opinion

The plasma viral load in this patient suggests either very poor adherence to ART and/or high-level resistance to the agents the patient has been prescribed. Strong consideration should be given to having an honest discussion about the medication adherence. He has had a previous AIDS-defining illness. His current CD4+ T-cell count is 100 cells/mm^3 and the HIV viral load is high. Consideration should also be given to changing the ART to a combination with the potential to fully suppress the patient's PVL and thereby raise the CD4+ T-cell count.

In order to optimise the ART regimen choice a genotypic antiretroviral resistance test should be requested, in addition to a genotypic test to assess the patient's viral co-receptor tropism (this latter test will provide information regarding the potential use of maraviroc, a CCR5 attachment inhibitor). Once these results are available the physician would construct a new ART regimen which should contain at least two - preferably three - fully active agents. Attention would need to be paid to the patient's past exposure to ARVs, a record (or recollection) that the patient had been intolerant or had virologically failed any of these. Once this had been established, to the best of the patient's and physician's ability the patient should commence the new optimised regimen.

Over the past few years a common 'salvage regimen' consisted of a combination of ritonavir-boosted darunavir 600/100mg q24h plus etravirine 200mg q12h (both of which maintain antiretroviral activity despite a degree of resistance to both those classes of ART), in addition to agents thought to offer ART activity from the resistance test. A balance must be found between an effective yet tolerable regimen in order to optimize the chance of patient adherence. In the setting of adequate adherence the patient would have an 80-90% chance of achieving full virological suppression within 20 weeks of initiation with a concomitant CD4+ T-cell count rise.

The patient would require prophylaxis with co-trimoxazole (Bactrim) 800/160mg q24h for PJP. He would not require prophylaxis against infections with Mycobacterium avium complex (Azithromycin) or cytomegalovirus (Ganciclovir).

The patient's CD4+ T-cell count may rise in response to the drop in viral load to a level where his risk of progression to AIDS would decrease, although the degree of CD4+ rise may be compromised by this low nadir and his relatively older age (both these variables are associated with a poorer CD4+ T-cell recovery). It is plausible that this response would be sustained in the presence of adequate adherence to ART.

Table 9: *Scenario 3: Prospective regimen/ service profile and costs involved*

Description	Item reference	Code	Unit cost	Year 1		Years 2-4	
				Frequency	Annual cost	Frequency	Cost over 3 years
MEDICAL							
General-practitioner consultations	MBS	23	$37.60	3 monthly	$150	3 monthly	$451
Specialist review consultation	MBS	116	$76.65	6 monthly	$153	6 monthly	$460
subtotal					$304		$911
DIAGNOSTICS							
FBE Liver enzymes/renal Glucose/lipids	MBS	65070	$16.95	3 monthly	$68	3 monthly	$203
CD4 T cell lymphocyte count	MBS	71139	$104.05	3 monthly	$416	3 monthly	$1,249
HIV viral load	MBS	69378	$180.25	3 monthly	$721	3 monthly	$2,163
Genotypic testing for HIV antiretroviral resistance (in a patient with confirmed HIV infection if the patient's viral load is greater than 1,000 copies per ml)	MBS	69380	$770.30	Maximum two tests within 12 months	$1,541	-	-
subtotal					$2,746		$3,615
PHARMACEUTICAL AGENTS							
etravirine 200 mg tablet, 60	PBS	10301E	$609.33	Two tablets a day	$7,921	Two tablets a day	$22,545

Description	Item reference	Code	Unit cost	Year 1		Years 2-4	
				Frequency	Annual cost	Frequency	Cost over 3 years
darunavir 600 mg tablet, 60	PBS	10329P	$920.29	Two tablets twice a day	$23,007	Two tablets twice a day	$67,181
raltegravir 400 mg tablet, 60	PBS	10286J	$655.92	One tablet twice a day	$8,527	-	-
ritonavir 100 mg tablet, 30	PBS	10273Q	$34.89	One tablet twice a day	$872	-	-
dolutegravir 50 mg tablet, 30	PBS	10283F	$689.20	-	-	Once daily	$25,500
tenofovir disoproxil fumarate 300 mg + emtricitabine 200 mg tablet, 30 (Truvada)	PBS	10347N	$232.80	-	-	Once daily	$8,613
trimethoprim 160 mg + sulfamethoxazole 800 mg tablet, 10 (Cotrimoxazole) (Prophylaxis for Pneumocystis Pneumonia)	PBS	2951H	$13.22	-	-	One tablet a day	$1,454
subtotal					$40,328		$125,294
Totals*				**$43,377**		**$129,820**	
TOTAL COST OVER 4 YEARS*				**$173,197**			
* Unit values are presented up to 2 decimal places. Total costs have been computed on these unit values, and rounded to the nearest whole number or to the nearest whole number of full pack size costs.							

Total PBS cost (year 1): $40,328

Total MBS cost (year 1): $3,050

Scenario 4 – HIV infection with HCV co-infection

A 44-year old man who was diagnosed with HIV infection in 1993, was later diagnosed with hepatitis C infection in 1999. The patient currently has a CD4+ T-cell count of 450 cells/mm^3. The hepatitis C antibody test is seropositive. Liver enzyme levels have been abnormal on recent and previous testing, with an alanine transaminase level of 70 U/L (normal, up to 30 U/L). There is no evidence of functional abnormality of synthesis, with albumin, prothrombin and INR in the normal range.

If the patient was prepared to commence treatment for hepatitis C infection, diagnostic tests to investigate the genotype, presence of cirrhosis and RNA load will be required. Assuming the infection is genotype 1, non-cirrhotic liver status and RNA load > 6 million IU/mL, a 12-week treatment regimen will include ledipasvir 90 mg orally and sofosbuvir 400 mg orally daily. In addition to the standard HIV care as in scenario 1, the additional costs are given in Table 10. Viral eradication is mostly likely to be achieved within 12 weeks, which needs to be confirmed 12 weeks after DAA therapy is completed (the so-called 'SVR12' [sustained virological response]).

Table 10: *Scenario 4: Additional costs over standard HIV care*

Description	Item reference	Code	Frequency	Unit cost	Once only cost (cure >90% likely)
MEDICAL					
Specialist consultations – initial treatment and management plan	MBS	132	Once	$267.85	$268
Follow-up consultations, specialist	MBS	116	monthly	$76.65	$920
Nurse support	MBS	10956	monthly	$62.25	$747
subtotal					$1,935
DIAGNOSTICS					
Hepatitis C virus antibody	MBS	69475	Once	$15.65	$16
Hepatitis C PCR	MBS	69445	Four times	$92.20	$369
Hepatitis C virus genotype	MBS	69491	Once	$204.80	$205
Liver enzyme levels, Full blood examination	MBS	66512	8	$17.70	$142
Liver ultrasound	MBS	55036	Once	$111.30	$111
Quantitation of HCV RNA load	MBS	69478	2	$29.25	$59
subtotal					$901
PHARMACEUTICAL AGENTS**					

Description	Item reference	Code	Frequency	Unit cost	Once only cost (cure >90% likely)
ledipasvir 90 mg + sofosbuvir 400 mg tablet, 28	PBS	10628J	Once daily for 12 weeks	$14,651.04	$43,953
TOTAL COST*					**$46,788**
* Unit values are presented up to 2 decimal places. Total costs have been computed on these unit values, and rounded to the nearest whole number or to the nearest whole number of full pack size costs. ** Refer to Scenario 1 for HIV treatment regimen costs					

Total PBS cost: $43,953

Total MBS cost: $2,836

Scenario 5 – Paediatric HIV infection

Nine-month-old boy from South East Asia, currently living in an orphanage, is being adopted by an Australian couple. The screening for blood borne virus revealed a positive HIV antibody test. No family or medical history is available.

Clinical Opinion

It is recommended that HIV virological testing be used to diagnose HIV infection in infants and children less than 18 months of age. Per the WHO algorithm for early infant diagnosis (Appendix B), it is advised that an HIV-exposed child receive testing with NAT. A positive NAT combined with the positive antibody result confirms this child is HIV infected.

For infants younger than three years who are not exposed to ARVs, or whose exposure to ARVs is unknown, ART should be initiated regardless of CD4 count or WHO clinical stage.

Costs will be similar to those given in scenario 1.

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