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CENTRE *for* EXCELLENCE
in HIV/AIDS

THERAPEUTIC GUIDELINES
MANAGEMENT
OF ACUTE HIV
INFECTIONS

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DISCLOSURES OF RELATIONSHIP WITH INDUSTRY AND OTHER ENTITIES IN THE PAST 2 YEARS

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I STRENGTH OF RECOMMENDATION TAXONOMY

(SORT) [RETRIEVED FROM BC CENTRE FOR EXCELLENCE IN HIV/AIDS PRIMARY CARE GUIDELINES (2015), TABLE 1, P. 7].

Assessment	Type of Evidence
Strength of Recommendation	
Grade A	Consistent, good quality patient-oriented evidence
Grade B	Inconsistent or limited quality patient-oriented evidence
Grade C	Consensus, disease-oriented evidence, usual practice, expert opinion, or case series for studies of diagnosis, treatment, prevention, or screening
Quality of evidence	
Level I	Evidence from at least 1 properly designed randomized, controlled trial
Level II	Evidence from at least 1 well designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

II EXECUTIVE SUMMARY

These guidelines were created by a group of experts at the BC Centre for Excellence in HIV/AIDS to provide evidence-based recommendations for the assessment, diagnosis and management of individuals newly diagnosed with acute HIV infection (symptomatic or non-symptomatic).

III SUMMARY OF RECOMMENDATIONS

1. A diagnosis of acute HIV infection (AHI) may be considered when individuals present with symptoms of AHI and an appropriate exposure history. A 4th generation HIV Ag/Ab test is preferred over point-of-care 3rd generation assays due to the shorter window period (**AII**). Moreover, given the possibility of a negative HIV Ag/Ab test in AHI, if acute HIV is clinically suspected and the individual belongs to a population with elevated risk for acute HIV infection (e.g. men who have sex with men or people who inject drugs) and reports high-risk unprotected sex or needle sharing in the previous month, pooled HIV nucleic acid testing (NAT) can reduce the window period for

HIV detection from about 18 days to 10 to 15 days. Pooled NAT can be arranged by contacting the medical microbiologist at the BC Centre for Disease Control (BCCDC) (604-661-7033) (**BI**).

- HIV-RNA plasma viral load used for therapeutic monitoring is not recommended for diagnostic testing.
2. Once a diagnosis of AHI is made based on positive HIV Ag/Ab and/or NAT test results, testing for plasma HIV-1 RNA levels, CD4 T lymphocyte counts, HLA-B*5701 status and baseline HIV genotype should be performed as recommended for patients with chronic HIV-1 infection (**AII**).
 3. All pregnant women with acute HIV-1 infection should start ART as soon as possible to prevent perinatal transmission of HIV-1
 4. Antiretroviral therapy (ART) is recommended for all individuals with HIV-1 infection, including those with acute or recent HIV-1 infection (**AI**). ART initiation should be offered immediately after diagnosis to people who are ready to start (**AII**).
 5. ART can be initiated before the drug resistance test (HIV genotype) result is available (**AII**).
 6. Because clinically significant transmitted resistance to protease inhibitors (PIs) is uncommon, a boosted PI (darunavir or atazanavir) and emtricitabine (FTC) plus tenofovir disoproxil fumarate (TDF) is recommended for initial treatment of AHI (**AIII**). An integrase inhibitor, preferably dolutegravir, can be added in order to induce rapid viral load suppression in individuals with symptomatic disease or at risk of onward transmission (**AIII**).
 7. Abacavir-containing ART is not recommended for empiric treatment of AHI. (**AI**).
 8. When results of drug resistance testing are available, the treatment regimen can be modified if warranted as per BC-CfE treatment guidelines (**AII**).

IV BACKGROUND

Acute HIV infection (AHI), also known as primary HIV infection, refers to the period within the first few days to weeks after HIV infection has occurred (1). Following initial binding and translocation at the mucosal surface (for sexual infection) the virus propagates by binding to local dendritic cells and CD4+ cells. HIV then disseminates initially to local lymph nodes over the course of 2-6 days and subsequently to gut-associated lymphoid tissues, with widespread dissemination thereafter. The initial dissemination period prior to detectable virus in plasma is known as the eclipse phase, followed by the viral expansion phase where the primary peak of viremia occurs (2), and finally by the viral containment phase as host immune responses attempt to control the virus (3, 4). Early initiation of antiretroviral therapy (ART) during AHI can be associated with improved markers of immune activation and inflammation within the gut (5-7), normalization of CD4:CD8 ratios (8, 9), decreased reservoir size and decreased HIV DNA burden (5, 10-13).

Detection of AHI depends on the use of assays that can detect evidence of early viremia or viral protein production (see below). In population-level studies, AHI has previously been found to make up only a small proportion (<1%) of overall diagnoses (14); however, in settings with a higher proportion of at-risk populations (e.g. sexual health clinics) or venues where individuals might present with symptoms (e.g. emergency rooms), a significant proportion (9-30%) of new HIV diagnoses have been found to be AHI (15-17). Approximately 26% of new diagnoses in British Columbia in 2016 were classified as stage 0 (AHI or having documented negative HIV test in prior 180 days).

Individuals with AHI have high levels of HIV viremia, and have been shown to contribute significantly to onward transmission (18). Mathematical models in high-endemic settings suggest AHI may contribute to approximately 40% of transmissions (19). Similarly, AHI in men who have sex with men (MSM) is associated with higher likelihood of transmission (adjusted odds ratio 8.9; 95% confidence interval 4.1 – 19.4) compared to later stage infection (20). In a study in Australia, 30% of MSM with acute seroconversion were found to have acquired infection from another individual with AHI (21). Early diagnosis can alter the risk of HIV transmission by leading to decreasing condomless sex acts and other behavioural strategies following HIV diagnosis, and by early initiation of ART (22-24).

V DIAGNOSTIC TESTING AND ASSESSMENT

Preferred Although clinical presentation of AHI is non-specific (25), classic symptoms include fever, malaise, myalgia, pharyngitis, rash and headache (26). Laboratory abnormalities including lymphopenia or thrombocytopenia may also be observed (26). Symptoms occur just prior to, and at peak viremia (27). Individuals presenting to health care facilities may often have atypical symptoms, predominantly gut-related, neurologic or respiratory in nature (28). Symptoms are common in those with AHI (>80% in some prospective cohorts) (27, 29); however, clinical suspicion for AHI may be low at time of first presentation (28).

Diagnosis of HIV in British Columbia consists of initial screening with a 4th generation enzyme immunoassay (EIA), followed by confirmatory immunoblot. Fourth-generation assays detect both HIV p24 antigen (Ag) and IgM and IgG antibodies (Ab) to HIV, and reduce the window period for detecting HIV infection to approximately two to three weeks; these assays have 99.9% accuracy by 42 days after infection

(30) when compared to third generation assays which only detect anti-HIV Ab. Samples which demonstrate weakly reactive 4th generation EIA signals are automatically tested for HIV RNA to assess if the EIA reactivity is due to acute HIV or the result of a false positive screening test. Pooled nucleic acid testing (NAT) for HIV can further reduce the window period to 10-15 days after infection and is able to detect pre-seroconversion HIV infections (31) (see Table 1). This test can be arranged by contacting the medical microbiologist at the BC Centre for Disease Control (BC CDC) (604-661-7033).

Use of these assays can allow delineation of the stage of AHI using criteria developed by Fiebig et al (33) (Table 2). Individuals with very early infection with only detection of HIV RNA are classified as Fiebig Stage I, while those with chronic infection would be Fiebig Stage VI.

VI TREATMENT RECOMMENDATIONS

Clinical trial data regarding the treatment of early HIV-1 infection are limited. However, a number of studies suggest that individuals who are treated during early infection may experience immunologic and virologic benefits (34-35).

Several studies have shown that ART during AHI significantly restricts the HIV reservoir size as compared with later treatment (36-38). Early ART may also reduce the contribution of the long-lived central memory CD4+ T cells to the total HIV reservoir, in humans and primates (39, 40). In addition, since early HIV-1 infection is often associated with high plasma HIV-1 RNA levels and thus increased transmissibility (41), and ART use by individuals is known to reduce HIV transmission to uninfected sexual partners (42), treatment during early HIV-1 infection is expected to substantially reduce the risk of onward HIV-1 transmission.

In patients with a diagnosis of AHI, standard baseline testing for plasma HIV-1 RNA levels, CD4 cell counts, HLA-B*5701 status, HIV genotype, and hematologic, hepatic, and renal assessment should be ordered prior to starting treatment (Table 3). However, ART should not be delayed pending the results of these tests.

Data from BC show a rate of overall transmitted drug resistance (TDR) of 17%, with non-nucleoside reverse transcriptase inhibitor (NNRTI) TDR of 11%, while clinically significant PI resistance was uncommon (43). Recent studies reported a prevalence of 5% integrase strand transfer inhibitor (INSTI)-resistant polymorphic virus in primary HIV infection (44, 45) with the E157Q polymorphism having an overall prevalence of 2.7% (44, 45). There have been case reports of virologic failure to raltegravir and elvitegravir when the E157Q mutation was present (45). Therefore, dolutegravir is preferred if an INSTI is to be used in the AHI setting. Before initiating ART in a person with early HIV-1 infection, a specimen for genotypic antiretroviral (ARV) drug resistance testing should be obtained and should include resistance testing for INSTIs; however, treatment initiation should not be delayed pending resistance testing results. Once the resistance test results are available, the treatment regimen can be modified if warranted as per BC-CfE treatment guidelines.

As in chronic infection, the goal of therapy during early HIV-1 infection is to suppress plasma HIV-1 RNA to undetectable levels. ART should be initiated with one of the combination regimens recommended for patients with chronic infection (46). If available, the results of ARV drug resistance testing or the ARV resistance pattern of the source person's virus should be used to guide selection of the ARV regimen. There are limited data on the best ART regimen to institute in AHI. Few studies evaluated the benefits of using standard three- drug therapy vs four- or five-drug therapy in AHI. In a small Thai study, patients receiving Mega-HAART (tenofovir DF/emtricitabine/efavirenz/raltegravir/maraviroc) achieved immune restoration and reduced reservoir size by 24 weeks of therapy (47).

Since therapy for early HIV infection should be started before the results of drug resistance testing are available, the following regimen is recommended:

- A pharmacologically boosted protease inhibitor (PI)-based regimen with ritonavir or cobicistat e.g., atazanavir/ritonavir (300mg/r 100mg) or darunavir/ritonavir (800mg/r 100mg or darunavir/cobicistat fixed dose combination) once daily

Plus

- An INSTI (preferably dolutegravir 50 mg once daily) should also be included in order to induce rapid viral load suppression in those with symptomatic presentation or risk for onward transmission.

Plus

- Emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg once daily

Given the increasing use of tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) as pre-exposure prophylaxis (PrEP) in HIV-negative individuals (48-50), early infection may be diagnosed in some patients while they are taking TDF/FTC for PrEP. In this setting, resistance testing should be performed; however, as described above, use of a pharmacologically boosted PI (e.g., boosted atazanavir or darunavir) and emtricitabine plus tenofovir disoproxil fumarate and dolutegravir remain reasonable treatment options pending resistance testing results.

Abacavir is not recommended for empiric treatment of acute infection unless the patient is known to be HLA-B* 5701 negative, information that is seldom available when patients with acute infection present for care.

VII RAPID INITIATION OF ART

Initiation of ART as soon as possible following diagnosis is recommended for all stages of HIV infection (51, 52), including AHI. The offer of rapid initiation, including same-day ART has been evaluated in the RAPID program in San Francisco where individuals with acute/recent infection or advanced HIV were offered same day initiation (53). Overall 94% of eligible participants began ART within 24 hours of diagnosis, and achieved faster viral load suppression (1.8 vs. 4.3 months) than those referred for a regular clinic visit (median time to ART prescription 22 days). Similarly, in San Diego amongst 86 individuals with newly

diagnosed HIV, 26% initiated ART at first clinic visit, and 79% of those achieved viral load suppression at week 12 vs. 59% (p-value 0.06) for those starting in a delayed fashion (54). Finally, a meta-analysis of clinical trials evaluating rapid ART following HIV diagnosis found that same-day ART was associated with better retention in care at 12 months (relative risk 1.11; 95% CI 0.99 – 1.26) and increased viral load suppression at 12 months (relative risk 1.17; 95% CI 1.07 – 1.27) vs. standard of care initiation.

Because early HIV-1 infection, especially in the setting of high level viremia, is associated with a high risk of perinatal transmission, all pregnant women with HIV-1 infection should start ART as soon as possible to prevent perinatal transmission of HIV-1 (55). In BC pregnant women with acute HIV infection should be urgently referred to Oak Tree Clinic (604-875-2212; [Oak Tree Clinic Website](#)).

As with chronic infection, patients with early HIV-1 infection must be willing and able to commit to treatment. If treatment during early infection is deferred, patients should be maintained in care and every effort should be made to initiate therapy as soon as they are ready.

VIII LABORATORY TESTING FOR INITIAL ASSESSMENT AND FOLLOW-UP MONITORING

Table 3 outlines the laboratory tests to be performed at initial assessment and subsequent follow-up. At initial assessment, the following screening tests should be ordered: HIV-RNA plasma viral load, CD4 cell count, HIV genotype, HLAB*5701 test, hematological, liver, renal and metabolic profile, as well as Hepatitis A, B and C serology and STI screening. We recommend repeating the plasma HIV-1 RNA testing after 2-4 weeks of therapy. The remainder of the safety laboratory tests and plasma HIV-RNA testing should be performed every 4 weeks until viral suppression, and thereafter, every 3 to 4 months as per standard of care monitoring. Counselling for safer sex and/or injection practises should occur at baseline, and as appropriate during follow-up.

IX DURATION OF THERAPY FOR ACUTE HIV-1 INFECTION

Once ART is initiated in patients with AHI, therapy should be continued indefinitely as in guidelines for patients with chronic infection. A large randomized controlled trial of patients with chronic HIV-1 infection found that treatment interruption was harmful in terms of increased risk of AIDS and non-AIDS events (56), and that the strategy was associated with increased markers of inflammation, immune activation, and coagulation (57). For these reasons and the potential benefit of ART in reducing the risk of HIV-1 transmission, indefinite continuation of ART is recommended in patients treated for acute or early HIV-1 infection.

Once patients have achieved and sustained undetectable plasma HIV-RNA levels, treatment simplification can be considered, by decreasing the number of active drugs (to a minimum of three) based on the baseline genotype results.

TABLE 1. HIV DIAGNOSTIC ASSAYS AND WINDOW PERIODS (32)

Diagnostic Test	Target Detected	Window Period	Comments
3rd generation assay	HIV IgG, IgM antibodies	22 (19, 25) days	
3rd generation point-of-care assay	HIV IgG, IgM antibodies	32 (28, 38) days	Optional, additional test for initial screening where available
4th generation assay	HIV IgG, IgM antibodies; HIV p24 antigen	18 (16, 24) days	Repeat test in 7-14 days may help identify acute HIV infection if pooled HIV RNA test unavailable.
HIV pooled NAT	HIV RNA (qualitative)	7-10 days	Use pooled or individual HIV RNA for the evaluation of suspected acute HIV infection, when available

TABLE 2. FIEBIG CLASSIFICATION OF ACUTE HIV INFECTION (33)

Stage	Marker						Duration in days (95% CI) ^a	
	RNA	P24 Antigen	Antibody (EIA)		Western blot	Individual	Cumulative	
			NS	S				
I	+	-	-	-	-	5.0 (3.1, 8.1)	5.0 (3.1, 8.1)	
II	+	+	-	-	-	5.3 (3.7, 7.7)	10.3 (7.1, 13.5)	
III	+	+	-	+	-	3.2 (2.1, 4.8)	13.5 (10.0, 17.0)	
IV	+	+/-	-	+	I	5.6 (3.8, 8.1)	19.1 (15.3, 22.9)	
V	+	+/-	+/-	+	+ ^b	69.5 (39.7, 121.7)	88.6 (47.4, 129.8)	
VI	+	+/-	+	+	+	Open-ended	Open-ended	

^aCalculations are based on a parametric Markov model.

^bWithout p31 band.

CI, Confidence interval; I, indeterminate; NS, not sensitive, refers to second-generation not IgM-sensitive enzyme immunoassay (EIA); S, sensitive, refers to IgM-sensitive third-generation EIA.

TABLE 3. LABORATORY TESTING FOR INITIAL ASSESSMENT AND MONITORING

Test	Initial Assessment	At 4 weeks after ART initiation	Q3 months	Q6 months
CD4 cell count	✓	✓	✓	
HIV-RNA (plasma viral load)	✓	At 2-4 weeks*	✓	
Genotype (resistance testing)	✓			
HLA-B*5701	✓			
Hep Bs Ag, Hep Bs Ab, Hep Bc Ab	✓			
Hep C Ab	✓			✓
Pregnancy test (if indicated)	✓			
STI screening	✓		✓ (if ongoing risk)	
Syphilis serology	✓		✓	
CBC and differential	✓	✓	✓	
Creatinine and eGFR	✓	✓	✓	
AST/ALT/ T Bilirubin	✓	✓	✓	
Urine ACR	✓			✓
Fasting lipid profile or apolipoprotein B	✓			✓ (if abnormal at baseline)
Fasting glucose or Hb A1C	✓			✓

Abbreviations. ART: Antiretroviral Therapy; Hep Bs Ag: Hepatitis B surface antigen; Hep Bs Ab: Hepatitis B surface antibody; Hep Bc Ab: Hepatitis B core antibody; Hep C Ab: Hepatitis C antibody; STI: sexually transmitted infection; AST: Aspartate transaminase; ALT: Alanine transaminase; ACR: Albumin to creatinine ratio; Hb A1C: hemoglobin A1C

*HIV-RNA viral load can be repeated monthly until it becomes undetectable (<40c/mL).

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