

ASSESSMENT AND TREATMENT OF PSYCHOSIS IN PEOPLE LIVING WITH HIV/AIDS

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The pathophysiology of psychosis and other forms of severe mental illness in HIV infection is complex, and multifactorial causation is likely in most instances. Severe mental illness has been identified as a risk factor for the acquisition of HIV infection and occurs as both a manifestation of opportunistic infections and a result of the neurotropic effects of the virus.¹ A full psychiatric assessment in people living with HIV/AIDS (PLWHA) presenting with psychosis is important but may prove difficult in many parts of South Africa. This paper presents a variety of algorithms to simplify the assessment and management of an HIV-infected patient with psychosis.

APPROACH TO PLWHA AND PSYCHOSIS (FIG. 1)

A comprehensive history from the patient and/or caregiver is needed. There should be special focus on the history of the current complaint, past psychiatric history, past and present substance abuse history, full medical history and sexual risk history and the patient's adherence to previous treatment regimens. Of equal importance is identification of social support systems.

A mental status examination will need to be conducted. In the psychotic patient one needs to focus specifically on the behaviour and appearance of the patient. His or her speech and speed of thoughts should be assessed, and mood symptoms, affect, suicidality and neuro-vegetative symptoms evaluated. Perceptual disturbances, thought form, thought content and finally insight and judgement also need to be assessed.

A comprehensive and meticulous physical and neurological examination should be performed to exclude any organic causes for the presenting psychiatric symptoms. A useful hierarchical approach has been suggested by Ambrosino *et al.*² One should first examine for signs of delirium and rule out HIV-associated cognitive disorders. Medical diagnoses should first be considered and only after that should a psychiatric diagnosis be entertained. The differential diagnosis needs to consider the course of the HIV infection, the presence of a pre-existing psychiatric illness, use of illicit substances and the presence of cognitive impairment.³

PSYCHOTIC DISORDERS IN PLWHA (FIG. 1)

A useful delineation may be to divide psychosis in the PLWHA into: (i) psychiatric disorders predating HIV infection; (ii) new-onset psychotic disorders; and (iii) disorders associated with medical conditions (delirium) or substance intoxication or withdrawal, and those that are likely to be complications of treatment (i.e. antiretrovirals or antituberculosis drugs).⁴

PSYCHOTIC DISORDERS PREDATING HIV INFECTION

Major psychiatric disorders presenting with psychosis and predating HIV infection include schizophrenia, bipolar mood disorder and major depressive disorder with psychotic features. These disorders present with significant impairment of functioning and follow a chronic course.⁵ Substance abuse may predispose and/or precipitate a substance-induced psychotic disorder. There are a multitude of substances that may cause psychotic symptoms or psychotic disorders, and a clear collateral history is vital.

NEW-ONSET PSYCHOTIC DISORDERS

New-onset psychosis in the HIV-infected patient is the development of psychotic symptoms (delusions, hallucinations, disorganised behaviour, negative symptoms or altered form of thought), either acutely or subacutely, in the absence of concurrent substance abuse, opportunistic infections, space-occupying lesions, cognitive impairment or various medications. It is hypothesised that this is caused by subcortical neurodegeneration and the direct neurotropic effects of HIV on the central nervous system (CNS), or is a manifestation of

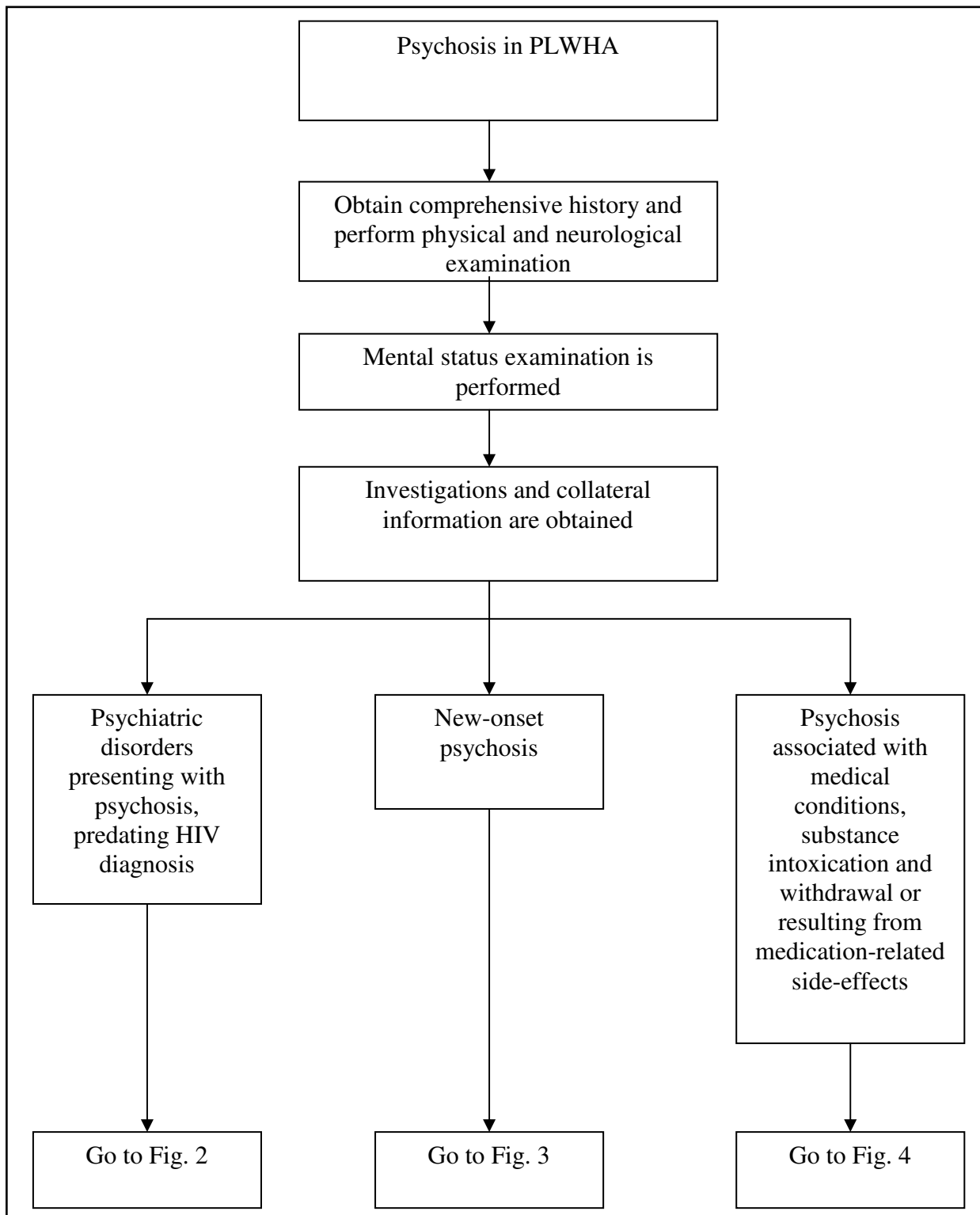


Fig. 1. Approach to the assessment of psychosis in PLWHA.

HIV-associated encephalopathy in the absence of severe HIV-associated dementia. Some suggest that it is due to an increase in intracellular free calcium.⁶ Rates of new-onset psychosis in HIV-positive patients have been reported to range from 0.5% to 15%.⁷

Psychotic symptoms may also occur in the presence of major HIV-related mood disorders. In a Ugandan study in which HIV-negative patients with primary mania and patients with HIV-related secondary mania were compared, the patients with secondary mania were more irritable, aggressive and disruptive and had a higher rate

of psychotic symptoms than those with primary mania.⁸ Finally, new-onset psychotic symptoms may also occur in the presence of HIV related-cognitive disorders.⁹

PSYCHOSIS ASSOCIATED WITH MEDICAL CONDITIONS, SUBSTANCE INTOXICATION, SUBSTANCE WITHDRAWAL OR AS A COMPLICATION OF MEDICATION

Delirium

Delirium often has multifactorial causation and manifests with an acute presentation of disturbance in consciousness, change in cognition and development

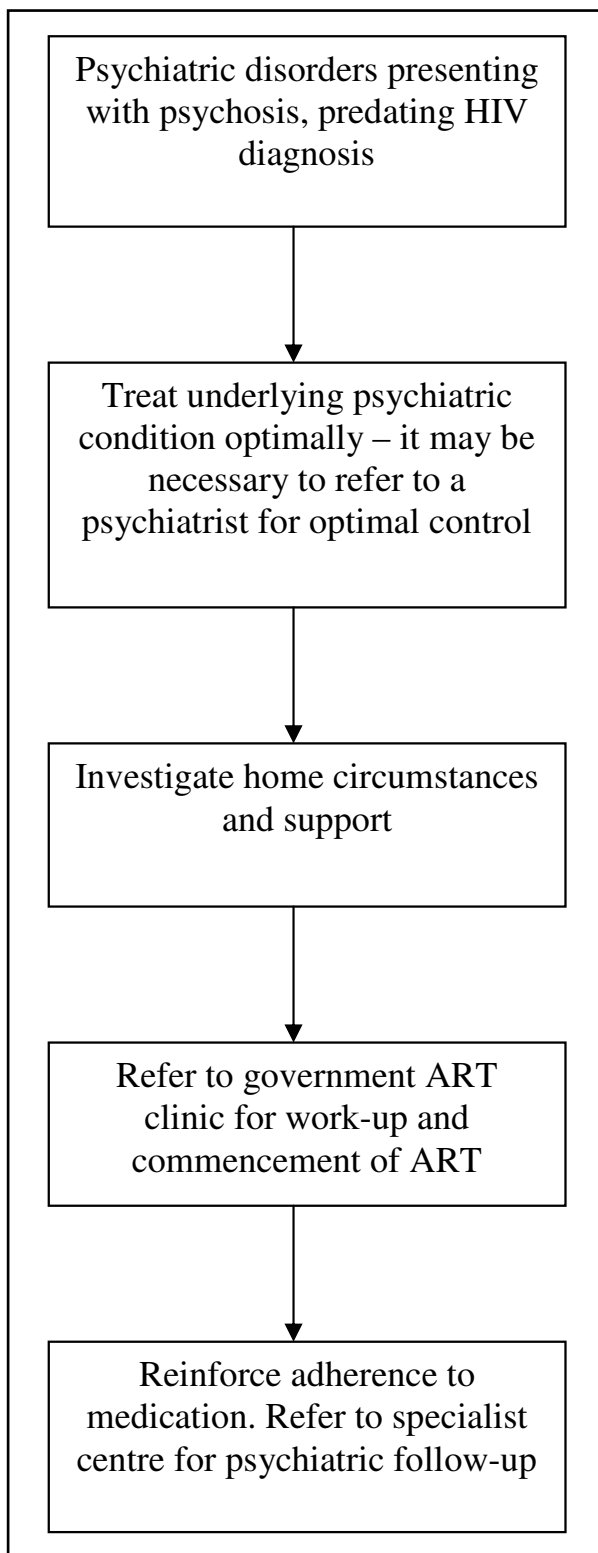


Fig. 2. Psychotic disorders predating HIV infection.

of perceptual disturbances, with a fluctuating course.¹⁰ It may be due to the presence of CNS opportunistic infections, metabolic disorders, neuropsychiatric side-effects of various drugs, or substance intoxication or withdrawal. Studies from before the era of highly active antiretroviral therapy (HAART) reported a prevalence of delirium of 12 - 29% among individuals with AIDS.¹¹ The diagnosis of delirium depends on accurate diagnosis of the underlying cause. A comprehensive physical examination, diagnostic work-up (biochemical and microbiological parameters, cerebrospinal fluid ex-

amination) and brain imaging (computed tomography) are needed to help make the diagnosis. Hospitalised patients with HIV should be assessed early and frequently for delirium, and treatment for the underlying cause should be initiated as soon as possible.

Substance intoxication or withdrawal

Substance intoxication and withdrawal are reversible substance-specific syndromes and may present with a delirium-type picture. HIV-infected individuals have a high prevalence of substance abuse, with lifetime rates as high as 50%.¹² HIV-positive drug abusers are reported to have higher rates of both HIV-associated dementia and HIV encephalopathy than HIV-infected people who do not abuse drugs.¹³ Drug abuse may increase the risk of developing delirium. Furthermore, it may not only affect disease progression but also be associated with reduced adherence to antiretroviral therapy (ART) and is therefore a very important co-morbidity to consider in the patient with 'triple diagnosis' disorders, i.e. psychiatric disorders, HIV infection and substance abuse disorders.¹⁴

Psychosis as a complication of medical treatment

Some medications used to treat HIV or the medical complications of HIV/AIDS may cause psychiatric disorders presenting with psychotic symptoms. Efavirenz has been associated with a wide range of neuropsychiatric side-effects. Psychotic symptoms associated with the commencement of efavirenz therapy are reported to occur early on and may necessitate its discontinuation.¹⁵

Other medications commonly used in HIV medicine that can be associated with mental state changes and psychotic symptoms include corticosteroids; other antiviral agents, e.g. ganciclovir; antifungal agents, e.g. amphotericin B; and some antibacterials, e.g. anti-tuberculosis drugs, dapsone and sulphadiazines.^{4,16}

These 'psychotoxic' reactions, which may manifest as psychosis, mania or delirium, have been associated with the commencement of treatment with isoniazid, ethionamide, ethambutol and some of the fluoroquinolones. A study in Peru found that severe psychiatric syndromes associated with isoniazid occurred in approximately 10% of patients with tuberculosis between 1991 and 1999.¹⁷ A careful history is therefore necessary to determine the temporal relationship between the development of psychotic symptoms and commencement of the drug, as this has very important implications in terms of management.

TREATMENT OF HIV-ASSOCIATED PSYCHOSIS

When a patient presents with psychotic symptoms in the presence of HIV infection it is essential to exclude life-threatening medical causes of the psychotic symptoms. This may be extremely difficult in the agitated,

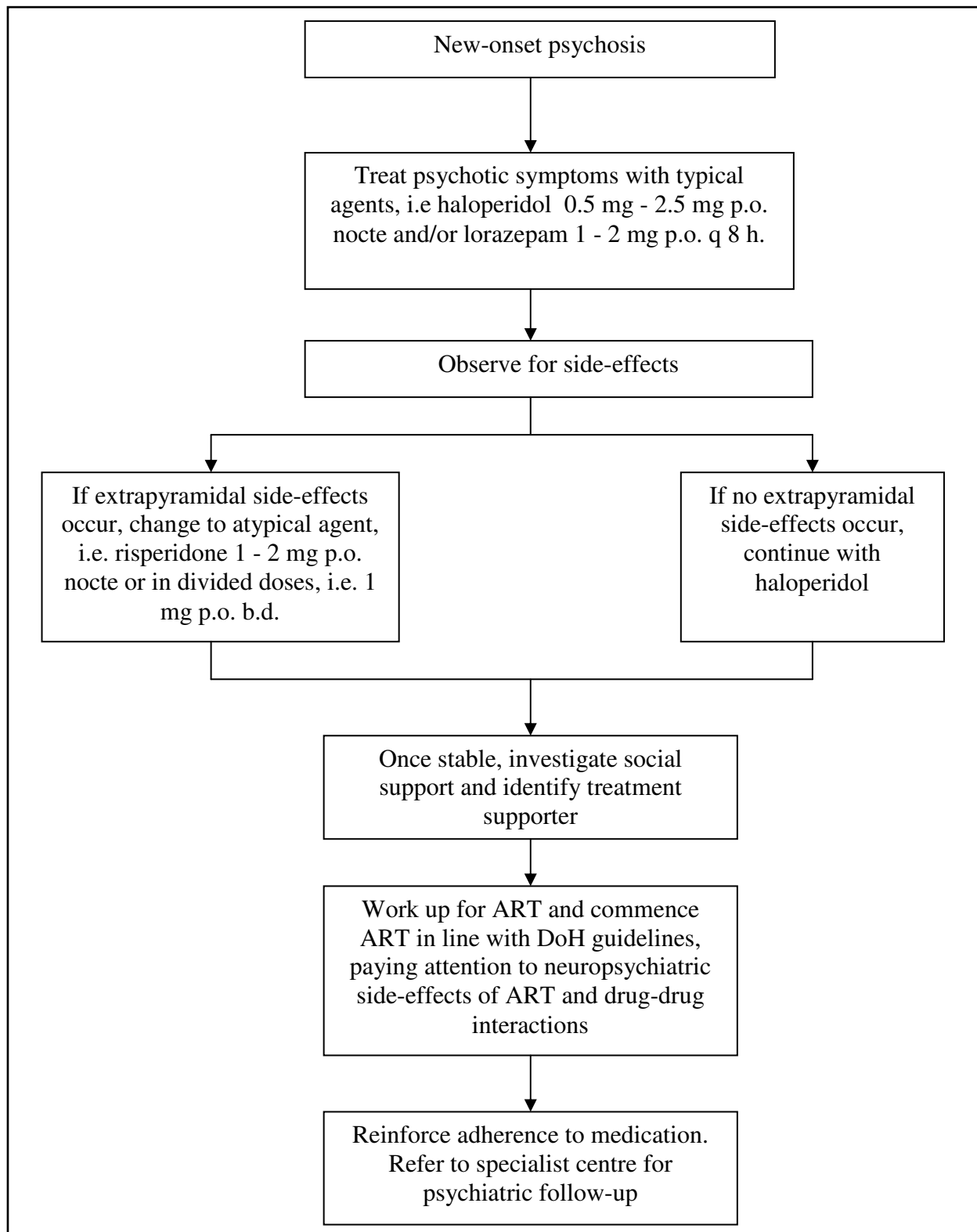


Fig. 3. New-onset psychosis.

disorganised or violent patient, and antipsychotic medications may need to be instituted before a thorough work-up is completed. Antipsychotic medications are safe and effective in the presence of HIV disease, but treatment modifications may be necessary and conservative dosing strategies may need to be implemented. Antipsychotic medication should always be used at the lowest possible dose for the shortest possible duration.

The choice of antipsychotic drugs depends largely on the patient, presenting symptoms, past response, potential side-effect profile, possible drug interactions, cost, and pill burden of the chronically ill patient. Many patients with new-onset psychosis or psychosis associated with various medical conditions may only require short-term treatment with antipsychotic medication. However, some patients may require long-term maintenance treatment with antipsychotic agents, and here special attention must be paid to the follow-

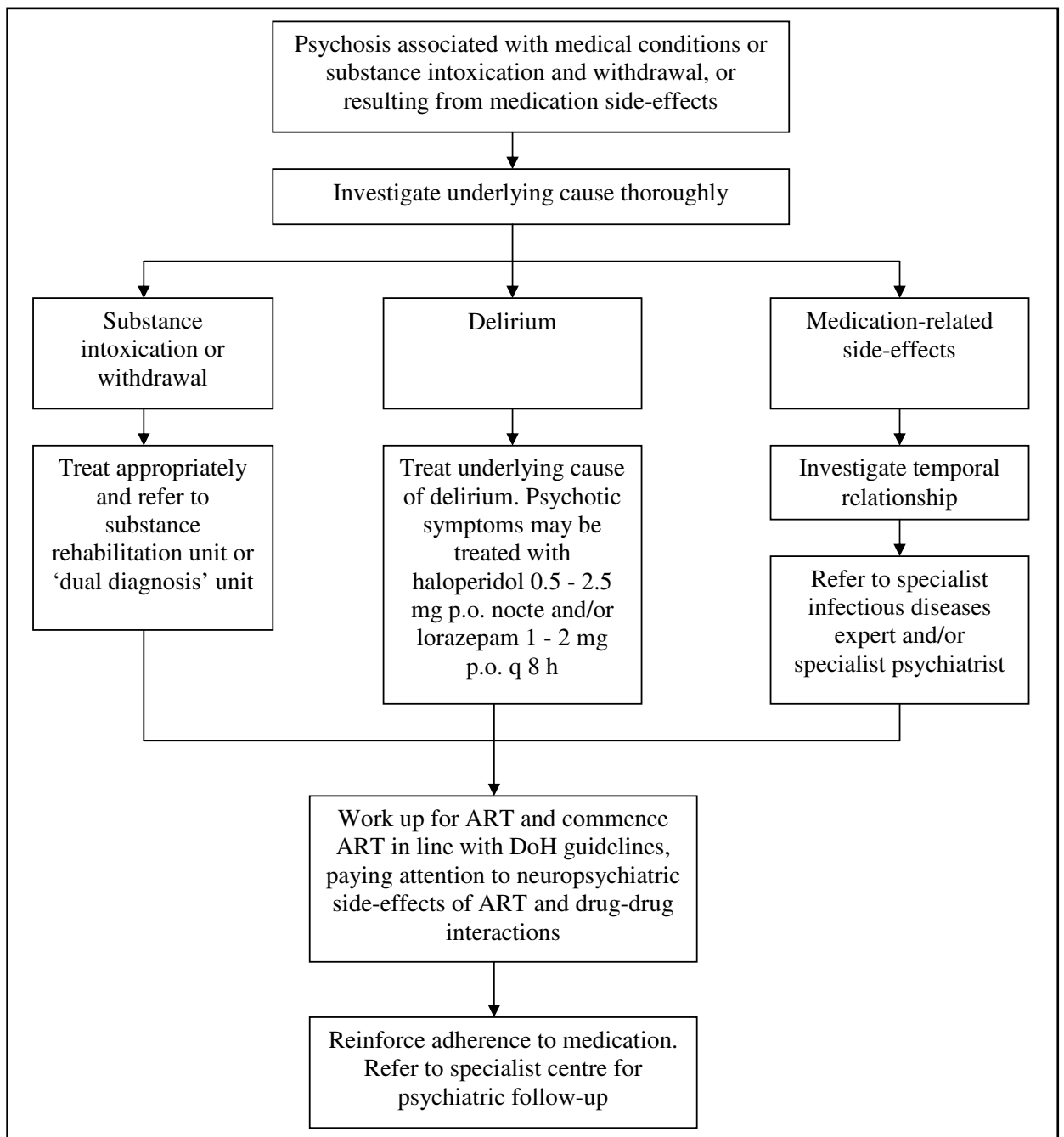


Fig. 4. Psychosis associated with medical conditions or substance intoxication/withdrawal, or resulting from medication-related side-effects.

ing factors. The typical antipsychotics are commonly used in resource-constrained settings. Here low doses of haloperidol (0.5 - 2.5 mg) and chlorpromazine (25 - 50 mg) have proven effective and safe. Vigilance is required with regard to extrapyramidal side-effects with haloperidol and anticholinergic side-effects with chlorpromazine.

Among the atypical antipsychotics, risperidone (1 - 4 mg/d) is commonly used, if available. This may be used in patients who present with or pose a risk of developing extra-pyramidal side-effects. The atypical antipsychotics are generally better tolerated than the typical antipsychotics, but they are associated with longer-term metabolic side-effects and the potential development of drug-drug interactions. Development of the metabolic syndrome, weight gain, abnormal li-

pid profiles and diabetes mellitus are well described with some of the atypical antipsychotics (olanzapine and clozapine). The lipodystrophy syndrome described in HIV-positive patients on ART predisposes these patients to the development of diabetes mellitus and coronary artery disease. The atypical antipsychotics with a propensity to develop metabolic syndrome and certain ART regimens (protease inhibitors (PIs) and the nucleoside reverse transcriptase inhibitors (NRTIs) in particular), taken together, may have serious long-term adverse effects.^{18,19}

Many psychotropic medications and ART (especially the PIs and NNRTIs) share the same cytochrome P450 (CYP) iso-enzymes for metabolism, and competition between the two is prominent.^{18,19} Interactions resulting in a decreased plasma concentration-time curve

for olanzapine may be clinically important.²⁰ For other important interactions, see the article in this issue on psychotropic prescribing.

It may be necessary to make use of benzodiazepines in the agitated, aggressive patient when antipsychotics alone do not provide sufficient containment. The use of benzodiazepines with few or no active metabolites is crucial. Lorazepam in small divided doses may be necessary, i.e. 1 – 2 mg orally every 8 hours. Caution is needed when using lorazepam in the patient with delirium, as one study found it to be ineffective and associated with significant adverse effects.²¹ However, this agent may be the only drug available in certain resource-limited settings, and benefit versus risk will need to be ascertained for each individual patient.

Psycho-education is imperative throughout all stages of treatment. Psychosocial interventions and regular follow-up with the multidisciplinary team (psychiatrist, psychiatric nurse, social worker, occupational therapist and psychologist) are important. Adherence should consistently be reinforced and improved. Referral to an occupational therapist who uses various activity groups, support groups and food garden/nutrition security groups to help improve adherence may be considered. Supportive therapy is vitally important as the patient recovers. Temporary placement in an appropriate facility may be necessary for patients who are difficult to treat and those who require longer in-patient care.

Ongoing viral replication in the brain is a risk factor for neuropsychiatric disorders, and in combination with degree of immunodeficiency and other factors that lower the threshold for developing psychosis (family history, substance abuse) these constitute a stress-within-a-stress diathesis model. It is often not realistic to start ART in a psychotic patient without antipsychotics as adherence is likely to be poor, but once the patient has reached a state of relative stability ART should be started as soon as possible to decrease the contribution of HIV replication in the brain. In patients with psychosis related to immunosuppression and brain dysfunction, treatment with antipsychotics and ART simultaneously may be necessary from the time of initial presentation. It is vitally important that the patient be monitored closely, either as an inpatient if difficult to contain, or very closely by caregivers to ensure intensive adherence. Adherence counselling at all stages of recovery is imperative to ensure understanding of the need for ART and adherence to prevent possible resistance.

It is difficult to recommend a time frame with regard to duration of antipsychotic medication, as there is a relative paucity of literature. A possible option is to wean the patient slowly off antipsychotics after psy-

chotic symptoms have remitted for 6 months, then take a watch-and-wait approach. This must only be done if good follow-up is possible so that antipsychotic medication can be reintroduced the moment symptoms recur.

In order to simplify the management of psychosis in the HIV-positive patient, three algorithms are presented. Fig. 2 describes the management of psychotic disorders pre-dating HIV infection, Fig. 3 details the treatment and referral procedure for new-onset psychosis, and Fig. 4 describes the process for the assessment, management and referral of psychosis associated with medical conditions, substance intoxication/withdrawal and symptoms resulting from medication-related side-effects.

COMMENCEMENT AND CHOICE OF ARV DRUGS FOLLOWING COMPREHENSIVE WORK-UP AND REMISSION OF PSYCHOTIC SYMPTOMS

Commencement of ART may be initiated in accordance with the Department of Health guidelines.²² Department of Health first-line regimens are used, but special attention needs to be paid to co-existing antituberculosis treatment, liver toxicity, drug-drug interactions and possible neuropsychiatric side-effects of various ARTs. Ideally commencement of ART in the patient with psychosis should be instituted in a multidisciplinary setting. Adherence is an important concern in preparing patients for lifelong ART, but it is also crucial not to exclude patients with serious mental illness from receiving ART because they may 'possibly' be non-adherent. Involvement of a treatment supporter is essential to assist with adherence, with the patient's consent or assent. Intensive pretreatment education and adherence counselling of the patient and treatment partner are vital in order to assess treatment appropriateness and commitment to long-term neuropsychiatric follow-up.

CONCLUSION

It is imperative to exclude an underlying medical cause for psychotic symptoms in the HIV-infected patient, and a careful differential diagnosis needs to be established based on the criteria set out above. Psychotic symptoms respond well to antipsychotic medication, but medication side-effects and drug-drug interactions must be vigilantly watched out for. It is important to remember that patients with mental illness are at an increased risk of being infected with HIV and of transmitting the virus. Prevention strategies, testing and referral of patients with mental illness and HIV/AIDS is vital. The algorithmic approach offered here serves to simplify and unite the assessment and treatment of psychosis in the HIV-positive patient at all levels of health care.

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