

Impact of depression on HIV outcomes in the HAART era

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Highly active antiretroviral therapy (HAART) has significantly decreased the morbidity and mortality of persons infected with HIV. The extent of the benefits, however, is not uniform, and certain factors including ethnicity, gender, baseline HIV viral load and CD4+ T lymphocyte count, adherence and intravenous drug abuse are associated with different immunological, virological and clinical outcomes. Mental health illness (MHI) and specifically depression may be associated with worse outcomes, although studies exploring the impact of MHI on HIV outcomes in both the pre-HAART and post-HAART eras have shown mixed results. The objective of the current paper is to review the available literature on the impact of MHI on HIV outcomes in the HAART era.

Keywords: AIDS, mental health, psychiatric

Introduction

Highly active antiretroviral therapy (HAART) has greatly improved the morbidity and mortality associated with HIV infection.^{1,2} The success rate of HAART, which appears to be increasing over time, varies depending on the population studied.^{1,3} Many factors have been identified that influence HAART success rates including ethnicity,^{4–6} gender,^{7,8} baseline HIV viral load,^{9–11} baseline CD4+ T lymphocyte count,^{9,11,12} adherence^{13–16} and intravenous drug abuse.⁸ The presence of a mental health illness (MHI) may also impact HIV disease progression and response to HAART.^{4,5}

Before the availability of HAART, studies reported mixed findings on whether MHI affected HIV disease progression. Some studies demonstrated faster progression to an AIDS-defining illness or death in HIV-infected persons with MHI,^{17–21} whereas others found no effect of MHI on these outcomes.^{22–24} Likewise, some^{22,25} but not all^{23,24,26,27} demonstrated a faster decline in CD4+ T lymphocytes in HIV-infected persons with depression. There have also been studies describing a more profound decline in natural killer (NK) cells in depressed persons compared with those without depression.^{25,28} The use of different mental health screening tools, different durations of follow-up and measurement of MHI at different time points relative to HIV seroconversion make it difficult to compare the above-referenced studies.

There are only a limited number of studies that have examined the impact of MHI on response to HAART. Some of these

studies have evaluated whether MHI affects HIV disease progression in the HAART era (usually defined as after 1996), but do not limit their analyses to only those receiving HAART, making interpretation of the results more complex. The purpose of the current paper is to review the impact of MHI on response to HAART and identify areas where research is required.

Covering all mental illnesses is beyond the scope of this paper, and the following discussion will focus mainly on the effects of depression, one of the most prevalent MHIs in HIV-infected persons. Substance abuse, which can clearly affect outcomes, is often present in those with MHI and HIV and has recently been reviewed.²⁹ In addition, MHI affects patients with HIV in both developed and developing countries. Addressing these issues in developing nations is of paramount importance to the successful treatment and prevention of HIV in these nations. A recent, well-written review covers this subject in detail.³⁰

Epidemiology of MHI in HIV-infected persons

The prevalence of MHI in HIV-infected persons is not well defined and is based mainly on small cohorts. Rates vary based on whether they are lifetime prevalence rates or rates of active psychiatric disorders. Most studies have not used strict diagnostic criteria [Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)], but have relied on physician reporting or structured screening surveys.^{31,32} Prevalence

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rates based on the DSM-IV diagnostic criteria may be lower than those based on screening instruments.³¹ In addition, not all manuscripts break down MHI into specific diagnoses, but rather classify patients based on symptoms.

Estimates of depression in HIV-infected persons vary widely ranging from <5% up to 48% depending on the population studied.^{29,33,34} A meta-analysis that analysed 10 studies prior to the advent of HAART estimated that HIV-infected persons were twice as likely to be diagnosed with major depression compared with HIV-uninfected persons.³⁵ The rates of MHI did not differ based on the stage of HIV infection in that study. Rates of dysthymia were similar between HIV-infected and non-infected persons.

Several studies conducted after the availability of HAART have also demonstrated higher rates of depression among those with HIV infection when compared with non-infected controls.^{31,36–38} Data from the Veterans Aging Cohort 5-Site Study demonstrated that HIV-infected veterans had higher rates of depression and substance abuse when compared with HIV-uninfected persons.³⁶ Importantly, this study showed that these rates increased with age in HIV-infected patients. Few studies have examined the impact of MHI, ageing and HIV, but with the growing number of older adults living with HIV infection, these studies are required.^{39,40}

Pence *et al.*³¹ estimated the rates of mood, anxiety and substance abuse disorders in a large HIV clinic ($n = 1125$ patients) in the southeastern USA in the post-HAART era. They reported that 39% [95% confidence interval (CI): 37–41] of the patients had a mood or anxiety diagnosis (based on DSM-IV criteria). An estimated 29% (CI: 27–31) of patients had clinically relevant depression, and overall mood disorders were four times more common in this population compared with the general population.

Some studies in the post-HAART era suggest an association between HAART and decreased rates of depression.^{37,38} Starace *et al.*³⁸ reported that in a cohort of 395 patients, those taking HAART were less likely to have depressive symptoms than those not taking HAART (14% versus 24%, $P = 0.05$). Out of a 90 patient cohort in Milan (with 54% of the patients on at least three antiretrovirals), Alciati *et al.*³⁷ found that only 4.4% of the patients had a mood disorder.

Unlike depression, where there is clear evidence that rates are higher in HIV-infected persons, data are conflicting as to whether rates of anxiety or adjustment disorders are higher in those with HIV infection. The rates of anxiety disorders in HIV-infected persons range from 4% to 19% and are similar or potentially lower than general population rates.^{31,32,41} The rates for adjustment disorders tend to be similar to those reported for anxiety disorders.³²

Effect of depression on response to HAART

Table 1 describes studies that have evaluated the impact of depression on the immunological, virological or clinical response to HAART. Most studies examining the impact of depression on HAART outcomes were not originally designed to test that effect and had small sample sizes. In addition, the studies used different methods to diagnose depression, including standardized screening instruments, physician reporting or patient self-reporting. Several of the earlier studies failed to

control for adherence, which may be decreased in patients suffering from depression.⁴² As a result, combining the findings from these studies is difficult.

Immunological outcomes

Studies conducted after the availability of HAART have shown conflicting results regarding the immunological changes associated with HAART in persons with HIV and depression.^{43–46} Ickovics *et al.*⁴³ evaluated 765 HIV-infected women from the HIV Epidemiological Research Study (HERS) and found that chronic depressive symptoms [Center for Epidemiologic Studies Depression Scale (CES-D) score >15 at 75% of visits] were associated with greater declines in CD4 counts. In that cohort, however, only half of the subjects were on HAART, and the results were not adjusted for adherence. Ironson *et al.*⁴⁷ also reported that depression was associated with faster declines in CD4 counts among a cohort of 177 patients from Florida (57% on HAART), even after controlling for adherence. In contrast, a large study of 961 women initiating HAART in the Women's Interagency HIV study (WIHS) did not find depression to be associated with immunological response (defined as CD4+ lymphocyte counts >100 cells more than nadir CD4 count); however, it was significantly associated with increased likelihood of immunological failure (defined as CD4+ lymphocyte counts below pre-HAART nadir level after immunological response) even after controlling for adherence (relative hazard 1.98).⁶

A more recent study showed no relationship between depression (Hamilton Depression Rating Scale higher than 20) and CD4 and CD8 count and percentage and CD4/8 ratio.⁴⁵ This study did demonstrate that HAART incompletely restored NK cells in depressed patients compared with those without depression. However, the study was small, only including 13 depressed HIV patients on HAART compared with 36 non-depressed patients on HAART. Previous studies showed similar results.^{28,48} The effect of depression on NK cells may partially explain why depression may be associated with worse outcomes; however, these results are still preliminary and need to be confirmed.

Virological outcomes

The majority of the studies that have evaluated the effect of MHI on virological response to HAART have found an association between MHI and decreased virological response (Table 1). In several studies, this association persisted after adjusting for adherence. A small study from infectious disease clinics in France ($n = 71$) reported that depression (7 item hospital anxiety and depression scale) was significantly associated with virological failure after controlling for adherence in patients taking non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens [adjusted hazard ratio (AHR) 2.5, CI: 1–6.4].⁴⁹ The WIHS study by Anastos *et al.*⁶ reported a decreased virological response among those with a CES-D score >15 (AHR 0.81, $P < 0.05$). The same study, however, showed no difference in virological rebound. In a cohort of 129 military beneficiaries, those patients without a mental health disorder ($n = 100$) were almost nine times more likely to reach viral

Table 1. Impact of MHI on HIV outcomes in the HAART era

Reference, study type	Population	Depression tool	Follow-up	Outcomes
Paterson <i>et al.</i> , ¹⁵ prospective cohort	81 patients (91% male) two Veteran's Affairs HIV Clinics depression in 21% illegal drugs (marijuana and cocaine) 7% all patients taking protease inhibitor	BDI score >14	6 months (median)	depression was associated with virological failure in the univariate analysis (RR 1.4, CI: 1–2.1); no significant interaction in the MVA (ARR 1.3, CI: 0.7–2.7); increased BDI scores associated with decreased adherence ($P = 0.05$)
Ickovics <i>et al.</i> , ⁴³ prospective cohort	765 HIV-positive women HIV Epidemiological Research Study chronic depression in 42% IVDA 15% 49% of patients on HAART (38% >1 year)	chronic depression defined as CES-D score >15 at 75% of visits	7 years	women with chronic depression were two times more likely (RR 2.0, CI: 1–3.8) to die than those with limited or no depressive symptoms; chronic depressive symptoms were associated with greater declines in CD4 counts; no adjustment for adherence
Kilbourne <i>et al.</i> , ⁵⁵ prospective cohort	881 patients (99% male) Veterans Aging Cohort 3 Site Study severe depression in 23% IVDA not reported 54% of the patients on at least three antiretrovirals (specific HAART use not reported)	severe depression defined as CES-D score >14	12 months	no association between depression and mortality in the adjusted model; increasing depression severity was associated with increasing HIV symptoms ($P < 0.001$)
Cook <i>et al.</i> , ⁴⁴ prospective cohort	1716 HIV-positive women Women's Interagency HIV Study chronic depression in 32% illicit drug use 39% 49% used HAART for >1 year	chronic depression defined as CES-D score >15 at 75% of visits	7.5 years	chronic depressive symptoms were associated with increased risk (ARR 1.7, CI: 1.1–2.7) of AIDS-related death; recent depressive symptoms were less likely among those taking HAART for >1 year; use of mental health services resulted in decreased risk of death (ARR 0.5, CI: 0.3–0.7); results were adjusted for adherence
Himelhoch <i>et al.</i> , ⁵⁶ retrospective review	315 patients (70% male) Johns Hopkins University HIV Clinic depression in 27% IVDA 38% time to HAART initiation was part of the study outcome	baseline reporting of diagnosis, use of psychotropic medications or diagnostic interview by psychiatrist	6 months	patients with psychiatric disorder were 37% more likely to receive HAART (AHR 1.4, CI: 1.01–1.9) and 40% more likely to survive (AHR 0.6, CI: 0.4–0.99); after adjusting for HAART use, the effect was no longer significant (AHR 0.9, CI: 0.5–1.5)
Parienti <i>et al.</i> , ⁴⁹ prospective cohort	71 patients (79% male) two ID clinics in France depression in 27% IVDA 17% 100% patients on NNRTI-based regimen	7-item hospital anxiety and depression scale	29 months (median)	patients with depression were more likely (AHR 2.5, CI: 1.0–6.4) to have virological failure after controlling for adherence
Anastos <i>et al.</i> , ⁶ prospective cohort	961 HIV-1-infected women Women's Interagency HIV Study depression in 51% IVDA 33% participants initiating HAART	CES-D score >15 at the time of visit that outcomes were measured	5.1 years (median)	depression was significantly associated with decreased virological response (AHR 0.8), increased risk of immunological failure (AHR 2.0), AIDS-defining incident (AHR 1.6) and a higher risk of all-cause (AHR 1.7) but not AIDS-related mortality (AHR 1.1) and virological rebound (AHR 1.2)
	887 patients (79% male)	single question in survey	15 months	

Barfod <i>et al.</i> , ⁹⁰ prospective cohort	ID clinics in Denmark and Copenhagen depression 47% IVDA 4%			patient reported feelings of being depressed or overwhelmed were associated with virological failure (AOR 2.1, CI: 1.2–3.7)
Bouhnik <i>et al.</i> , ⁴⁶ prospective cohort	all patients taking HAART 243 patients (72% male) French cohort of HIV-positive drug users (MANIF 2000) probable depression in 46% IVDA 17%	CES-D score >15	at least 12 months (up to 60)	depressive symptoms were associated with clinical progression (CD4 <200 or AIDS-related event) (AHR 5.3, CI: 2.4–32.1)
Ironson <i>et al.</i> , ⁴⁷ prospective cohort	all patients initiating HAART 177 patients (70% male) Florida patients recruited through physician offices, hospitals and service organizations depression not reported as distinct rate excluded patients with active IVDA or drug dependence 57% patients on HAART	BDI	24 months	patients with high baseline depression scores (>75th percentile) had three times increased risk of higher viral load even after controlling for adherence; depression was associated with CD4 decline
Mijch <i>et al.</i> , ⁵² retrospective and prospective cohort	2981 patients Melbourne, Australia MHD 17.6% (included substance abuse, schizophrenia and personality disorders; 54% with unknown disorder) IVDA unavailable (substance abuse 16%) HAART in 31% of patients with MHD and 26% patients without MHD	ICD-9 codes	minimum 3 months	hospitalizations for psychiatric and non-psychiatric disorders were more common among those with MHD (AOR 5.4, CI: 3.7–8.2); survival was not affected by MHD; no adherence data
Hartzell <i>et al.</i> , ⁵ retrospective review of prospective cohort	129 patients (82% male) Walter Reed Army Medical Center reported depression in 22% no IVDA participants initiating HAART	physician reporting and chart review	24 months	patients without a mental health diagnosis were more likely to reach virological suppression (AOR 8.7, CI: 2.4–32.1); no control for adherence
Lima <i>et al.</i> , ⁶⁰ prospective cohort	563 participants (91% male) British Columbia Center for Excellence in HIV/AIDS depression in 51% IVDA in 28% participants initiating HAART	CES-D score >15 at the time of visit that outcomes were measured	4 years (median)	the presence of depressive symptoms among non-adherent patients was associated with increased mortality in patients starting HAART (AHR 5.9, CI: 2.6–13.7); there was no association when the analysis was restricted to only adherent patients (AHR 1.4, CI: 0.6–3.1)
Mugavero <i>et al.</i> , ⁵³ prospective cohort	489 patients (69% male) coping with HIV/AIDS in the southeast cohort (CHASE) BSI (0.3 median) illicit drug use (other than marijuana) 11% reported majority of patients on HAART	BSI	30 months (median)	increased HIV-related events (opportunistic infection or AIDS-related mortality) in patients with depressive symptoms in the bivariate analysis (HR 1.4, CI: 1.1–1.9); no significant impact in the MVA (AHR 1.1, CI: 0.9–1.5); a history of psychosocial trauma was associated with increased HIV-related events in the MVA (AHR 2, CI: 1.0–3.8); the analysis included adherence and HAART usage

Continued

Table 1. Continued

Reference, study type	Population	Depression tool	Follow-up	Outcomes
Pence <i>et al.</i> , ⁵⁰ prospective cohort	198 patients (65% male) University of North Carolina Hospitals Infectious Disease Clinic chart reported depression/anxiety 28% substance abuse (not alcohol) 23% participants initiating HAART	substance abuse and mental illness symptoms screener and chart documented	30 months (median)	predicted psychiatric disorder associated with slower rate of viral suppression (AHR 0.9, CI: 0.8–0.98 per 5% increment) and faster virological failure (AHR 1.2, CI: 1.1– 1.4); predicted depression associated with slower virological suppression (AHR 0.8, CI:0.6–0.98) and trend towards virological failure (HR 1.2, CI: 0.97–1.4); adherence data not included
Pence <i>et al.</i> , ⁴ prospective cohort	611 patients CHASE cohort depression (BSI score 58) addiction severity index score 1.6 194 patients on HAART included for virological failure analysis	BSI	36 months	increasing depressive symptoms were not associated with ART discontinuation (AOR 1.2, CI: 0.8–1.8) or virological failure (AOR 1, CI: 0.7–1.3); adherence not explicitly measured or reported
Leserman <i>et al.</i> , ⁵⁴ prospective cohort	611 patients (490 included for analysis) 69% male CHASE cohort depression 34% above 90th percentile for depressive symptoms 80% of patients receiving antiretroviral therapy at baseline	BSI	2.2 years (median)	lifetime trauma was associated with increased all-cause mortality (AHR 1.2, CI: 1.02–1.3) and AIDS-related mortality (AHR 1.2, CI: 1.03–1.5); depressive symptoms were associated with AIDS-related mortality (AHR 1.49, CI: 1–2.2) but not all-cause mortality (AHR 1.2, CI: 0.9–1.6); no control for adherence
Horberg <i>et al.</i> , ⁵¹ retrospective cohort	3359 patients (83% male) patients from eight states enrolled in Kaiser Permanente and Group Health Cooperative depression 42% all initiating new HAART regimen	coded outpatient or inpatient diagnosis of depression	12 months	depression was associated with lower odds of HIV RNA levels <500 copies/mL (AOR 0.8, CI: 0.6–0.95); depression was associated with decreased odds of achieving >90% adherence (AOR 0.81, CI: 0.7–0.98); depressed patients adherent to SSRIs had HAART adherence and virological outcomes similar to non-depressed patients; CD4 counts were similar between depressed and non-depressed patients, although those taking SSRIs had significantly increased CD4 counts

IVDA, intravenous drug abuse; ID, infectious disease; BDI, Beck Depression Inventory; CES-D, Center for Epidemiological Studies Depression Scale; BSI, Brief Symptoms Inventory; MVA, multivariate analysis; RR, relative risk; ARR, adjusted relative risk; OR, odds ratio; AOR, adjusted odds ratio; HR, hazard ratio; AHR, adjusted hazard ratio; MHD, mental health disorder; CI, 95% confidence interval.

suppression compared with those with a mental health diagnosis [adjusted odds ratio (AOR) 8.7, CI: 2.4–32].⁵ The study's strengths included equal access to care, including psychiatric care, and medications for all beneficiaries; however, it was limited by lack of information on adherence and small sample size. A study of 198 HAART-naïve patients initiating HAART in North Carolina⁵⁰ used a previously validated model to predict psychiatric illness. Patients with a predicted psychiatric disorder were slower to reach viral suppression (AHR 0.86 per 25% increment, CI: 0.75–0.98) and had a faster time to virological failure (AHR 1.2, CI: 1.06–1.4). These results were similar for predicted depression (AHR 0.79, CI: 0.63–0.98). The authors suggested that the difference may have been attributable to adherence, but it was not reported in the study, preventing firmer conclusions. Lastly, a recent study of 3359 HIV-infected patients initiating HAART from Kaiser Permanente and Group Health Cooperative found that depression was associated with lower odds of achieving an HIV viral load <50 copies/mL (AOR 0.8, CI: 0.6–0.95), and the difference persisted after controlling for adherence.⁵¹ An association between depression and decreased odds of >90% adherence to HAART was also seen.

In contrast to the above-mentioned studies, there have been a few studies that did not find an association between depression and decreased virological response to HAART. In a study in the southeastern USA of 194 patients on HAART with a viral load below detection at enrolment, increasing depressive symptoms [Brief Symptoms Inventory (BSI) score] were not associated with either antiretroviral discontinuation or virological failure.⁴ The fact that this study selected for patients who already achieved an undetectable viral load may explain why the findings are discordant with the studies mentioned earlier. A study of 81 veterans taking protease inhibitors found that a Beck Depression Inventory (BDI) score of >14 was not associated with virological failure in the multivariate analysis; however, the sample size of this study is small.¹⁵

Clinical outcomes

There have been several studies examining the effects of MHI on clinical response to HAART, with the majority demonstrating that depression leads to worse clinical outcomes.^{6,44,52} Patients with depression initiating HAART in the WIHS cohort had increased AIDS-related mortality (AHR 1.7) and increased rate of incident AIDS-defining illness (AHR 1.6).⁶ There was no difference in all-cause mortality. An earlier study from the WIHS cohort reported on 1716 HIV-infected women, of whom ~50% were on HAART.⁴⁴ Depressive symptoms, defined by a CES-D score >15 at 75% of the visits, were associated with increased risk [adjusted relative risk (ARR) 1.7, CI: 1.1–2.7] of AIDS-related death. Importantly, they found that depressive symptoms decreased among those taking HAART for >1 year, and the use of mental health services decreased the risk of death (ARR 0.5, CI: 0.3–0.7). In the HERS cohort, women with depressive symptoms were two times more likely (relative risk 2.0, CI: 1–3.8) to die than those with limited or no depressive symptoms.⁴³ In this study, however, only 49% of the patients were taking HAART, and there was no adjustment for medication adherence.

A recent study of 489 patients from the southeast USA (CHASE cohort) demonstrated that increasing scores on the BSI

were associated with increased HIV-related events (opportunistic infection or AIDS-related mortality) in the bivariate analysis (hazard ratio 1.4, CI: 1.1–1.9), but not in the multivariate analysis (AHR 1.1, CI: 0.9–1.5).⁵³ A history of psychosocial trauma was associated with increased HIV-related events in the multivariate analysis (AHR 2, CI: 1.0–3.8). The authors suggest that the lack of effect of depression seen in the multivariate analysis was secondary to co-linearity with psychosocial trauma. This study did control for adherence.

A similar study from the CHASE cohort looked specifically at the effects of lifetime trauma and depressive symptoms on mortality. Lifetime trauma (murder of close family member, death of a child, spouse or partner or other trauma judged by the author to be similar to those mentioned earlier) was associated with both all-cause mortality and AIDS-related mortality. Depressive symptoms were only associated with AIDS-related mortality. The study, however, only had a small number of deaths and did not control for medication adherence.⁵⁴

In contrast to the aforementioned studies, a large study of 881 patients from three Veterans' Medical Centers did not find an association between depression and worse clinical outcomes in response to antiretroviral therapy.⁵⁵ The study reported no association between depression and mortality in the adjusted model. Increasing severity of depression, however, was associated with increasing HIV symptoms ($P < 0.001$). This study was conducted early in the HAART era with only 54% of the patients taking at least three antiretroviral agents and did not report actual HAART usage. This fact may explain the conflicting results with the previous studies.

A retrospective cohort study from the Johns Hopkins HIV Clinic reviewed clinical outcomes of 549 persons with AIDS.⁵⁶ In this study, persons with psychiatric disorders (determined by patient reporting, use of psychiatric medicine or psychiatrist diagnosis) were 40% (AHR 0.6, CI: 0.37–0.99) more likely to survive than those without a psychiatric disorder. The effects, however, were largely a result of increased HAART usage among patients with psychiatric disorders. The study is encouraging because it suggests that patients with HIV/AIDS and mental health diagnoses can have favourable outcomes when treated.

Impact of MHI on treatment with HAART

The treatment of HIV infection in persons with depression or other MHI is complicated by many factors including real or perceived difficulties in medication adherence, lack of access to the healthcare system, potential side effects of antiretroviral medications and potential drug–drug interactions between antiretroviral and psychotropic medications. All of these factors can influence the HAART-associated outcomes in HIV-infected patients with MHI.

Strict adherence is crucial in obtaining favourable responses to HAART.^{13–16,57} Having an MHI may make following a daily routine more difficult and therefore complicate one's ability to adhere to a medicine regimen.^{15,42,58,59} However, several studies have found significantly worse outcomes in depressed compared with non-depressed persons even after adjusting for adherence, suggesting that the variable adherence is not the sole cause of differences in outcomes.^{44,46,47,49} Conversely, a recently published study of 563 antiretroviral-naïve persons evaluating the

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association of depression and adherence with mortality found that when the analysis was limited to only adherent subjects, depression was no longer significantly associated with mortality. The authors noted that depression and non-adherence may have multiplicative effects on mortality, but only non-adherence was independently associated with the outcome.⁶⁰

Depression and other MHIs are also associated with high-risk sexual behaviour and substance abuse.^{29,58,61,62} In individuals with HIV infection, both may increase the risk of superinfection with multiple strains of HIV, including drug-resistant ones, and may increase the number of other sexually transmitted diseases. Co-infection with herpes simplex virus-2 may increase HIV replication, and both ulcerative and non-ulcerative STDs may increase HIV transmission to others.^{63–69} Those with substance abuse problems often have financial difficulties and may not be able to access the healthcare system. The use of urgent care clinics over continuity clinics complicates management of chronic diseases such as HIV infection.⁷⁰

Having a diagnosis of depression or other MHIs may also affect the timing of HAART initiation. A survey of HIV providers revealed that 69% of the providers associate depression with poor adherence. The providers also stated that they would be hesitant to initiate HAART if they judged the patients likely to be non-adherent.⁷¹ Although several studies have shown that providers are more likely to delay HAART initiation in persons with MHI,^{72–74} a study of 435 patients from the southeastern USA did not find a significant difference in HAART receipt, according to current depressive symptoms, current drug use or lifetime trauma exposure.⁴ In this study, psychosocial characteristics were measured at the time of study enrolment, not at HAART initiation, and the authors note that the cohort may reflect a survivor's bias. Another study of 549 antiretroviral-naïve HIV-infected patients from an urban setting found that those with a psychiatric disorder were 37% more likely to receive HAART, compared with those without a psychiatric disorder (AHR 1.37, 95% CI: 1.01–1.87).⁵⁶ Furthermore, those with a diagnosis of MHI who were on psychotropic medications at baseline were as likely to receive HAART as those with MHI who were not on psychotropic medications at baseline. The authors postulated that the higher rate of HAART receipt in those with MHI may have been due to the availability of on-site psychiatric care, which may have allowed HIV providers to feel more comfortable prescribing antiretroviral therapy.

If HAART is initiated, the antiretroviral agents chosen by providers may be different in those with depression or other MHIs. Providers may be less likely to use efavirenz, a first-line NNRTI, in individuals with depression due to its neuropsychiatric effects. Controversy exists as to whether individuals with a history of MHI are more predisposed to developing such side effects.^{75–78} Providers may also be concerned about potential drug–drug interactions between the antiretroviral and psychotropic medications, both of which may be metabolized by the cytochrome p450 system.⁷⁹ The clinical significance of these interactions needs further study.

Effects of treatment of MHI on response to HAART

Both pharmacological treatments and cognitive therapies are effective in the treatment of psychiatric disorders in HIV-infected patients, and treatment of depression may also lead

to increased HAART utilization.⁸⁰ Both the treatment strategies and their outcomes have recently been reviewed.^{81–83} Importantly, there are studies that show antiretroviral adherence can be improved by treating depression.⁸⁴ A large study recently published by Horberg *et al.*⁵¹ discussed briefly above (under virological outcomes) demonstrated that patients whose depression was treated with a selective serotonin reuptake inhibitor (SSRI) had both HAART adherence and virological outcomes similar to their non-depressed counterparts. Interestingly, depressed patients taking an SSRI also had significantly greater rises in CD4 counts when compared with depressed patients not taking SSRIs. A retrospective analysis of 1713 patients (57% with depression) from an urban healthcare system found that adherence to antiretroviral therapy was greater in those with depression who were adherent to antidepressant treatment than in those with depression not prescribed or not adherent to antidepressant treatment.⁸⁵

There are also studies that support the effectiveness of HAART in improving mental health symptoms among HIV-positive patients.^{86–89} The reasons for this effect are unknown and may be multifactorial, but it provides a strong argument for treating depressed patients with HAART when they would otherwise require treatment for their HIV. From the available data, successful outcomes are most likely to occur when HIV-infected patients suffering from MHI (specifically depression) are treated with both HAART and antidepressants.

Conclusions

MHI and particularly depression appear to be more frequent in those infected with HIV. The available data suggest that depression leads to worse outcomes in HIV-infected persons. These effects appear not to be solely due to differences in adherence, although studies on this remain mixed. Research is required in several areas of MHI including its incidence in those taking HAART, the mechanisms of its effects on HIV clinical outcomes in the HAART era and the effects of its treatment on HIV clinical outcomes. All future studies exploring predictors of HAART response rates should include psychiatric disorders as a potential variable. In addition, future studies should use previously validated test instruments and DSM-IV criteria when possible to allow for comparability between studies. Effective treatment for depression in HIV-positive patients exists and is fundamental in improving outcomes.

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