Expanding access to HIV antiretroviral therapy among marginalized populations in the developed world

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Introduction

Since its introduction in the mid-1990s, the benefits of antiretroviral therapy for the management of HIV disease have been well established [1,2]. New antiretroviral regimens have proved to be effective in decreasing HIV plasma viral load, improving CD4 cell counts, and have substantially altered the natural history of HIV infection [3,4]. As a result, substantial improvements in HIV-related morbidity and mortality have been documented among persons receiving appropriate antiretroviral regimens, and in many areas of the world, HIV infection is increasingly being viewed as a chronic and manageable illness [5,6].

Nevertheless, the clinical management of HIV disease continues to present major challenges. Treatment of HIV disease with the regimens that are presently available aims to prevent progression to AIDS or death by reducing plasma HIV RNA to as low a level as possible for as long as possible [7,8]. The eradication of HIV from the individual is not considered possible with presently available therapeutic agents. As such, persons undergoing treatment for HIV disease must take a daily regimen of at least three antiretroviral drugs (i.e., highly active antiretroviral therapy, or HAART), and follow a scheduled dosing protocol that often involves coordination of dietary intake [9]. To date, a great deal of effort has been expended in evaluating patient, physician, and

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healthcare delivery-related factors that may limit or enhance daily adherence to antiretroviral therapy [10–15].

A related challenge, which is the focus of this review, involves the lesser-studied problem of access to antiretroviral therapy. While issues surrounding access to antiretroviral therapy are most pressing in the developing world, where HIV treatment remains prohibitively expensive [16], emerging data suggest that high levels of ongoing HIV/AIDS mortality persist in the developed world, in a large part due to limited use of HAART [17]. Although a proportion of these deaths are probably due to sub-optimal adherence to daily antiretroviral therapy and inability to tolerate the side effects of HAART [18], there is growing evidence that a high proportion of the ongoing AIDS mortality in the developed world is due to poor access to therapy among disadvantaged or marginalized populations.

Limited access to HAART may be of particular concern for specific populations, and may involve treatment discontinuation and/or intermittent use of antiretrovirals, as well as premature mortality among those who never accessed HIV treatment prior to AIDS diagnosis or death. There is evidence that both of these concerns are common in developed world settings, even in countries where HIV/AIDS patients are eligible for antiretroviral therapy and medical care free of charge [19,20]. The following review will outline the evidence that suggests that limited retention in treatment and poor access to antiretroviral therapy are contributing to ongoing AIDS mortality in developed world settings. In addition, we will review the research to date on barriers to access and retention in HIV treatment, as well as strategies that may improve access to antiretrovirals among at-risk populations.

Populations at risk of poor access to HAART

There is growing evidence that emerging disparities in HIV-related mortality are due to problems with access to antiretrovirals and retention in treatment among specific sub-populations. These populations include groups that have traditionally been at risk of inferior access to health care such as persons of lower socio-economic status, ethnic minorities, and injection drug users (IDU) [21–23]. Limited access may stem from issues ranging from physician reluctance to prescribe HAART based on presumed inability to adhere to therapy, to cultural barriers that may result in individuals refusing HAART when it is offered. As will be discussed below, among persons with HIV infection, female gender has also been consistently associated with poorer access to antiretroviral therapy.

The role of socio-economic status in HIV disease progression has been the focus of much study since it was first found to be an independent predictor of HIV disease progression prior to the advent of HAART [24,25]. This finding was consistent with what has been observed for many other diseases [26], and subsequent studies suggested that differences may be due to poor access to HIV/AIDS care among lower income patients [27,28]. A recent Canadian study has demonstrated substantially elevated mortality after the initiation of antiretroviral therapy among lower income HIV-infected patients, due to the more common use of sub-optimal dual therapy in lower income individuals [29]. In this study, the prescription of sub-optimal dual therapy persisted after adjustment for baseline clinical characteristics including plasma HIV RNA and CD4 cell count. Since provision of antiretroviral therapy is free in this setting, prescription of dual therapy to lower income individuals must be attributed to non-financial concerns, such as physician unwillingness to prescribe protease inhibitors to patients perceived to be non-adherent. Other studies have similarly demonstrated that persons of lower socio-economic status are less likely to be prescribed antiretroviral therapies [30,31], and these implications have been well described [32].

Ethnic minorities and females have also been shown to have poorer access to antiretroviral therapy. These concerns were first reported prior to the advent of HAART. In one US study, it was demonstrated that AIDS mortality and opportunistic infections were elevated among African American patients, and that the differences were attributable to more advanced HIV disease at presentation for zidovudine therapy and less frequent use of PCP prophylaxis among this population [28]. A subsequent study, demonstrated that African Americans were significantly less likely to have been prescribed antiretroviral therapy or PCP prophylaxis at the time of being referred to an HIV clinic [33]. With regard to gender, another US study demonstrated that 58% of women delayed entry into specialized HIV care for ≥ 3 months following an HIV diagnosis, and that upon entry 65% were symptomatic and 40% were severely immunocompromised [34].

These ethnic and gender disparities have persisted since the introduction and widespread use of HAART. For instance, a large representative sample of HIV-infected adults from across the US demonstrated that, while problems with access to HIV care have diminished over time, as late as 1998 fewer African Americans and women had started taking antiretroviral medication after adjustment for CD4 cell count [35]. Similarly, another sample of that cohort looked carefully at inhibitors and facilitators of access and found that women, African Americans, and the

least educated were less likely to access HAART [30]. These findings are consistent with the results from studies evaluating access at the state and city level [36–38].

Although social and cultural factors may explain some of the association between socio-economic status, race, gender, and poor access to therapy, there is little doubt that much of the association is due to the fact that in comparison with HIV-infected individuals with higher access to therapy, in particular gay and bisexual males [39], HIV-infected illicit drug users may be more likely to be women, ethnic minorities, and have lower incomes. In addition, those infected through sexual contact with IDU and/or through the sex-trade may be more likely to reside in lower income areas, to be female, and to be ethnic minorities.

Numerous studies have shown illicit drug use to be a major barrier to accessing antiretroviral therapy [30]. For instance, a Swiss study demonstrated that active injection drug users outside a drug treatment program, and those who acquired HIV infection through injection drug use had a significantly higher risk of inadequate treatment [40]. An Italian study that stratified patients by HIV exposure category found that IDU began pre-AIDS antiretroviral therapy significantly later than homosexual men and heterosexuals, and that the risk of disease progression was elevated among IDU within a cohort primarily using zidovudine [41]. A subsequent Italian study found that patients with a history of injection drug use were significantly less likely to be prescribed protease inhibitors among a population eligible for antiretroviral therapy [42]. Similarly, a French study demonstrated that despite regular access to AIDS specialized hospital care, continued drug use was a major barrier to being prescribed antiretroviral treatment [43]. Similar findings have been reported from the US where it has been found that HIV-infected IDU who were not receiving antiretrovirals have tended to be active drug users [37,44]. Among injection drug users in Canada, younger age and female gender has been associated with being less likely to have ever received any antiretroviral therapy after adjustment for HIV RNA and CD4 cell count [45]. Interestingly, in comparing access to antiretroviral therapy among medically eligible IDUs in Vancouver and Baltimore between 1996 and 1998, similar proportions had not received any therapy (49 versus 40%, respectively), but IDUs in Vancouver were less likely to receive monotherapy (6 versus 14%, respectively) [44,45].

A final population that may be at risk of poor access and outcomes on HAART are those that are reluctant to seek HIV testing, and hence initiate antiretroviral therapy at a very late stage of HIV infection when the effectiveness of HAART may be compromised and opportunistic infections may preclude the use of antiretroviral therapy. This concern has been demonstrated in various settings in Europe [46] and North America [6]. The scale of this concern is highlighted by an international collaboration of 13 observational HIV treatment databases which demonstrated that of the 12 574 patients included in the study 5224 (41.5%) initiated HAART with a CD4 cell count $< 200 \times 10^6$ cells/l [47]. Previous studies have demonstrated that some populations, particularly injection drug users, ethnic minorities (both African Americans and Hispanics, and recent immigrants in from developing countries), and persons infected through heterosexual contact may initiate therapy at lower CD4 cell counts [31,48–51].

Access to and discontinuation of HIV treatment

As most studies have been conducted among cohorts still living with HIV, it is presently not known to what extent apparent disparities in access to antiretrovirals will improve as HIV-disease becomes more advanced among those with lower access [17]. For instance, there is evidence that differences in access between populations may diminish to some extent over time, [52] and that some populations, particularly injection drug users, may initiate therapy at lower CD4 cell counts [31, 48,49].

Nevertheless, there is emerging evidence to suggest that these disparities often persist until AIDS and/or death. For example, although the numbers of AIDS deaths and AIDS diagnoses decreased dramatically in the US with the advent of HAART, the proportional decreases in mortality were smallest among African Americans [20]. These findings are not unique to the United States. For instance, in the province of British Columbia, Canada, where HIV antiretroviral therapy is available free of charge, of the 1239 deaths that were attributed to HIV-infection during the period 1995 to 2001 406 (32.8%) occurred amongst persons who never accessed any HIV treatment [19]. Preliminary analysis of these data suggest that both females and ethnic minorities are more likely to die without ever receiving antiretroviral treatment [19].

In addition to complete lack of access to antiretroviral therapy prior to death, treatment discontinuation and 'intermittent' use of antiretrovirals have also become a growing concern. Studies have commonly identified both side effects of antiretroviral therapy and history of injection drug use to be associated with therapy discontinuation [53–55]. An acknowledged limitation of these studies stems from the fact that they are

commonly based on selected samples of patients who return to clinics and/or fill out surveys, and population-level estimates of treatment discontinuation are less commonly available. However, evidence of the high prevalence and negative impact of poor retention in treatment comes from population-based studies that have sought to derive population-level estimates of patient adherence by using prescription refill compliance as a surrogate. Several recent studies have applied this approach to estimate the impact of exposure to therapy on disease progression, and have demonstrated that 'adherence,' defined based on prescription refills, is strongly and independently associated with survival [56,57]. For instance, among the 1422 treatment naïve patients who initiated HAART in British Columbia, Canada since July 1996, 355 (25%) picked up medications < 75% of the time during their first year on therapy. Among those who picked up antiretrovirals < 75% of the time, there was nearly a three-fold increased risk of death compared to those who picked up antiretrovirals at least 75% of the time. Although further evaluation of these data are necessary, among the 193 (13.6%) deaths observed among this cohort of patients as of 31 March 2002, 27 (14%) were among individuals who discontinued therapy within 1 month of initially starting HAART and did not re-initiate therapy again prior to death (BC Centre for Excellence in HIV/AIDS unpublished data).

Barriers to the use of antiretroviral therapy

The provision of healthcare services to marginalized populations has historically been compromised by an array of complex social dynamics. This is particularly the case for those addicted to drugs and alcohol, the mentally ill, and the homeless [58]. Among the greatest challenges for the increasing population infected with HIV through injection drug use stems from the fact that, in most countries around the world, the most commonly applied approach to reducing drug use-related problems is to impose criminal sanctions on those who use illicit drugs. This is demonstrated by a recent report which estimated that 20 to 26% of all people living with HIV in the United States in 1997 passed through a correctional facility that year [59]. As a result of enforcement efforts in the community, those addicted to illicit drugs are often driven physically and socially into environments where they are extremely difficult to reach for the purpose of providing medical services [60–63]. Among patients who are incarcerated, transition between prison and the community is often associated with interruptions in care and treatment.

In addition, a commonly reported barrier to accessing

antiretrovirals may be physicians who are skeptical about injection drug users' ability to adhere to therapy, and it is likely that concerns regarding possible transmission of antiretroviral resistant virus has influenced prescribing decisions [64]. This is supported by previous surveys of physicians showing that physician's judgment of patient adherence is critical for the prescription of HAART [40,43]. Physicians have noted that patient homelessness, heavy alcohol use, injection drug use, and prior psychiatric hospitalization have all contributed to their reluctance to initiate HAART [65].

These findings raise concerns for several reasons. First, a recent study demonstrated that a substantial proportion of homeless and marginally housed individuals managed high adherence to antiretroviral therapy including protease inhibitors (PIs), and that resistance to PIs were rare among those that were non-adherent [66]. Furthermore, ethical analyses have suggested that physicians should not indefinitely withhold HAART from patients who are presumed to be poorly adherent [58,67,68]. This argument is strengthened by the studies that have consistently demonstrated that providers may be poor judges of patient adherence [69–71].

Other service delivery barriers to accessing antiretroviral therapy may range from geographic to cultural barriers. For instance, an earlier review suggested that geographic location may influence access to HAART, with more accessible locations possibly being associated with better access [31]. This is consistent with other studies that have found missing clinic visits to be a strong predictor of virological failure [72]. Finally, the consistent associations between ethnic minority status and poor access suggest that cultural differences, as a result of language differences, perceived or real stigma, or other social barriers contribute to limited access [30,33,36–38].

Finally, even when physicians are willing to prescribe antiretroviral therapy and no other barriers are in place, illicit drug use, mental illness, and homelessness may all present major barriers to accessing and retention in an HIV treatment program [37,44,58,73]. While each of these issues presents unique challenges, there are promising strategies that may help to address these concerns.

Strategies for improving access and retention

Whereas interventions to improve daily adherence to antiretroviral therapy have received a growing amount of attention [74–76], limited data exist with regard to

strategies that may optimize access and retention in HIV treatment among populations that have traditionally had poor access to antiretroviral therapy. Nevertheless, through what is known about the significant barriers that presently exist, and what has been learned from experience with other chronic diseases, several strategies deserve further consideration.

Among the best sources of evidence for strategies that may improve access and retention in HIV/AIDS treatment arise from interventions that have successfully delivered healthcare to other marginalized populations. Among adherence interventions, the highest rates of treatment retention and adherence to therapies have been observed with patients enrolled in directly observed therapy (DOT) programs for the treatment of tuberculosis [77,78]. In one DOT study, 77% of IDU took 100% of prescribed isoniazid therapy to prevent tuberculosis, a markedly higher adherence rate in comparison to those randomized to self-administered therapy regardless of counseling and education, although both groups were successfully retained in the study up to 6 months [78].

However, doubts have been raised about the feasibility of directly observed therapy for HIV infection for several reasons, not the least of which is that it may require many years of supervised therapy. In addition, challenges presented by extending directly observed therapy to the treatment of HIV include the potentially negative impact on individual freedoms, as well as concerns that patients may be reluctant to disclose toxicities and side effects out of fear of interrupting scheduled reimbursement [79,80]. Furthermore, among the few studies of directly observed therapy for HIV infection that have been reported [81,82], it has been noted that it is difficult to determine what effect direct supervision or other aspects of assisted adherence programs have had the largest effect [80]. Nevertheless, the ability to retain patients in treatment and ensure high adherence suggests that the directly observed therapy model deserves further consideration.

With regard to physician−patient relationships, whereas physician reluctance to prescribe antiretrovirals has been shown to be a barrier to access, it is important to note that certain physician-related characteristics have also been strongly associated with better access, adherence, and retention in treatment. For instance, satisfaction with one's physician has been associated with higher levels of adherence [14], and willingness to initiate HAART has been associated with patient trust in their physician [83]. In addition, among injection drug users, being treated by a physician with greater experience treating HIV disease was associated with accessing antiretroviral therapy [45,84]. These findings demonstrate both that the physician−

patient relationship is critical [85], and that care for populations at risk of poor access is best delivered by highly experienced physicians, especially considering that patients at risk of poor access may face additional challenges such as HCV co-infection, mental illness, and addiction.

In addition, studies have consistently shown that the provision of drug treatment services can enhance adherence and retention in HIV treatment for illicit drug users. Among the most well-evaluated strategies has been the provision of methadone maintenance therapy (MMT) with antiretroviral therapy, which has been demonstrated to improve outcomes from HAART among HIV-infected IDU [86,87]. As such, efforts should be made to remove barriers to the use of MMT among opiate-dependent, HIV-infected patients who are willing to initiate substitution therapy with MMT [88]. However, there is sufficient evidence to demonstrate that wider access to methadone alone will not be sufficient to close that gap for many opiate-dependent patients. First, many studies of patients successfully treated with antiretrovirals and MMT are often based on selected clinic-based samples, and both observational and randomized studies have demonstrated the high rates of loss to follow-up among patients initiating MMT [89,90]. Although still controversial in many settings, heroin prescription programs appear to have substantial potential to improve retention and treatment outcomes among intractable opiate addicts [91,92]. The randomized trial that has been proposed to take place in three Canadian cities does not exclude HIV-infected opiate addicts, and it will be interesting to see if differences emerge between the control arm (MMT) and prescribed heroin with regard to antiretroviral access and retention in HIV treatment [93].

The growing number of HIV-infected individuals who are using methamphetamine or cocaine may be even more difficult to reach with health care services, and present even greater challenges with regards to the delivery of HAART [94]. These challenges stem from the effects of the drugs themselves, which often lead to chaotic behavior, as well as the higher frequency of injections and lack of pharmacologic replacement as in the case of heroin/methadone [95]. For these individuals, efforts should be made by the physician to help stabilize them when possible [58,85], and there is also evidence that meeting users on their own turf has substantial potential. For instance, a novel project initiated in San Francisco runs out of a storefront office in the heart of a high HIV prevalence inner-city neighborhood [96]. The program offers both medical and social services, several of which have been shown to improve access to antiretrovirals, including HIV specialist nurses, access to medical services without appointment, and

an onsite pharmacist [30,44,97]. Interestingly, the project also offers harm reduction services including needle exchange, which may help to attract eligible patients into their other programs including drug treatment and medical care [98]. Among HIV-infected individuals retained in the program, 64% achieved HIV RNA $< 500 \times 10^6$ cells/l, and only two patients had shown an increase in HIV RNA relative to their pre-program levels [96]. Programs that seek to improve access to healthcare by reducing socio-cultural and geographic barriers are an important area for further study [99].

Summary

We now have a great deal of evidence demonstrating that lower income populations, women, ethnic minorities, and illicit drug users are at risk of poor access to antiretroviral therapy and higher rates of treatment discontinuation. Although the majority of these studies have been conducted among living cohorts, data is emerging to suggest that limited access is contributing to the ongoing HIV/AIDS mortality rates in the developed world.

Fears regarding the potential for community-wide transmission of antiretroviral resistant HIV among the homeless, mentally ill, and injection drug users have thus far largely been unfounded [58,64, 66,100]. Although this concern deserves continued monitoring, in many instances it is likely that resistance is not observed because a proportion of these patients will cease antiretroviral therapy outright or will be insufficiently adherent for resistance to develop [66].

The above issues have several implications. First, interventions to improve retention among those who initiate therapy are urgently required, and efforts are needed to ameliorate barriers to treatment retention and adherence. Second, among individuals who have not accessed therapy, strategies to improve contact with HIV care providers are needed. When contact is made, guidelines for physicians must be based on available evidence [69–71]. This evidence suggests that physicians should seek to address modifiable barriers to adherence and retention in HIV treatment prior to the start of therapy among patients not requiring immediate treatment [58,68]. In addition, no patient should be denied the opportunity to initiate HAART regardless of perceived or real barriers to optimal adherence including continued illicit drug use. Given that the extent of the HIV/AIDS public health crisis, and since the full benefits of HAART are not compromised when patients are successfully retained in treatment, regardless of ethni-

city, gender, and history of injection drug use [55,101], efforts to address social, cultural, and medical barriers are an urgent priority.

Acknowledgement

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