Clinic-Based Treatment of Opioid-Dependent HIV-Infected Patients Versus Referral to an Opioid Treatment Program
A Randomized Trial

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Background: Opioid dependence is common in HIV clinics. Buprenorphine–naloxone (BUP) is an effective treatment of opioid dependence that may be used in routine medical settings.

Objective: To compare clinic-based treatment with BUP (clinic-based BUP) with case management and referral to an opioid treatment program (referred treatment).

Design: Single-center, 12-month randomized trial. Participants and investigators were aware of treatment assignments. (ClinicalTrials.gov registration number: NCT00130819)

Setting: HIV clinic in Baltimore, Maryland.

Patients: 93 HIV-infected, opioid-dependent participants who were not receiving opioid agonist therapy and were not dependent on alcohol or benzodiazepines.

Intervention: Clinic-based BUP included BUP induction and dose titration, urine drug testing, and individual counseling. Referred treatment included case management and referral to an opioid-treatment program.

Measurements: Initiation and long-term receipt of opioid agonist therapy, urine drug test results, visit attendance with primary HIV care providers, use of antiretroviral therapy, and changes in HIV RNA levels and CD4 cell counts.

Results: The average estimated participation in opioid agonist therapy was 74% (95% CI, 61% to 84%) for clinic-based BUP and 41% (CI, 29% to 53%) for referred treatment (P < 0.001). Positive test results for opioids and cocaine were significantly less frequent in clinic-based BUP than in referred treatment, and study participants receiving clinic-based BUP attended significantly more HIV primary care visits than those receiving referred treatment. Use of antiretroviral therapy and changes in HIV RNA levels and CD4 cell counts did not differ between the 2 groups.

Limitation: This was a small single-center study, follow-up was only moderate, and the study groups were unbalanced in terms of recent drug injections at baseline.

Conclusion: Management of HIV-infected, opioid-dependent patients with a clinic-based BUP strategy facilitates access to opioid agonist therapy and improves outcomes of substance abuse treatment.

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Opioid agonist treatment used to be available only in highly regulated programs. In 2002, the U.S. Food and Drug Administration approved the sublingual combination tablet buprenorphine–naloxone (BUP) for office-based treatment of opioid dependence (1, 2). Treatment of opioid dependence in medical settings has particular resonance in HIV care. Injection drug use is a major risk factor for HIV, and opioid dependence is highly prevalent in HIV clinics.

It is not known how treating opioid-dependent patients with BUP in an HIV clinic compares with the traditional model of referral to specialized opioid treatment programs. To address this, we conducted a single-center, nonblinded, 12-month randomized trial comparing clinic-based treatment with BUP (clinic-based BUP) with case management and referral to an opioid treatment program (referred treatment) for opioid-dependent persons in an urban HIV clinic. We hypothesized that clinic-based BUP would improve engagement with and outcomes for both substance abuse and HIV treatment better than referred treatment.

METHODS

Setting

We performed this study in the Johns Hopkins HIV Clinic between November 2005 and April 2009. Our study was 1 of 10 sites supported by the Health Resources Services Administration Special Projects of National Significance to conduct demonstration projects that included the integration of BUP treatment into HIV primary care (www.bhives.org). The Johns Hopkins Medicine and New York Academy of Medicine institutional review boards approved this study.
Participants were eligible for the study if they were 18 years of age or older, received care in the Johns Hopkins HIV Clinic; met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (3), criteria for opioid dependence; had a positive result for opioids on a urine drug test, sought opioid agonist therapy (and were willing to receive either BUP or methadone); and provided written informed consent. We excluded persons who were receiving opioid agonist therapy, women who were pregnant or unwilling to use birth control (because of inadequate safety data on BUP in this population), were allergic to BUP, required long-term opioid treatment of pain, or had an alanine amino transferase level greater than 5 times the upper limit of normal. In addition, because of safety concerns regarding use of BUP in combination with abuse of benzodiazepines or alcohol, we excluded persons with active benzodiazepine or alcohol dependence at screening.

Using a statistical software package, we generated a random, nonstratified treatment allocation list before study inception, with block sizes that varied randomly between 2 and 10. A person not involved with the study placed treatment assignment cards into sequentially numbered, opaque envelopes. When a participant enrolled in the study, the study coordinator opened the next treatment allocation envelope in the sequence and recorded the treatment assignment and envelope sequence number. Neither participants nor investigators were blinded to treatment assignments.

Interventions

The clinic-based BUP group was managed by a licensed practical nurse with training and experience as a substance abuse counselor (interventionist). The interventionist met briefly with participants after randomization to schedule a physician visit and BUP induction date (generally within 7 days) and to instruct participants on how to prepare for induction. We used a 2-day BUP induction protocol in which up to 3 BUP doses were given each day according to the severity of opioid withdrawal, as measured by the Clinical Institute Narcotic Assessment (4). After induction, participants received BUP doses in the clinic 3 times weekly for 2 to 4 weeks until their condition stabilized, at which point they were switched to weekly reporting. A treatment team physician met with participants 4 to 6 weeks after initiation of BUP therapy and at other times as indicated. Participants who missed more than 3 consecutive days of BUP dosing had to repeat BUP induction (5).

At reporting visits, which lasted 10 to 40 minutes, clinic-based BUP participants received unstructured individual counseling, provided urine samples for point-of-care urine drug tests, took BUP doses under observation, and received take-home supplies of BUP to last until their next visit. A treatment team, comprising the interventionist and 2 to 5 BUP-prescribing physicians, met weekly to discuss participants’ progress in treatment. The treatment team set reporting frequencies, which ranged from 3 times weekly to monthly, according to drug test results and other factors. We required at least 4 consecutive negative results for opioids and cocaine before we increased reporting intervals beyond 1 week. Participants’ primary HIV care providers were variably involved with BUP treatment, but involvement was not required in our model.

Participants assigned to referred treatment were enrolled in an intensive case management program that has operated in the clinic since 1998. We used study funds to support staff time devoted to this project. However, the case managers had no investment (positive or negative) in the trial or its outcome. A social worker or registered nurse in the case management program met with referred-treatment participants shortly after randomization and made treatment plans that were primarily focused on linking participants to opioid treatment programs, but may have included such issues as food and housing needs. Case managers used the Baltimore Substance Abuse Systems hotline to find opioid treatment programs according to proximity, insurance requirements, treatment availability, and participant preference. Because several opioid treatment programs in the area had Ryan White grant support to treat uninsured HIV-infected persons (including a Johns Hopkins–affiliated opioid treatment program), lack of medical insurance was not a barrier to program entry. After referral to an opioid-treatment program, case managers followed participants to ascertain whether they had attended scheduled appointments and assisted with rescheduling if needed.

Participant Follow-up

At each study visit (baseline and 1, 3, 6, 9, and 12 months), participants provided urine samples for drug tests and answered questions administered by audio computer-assisted self-interview (6). Only drug test results obtained at study visits, and not by opioid treatment programs or clinic-based BUP intervention, were used for study out-
comes. We measured CD4 lymphocyte counts and HIV RNA levels at baseline, 6 months, and 12 months. Participants received modest reimbursement for study visits to compensate for travel and time. We abstracted clinic medical records at baseline and quarterly to assess visits with HIV primary care providers and use of antiretroviral therapy (ART).

Outcomes

Outcomes included self-reported participation in opioid agonist therapy at study visits, results of urine tests positive for opioids (opiates or oxycodone) or cocaine, visits with primary HIV providers, months of ART use, changes in HIV RNA levels and CD4 cell counts, and proportion of participants with emergency department visits or hospitalizations.

Statistical Analysis

We selected a sample size of 120 persons to provide 80% power to detect a relative hazard for initiation of opioid agonist therapy of 2.0 or greater, assuming 50% of participants overall would start opioid agonist therapy and a 2-sided type I error of 0.05.

We adhered to the intention-to-treat principle in all analyses. Stata, version 10/11 (StataCorp, College Station, Texas), and R (www.r-project.org) software were used for statistical analyses. We used the Fischer exact test and the Wilcoxon rank-sum test to compare discrete and continuous variables, respectively. We compared time to initiation of opioid agonist therapy in the study groups by using the log-rank test, censored at time of death or last study visit. Mixed-effects logistic and linear models were used to assess longitudinal outcomes (7), including participation in opioid agonist therapy, drug test results for opioids and cocaine, HIV RNA levels, and CD4 cell counts. For discrete outcomes, we obtained marginal probabilities from mixed-effect models by using the glamm procedure in Stata (8).

To assess the influence of missing data on longitudinal outcomes, we conducted random-effects pattern-mixture models, in which patterns of missing observations were incorporated as covariates into models (9–11). In addition, because recent injection drug use differed between the study groups at baseline, we did post hoc sensitivity analyses that included a term for recent injection drug use in the models.

Role of the Funding Source

This study was funded by the Health Resources and Services Administration Special Projects of National Significance program. The funding source had no role in the study design or implementation or in the interpretation of results.

RESULTS

Participant Disposition and Characteristics

A total of 220 persons were screened for the study, of whom 96 were randomly assigned (Figure 1). Of the 117 persons who were excluded, 40 (34%) were not opioid dependent, 24 (21%) were not treated in the HIV clinic, 21 (18%) were receiving methadone, 13 (11%) met criteria for alcohol dependence, and 19 (16%) were excluded for other reasons. Two participants assigned to clinic-based BUP and 1 participant assigned to referred treatment were excluded because of protocol violations identified shortly after enrollment (2 were not using opioids and 1 was HIV-seronegative).

A total of 93 participants (46 assigned to clinic-based BUP and 47 to referred treatment) were included in intention-to-treat analyses. Of these, 5 participants died during the study: One in the clinic-based BUP group died of complications of end-stage renal disease, and 4 in the referred treatment group died (end-stage renal disease in 1 participant, pneumonia and sepsis in 1 participant, and...
unknown causes in 2 participants. Visits at 9 and 12 months were administratively censored in 1 and 6 participants, respectively, at cessation of study follow-up on 15 April 2009. Attendance of follow-up visits was similar in the 2 groups (Figure 1). Baseline characteristics were similar in the study groups (Table), with the exceptions that clinic-based BUP participants were less likely to report injection drug use in the 30 days before enrollment ($P = 0.001$) and were less likely to be co-infected with hepatitis C virus ($P = 0.045$).

**Services Provided**

Of 46 participants assigned to clinic-based BUP, 41 (89%) received at least 1 dose of BUP. The median daily BUP dose was 16 mg (interquartile range [IQR], 8 to 24 mg). Of 41 participants who initiated BUP treatment, BUP was reinduced in 12 (29%) and twice or more in 6 (15%).

Of 47 participants assigned to referred treatment, 37 (78%) met with a case manager, usually on the day of randomization. Participants in the case management program had a median of 3 contacts with case managers during the study (IQR, 2 to 5 contacts). Of 10 participants in referred treatment in whom case-manager documentation specified a referral date to an opioid treatment program, the average wait for the appointment was 6.7 days (range, 2 to 15 days). During the study, the average delay between first contact at an opioid treatment program and enrollment to the program was 12 days, decreasing from 15 days in 2005 to 9 days in 2009 (Rusinko W. Personal communication.). A total of 30 participants (64%) in referred treatment started opioid agonist therapy during the study. Of these, 16 and 14 reported receiving methadone and BUP, respectively.

**Substance Abuse Treatment Outcomes**

Initiation of opioid agonist therapy was substantially more rapid in the clinic-based BUP group than in the referred-treatment group: At 2 weeks, 84% (95% CI, 72% to 93%) of the clinic-based BUP group had started opioid agonist therapy compared with 11% (CI, 5% to 24%) of the referred-treatment group ($P < 0.001$). Clinic-based BUP participants were significantly more likely to participate in opioid agonist therapy throughout 12 months of follow-up (Figure 2). After randomization, the average estimated participation in opioid agonist therapy was 74% (CI, 61% to 84%) in the clinic-based BUP group and 41% (CI, 29% to 53%) in the referred-treatment group ($P < 0.001$, likelihood ratio test). Figure 3 shows drug test results for opioids and cocaine in the 2 groups. After randomization, the average estimates of opioid and cocaine use were significantly lower in clinic-based BUP than in referred treatment (for opioids, 44% [CI, 32% to 58%] vs. 65% [CI, 52% to 76%] $P = 0.015$; for cocaine, 51% [CI, 39% to 61%] vs. 66% [CI, 54% to 76%] $P = 0.012$).

**HIV Treatment Outcomes**

Clinic-based BUP participants had significantly more visits with their primary HIV care providers during the study than referred-treatment participants (median, 3.5 visits [IQR, 2 to 4 visits] vs. 3.0 visits [IQR, 1 to 3 visits], $P = 0.045$).

<table>
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<th>Table. Participant Characteristics at Baseline</th>
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<td>Women, n (%)</td>
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<td>African American, n (%)</td>
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<td>Median age (IQR), y</td>
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<td>High school graduate or equivalent, n (%)</td>
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<td>Stay with family or friends</td>
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<td>Homeless, shelter, or single-room occupancy, n (%)</td>
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<td>Median years of opioid use (IQR)</td>
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<td>Hospitalized in previous 3 mo, n (%)</td>
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<td>Positive for hepatitis C antibody, n (%)$\dagger$</td>
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<td>Receiving antiretroviral therapy, n (%)</td>
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<td>Median nadir CD4 count (IQR), $\times 10^3$ cells/L</td>
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<td>Median current CD4 count (IQR), $\times 10^3$ cells/L</td>
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<td>HIV RNA level &lt;400 copies/mL, n (%)</td>
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<td>Median HIV RNA level in persons with HIV RNA level &gt;400 copies/mL (IQR), $\log_{10}$ copies/mL</td>
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BUP = buprenorphine-naloxone; IQR = interquartile range.

* Center for Epidemiologic Studies–Depression scale 10-item survey addressing symptoms in the previous week; higher scores correspond to more severe depressive symptoms (12).

† $P = 0.001$ compared with referred-treatment group.

‡ Hepatitis C status was unknown for 4 persons.

§ $P = 0.045$ compared with referred-treatment group.

‖ $P = 0.089$ compared with referred-treatment group.
The number of months during which participants received ART did not significantly differ between groups (11 months [IQR, 0 to 12 months] for clinic-based BUP vs. 12 months [IQR, 0 to 12 months] for referred treatment; $P = 0.85$). Changes from baseline in HIV RNA levels and CD4 cell counts did not significantly differ between groups ($P = 0.31$ and 0.161, respectively). A total of 35% of participants assigned to clinic-based BUP and 36% assigned to referred treatment had 1 or more emergency department visits or hospitalizations during the study ($P = 1.00$).

Sensitivity Analyses

We used random-effects pattern-mixture models to assess the influence of missing data on repeated measure outcomes. The inclusion of missing pattern groups (main effects and interactions with covariates of interest) significantly improved the fit of the model for participation in opioid agonist therapy ($P = 0.023$). However, the inferred study-group treatment difference in this outcome was unchanged (Appendix Figure, available at www.annals.org). Pattern-mixture modeling did not improve the overall fit of the models for opioid- or cocaine-positive drug test results (likelihood ratio tests, $P = 0.31$ and 0.80, respectively).

In a post hoc analysis, we examined the sensitivity of key study outcomes to adjustment for an imbalance between groups in recent drug injection at baseline. Inclusion of a term for recent drug injection at baseline did not significantly improve model fit for participation in opioid agonist therapy or for opioid- or cocaine-positive drug test results (likelihood ratio test range, $P = 0.157$ to 0.65) and did not alter the statistical inferences from the models.

DISCUSSION

We conducted a randomized, controlled trial comparing clinic-based BUP with referred treatment in opioid-dependent patients in an HIV clinic. Compared with referred treatment, the clinic-based BUP strategy was associated with higher participation in opioid agonist therapy over 12 months of follow-up and with significantly reduced rates of positive drug test results. In addition, clinic-based BUP participants attended more visits with their primary care providers during follow-up than referred-treatment participants. However, we found no evidence that treatment group was associated with use of ART or with changes in HIV RNA, CD4 cell counts, or emergency department visits and hospitalizations.

Streamlined access to opioid agonist therapy was probably a major mechanism underlying our results. Two weeks after randomization, 84% of clinic-based BUP participants had initiated opioid agonist therapy compared with just 11% of referred-treatment participants. Even when expedited by a case-management program, referred treatment entailed following up for an intake appointment at a new clinic, completing intake evaluation, and usually waiting until a treatment slot became available. The average wait time for an opioid treatment program assessment visit was 7 days, and the average delay in Baltimore between first contact at an opioid treatment program and intake was 12 days. Of note, rapid treatment intake in the clinic-based BUP group seemed to yield benefits that persisted for 12 months.

Many studies (13) have compared the efficacy of BUP and methadone in head-to-head clinical trials, which was not the goal of our study. Consistent with the tenets of comparative effectiveness research (14), our objective was to compare the effectiveness of 2 treatment strategies, clinic-based BUP and referral to an opioid treatment program, that may be available to opioid-dependent HIV-infected patients. Two previous studies (15, 16) randomly assigned persons recruited from substance-abuse treatment settings to an opioid treatment program or to office-based treatment. One study (15), which randomly assigned participants who were receiving methadone at an opioid treat-
ment program to continue in the program or to receive methadone in an office setting, found similar outcomes in the 2 groups but higher participant satisfaction with the office-based strategy. The second study (16) randomly assigned participants from the waiting list of an opioid treatment program to either program-based or office-based treatment with BUP and found office-based BUP to be associated with higher retention at 12 weeks and lower rates of opiate-positive drug test results compared with program-based BUP.

Our study differed from these studies in 2 ways. First, participants in our study were recruited from a medical setting (HIV clinic) rather than a substance abuse setting. Second, participants in our comparison group were referred to opioid treatment programs, as they would be in clinical practice. Successful referral of substance-dependent persons from medical care settings to substance abuse treatment is challenging. For example, 1 observational study (17) that followed 40 patients with substance-related medical conditions after hospital discharge found that only 1 patient (3%) followed up with outpatient substance abuse treatment to which he had been referred.

In addition to lower rates of opioid use, we found that rates of cocaine use were also lower with clinic-based BUP than with referred treatment. We hypothesize that this difference was due to greater treatment engagement in the former group rather than to a pharmacodynamic effect of BUP. In a randomized trial comparing BUP and methadone in opioid-dependent cocaine abusers (18), BUP was no more effective than methadone in reducing cocaine use.

Our study has limitations. First, as a single-center study, our results may not generalize to other settings. Our treatment model was relatively intensive and may not be practical in smaller treatment centers. In addition, the performance of our control condition, referred treatment, inherently depended on the availability of opioid treatment services in our area. The relative effectiveness of clinic-based BUP may differ in settings where opioid treatment services are much more or less available than in our community. To ensure that referred treatment was consistently implemented in our study, all participants allocated to this group were enrolled in an established case management program in the HIV clinic. Second, the manufacturer provided BUP to sites participating in this demonstration project for use in participants who had no source of payment, eliminating medication insurance coverage as a barrier to treatment in the clinic-based BUP group. This highlights the public health importance of facilitating access to BUP when treatment with this drug is indicated.

Third, because of the constraints of enrolling from a single clinic, our sample size was small, and we enrolled only 78% of our target. This limited our ability to detect smaller but potentially clinically significant differences in HIV treatment outcomes between the groups. Larger, multicenter clinical trials of BUP delivery in HIV care settings are warranted to confirm and extend our findings. Fourth,
follow-up rates in the study were only moderate; however, although sensitivity analyses with pattern-mixture models provided evidence that differences in opioid agonist therapy participation were sensitive to missing data, the inferences remained the same (that is, higher participation in clinic-based BUP). Finally, the groups were unbalanced with regard to recent drug injection, with statistically significantly more participants in referred treatment reporting recent injection than in clinic-based BUP. Of note, the study groups were well matched with regard to demographic and socioeconomic factors and other indicators of drug-use severity, including years of use, history of incarceration, and concurrent cocaine or alcohol use. Injection drug use may be an indicator of more severe drug dependence and may be associated with poorer response to treatment (19), which could bias study outcomes in favor of clinic-based BUP. In post hoc analyses, we found that outcome differences between the groups were not appreciably altered by adjustment for baseline injection drug use in multivariate models.

Our study has several implications. Provision of clinic-based BUP should be considered in all HIV treatment settings where opioid dependence is common, and HIV care policymakers should consider including clinic-based BUP as a core quality-of-care measure. Treatment models that integrate substance abuse and medical services have been proposed as a means to improve outcomes for both types of conditions and to improve patient satisfaction (20–23). The availability of effective clinic-based treatment of opioid dependence can arguably have the greatest effect in HIV clinics (24). Opioid dependence is highly prevalent in many HIV treatment settings and is detrimental to retention in care and adherence to life-saving ART (25–27). Moreover, ongoing drug use in HIV-infected persons sustains behaviors that risk transmission to others.

In summary, we conducted a randomized trial comparing 2 treatment strategies for opioid-dependent persons attending an urban HIV clinic. Compared with referred treatment, clinic-based BUP led to more rapid initiation of opioid agonist therapy, greater use of opioid agonist therapy over 12 months of follow-up, fewer urine drug test results positive for opioids and cocaine, and more visits with HIV primary care providers during follow-up.

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Appendix Figure. Probability of receiving opioid agonist therapy at study follow-up visits.

Observed estimates are shown for clinic-based buprenorphine–naloxone (BUP) (solid circles) and referred treatment (diamonds); vertical lines represent 95% CIs. We used pattern-mixture models to assess the influence of missing data on estimated study group differences in participation in opioid agonist therapy. Inclusion of pattern-mixture variables improved the fit of the model (P = 0.023, likelihood ratio test). Estimates are shown for participants who missed no study visits in clinic-based BUP (squares) and referred treatment (open circles); green shading represents 95% confidence bands. Estimates are also shown for participants who missed 1 or more follow-up visit in clinic-based BUP (triangles) and in referred treatment (asterisks); diagonal shading represents 95% confidence bands. In the pattern-mixture model, the estimated average participation in opioid agonist therapy was significantly higher for clinic-based BUP than for referred treatment (P < 0.001).