

# Human Immunodeficiency Virus Infection: Complications and Outcome of Orthopaedic Surgery

*James V. Luck, Jr, MD, Laurence R. Logan, MD,  
Daniel R. Benson, MD, and Dale B. Glasser, PhD*

## Abstract

*Orthopaedic surgeons practicing in areas with a high prevalence of human immunodeficiency virus (HIV) infection may expect that up to 7% of their patients who undergo emergent procedures and 1% to 3% of those who undergo elective surgery will be HIV-positive. Although basic science studies have demonstrated impairment of defenses to routine orthopaedic pathogens as well as to opportunistic organisms, clinical studies have shown that this impairment has not resulted in an increased incidence of postoperative infections or failure of wound healing in the asymptomatic HIV-positive patient. Even for the symptomatic patient, current medical management appears adequate to reduce the risk of early postoperative infection. The HIV-positive patient with a prosthetic implant may be at increased risk for late hematogenous implant infection as host defenses diminish. Regular medical attention, prophylactic antibiotic therapy before dental work and invasive procedures, and early evaluation and treatment of possible infections are especially important in this setting. Decisions regarding elective surgery should be made on a risk-benefit basis. Because the risk of surgical complications increases with progression of the disease, guidelines for elective surgery should include an assessment of the HIV-positive patient's immune status, including the CD4 lymphocyte count, history of opportunistic infection, serum albumin level, the presence of skin anergy, and the state of nutrition and general health.*

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It has been estimated that 0.5% of the US population is seropositive for the human immunodeficiency virus (HIV).<sup>1</sup> The distribution of HIV-positive persons is not even, being most highly concentrated in coastal, urban areas. In high-prevalence areas, trauma centers report that as many as 10.4% of their emergency trauma patients are HIV-positive.<sup>2</sup> In anonymous serosurveys conducted by the Centers for Disease Control and Prevention (CDC) at multiple institutions, 0.2% to 8.9% of emergency

room patients and 0.1% to 7.8% of all patients admitted to hospitals were found to be HIV-positive.<sup>3</sup> Orthopaedic surgeons practicing in high-prevalence areas may expect that 3% to 10% of their acute trauma patients will be HIV-positive. In an emergent situation, the patient's status is often unknown but could be critical in management of the case. The incidence rates for elective surgical cases are highly variable. As an example, in the elective case load of one of the authors (J.V.L.), who has responsi-

bility for orthopaedic care in a large hemophilia center, about 10% of the patients are HIV-positive.

Surgery on the HIV-positive patient, whether elective or emergent, involves special risks, which may be divided into two categories: risk to the patient and risk to health-care personnel. Because of concern about these issues, some orthopaedic surgeons may pursue nonoperative management of frac-

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*Dr. Luck is Clinical Professor, Department of Orthopaedics, University of Southern California, and President and Medical Director, Orthopaedic Hospital, Los Angeles. Dr. Logan is Associate Clinical Professor, Department of Medicine (Hematology), University of Southern California School of Medicine, and Director of Adult Hematology, Orthopaedic Hospital Hemophilia Center. Dr. Benson is Professor and Chief of Spine Surgery, Department of Orthopaedics, University of California at Davis, Sacramento. Dr. Glasser is Associate Director, Department of Safety Evaluation and Epidemiology, Pfizer Pharmaceuticals, Inc, New York.*

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*Reprint requests: Dr. Luck, Orthopaedic Hospital, 2400 South Flower Street, Los Angeles, CA 90007.*

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tures usually treated surgically because they are reluctant to recommend elective surgery for HIV-positive patients. Both types of risk must be understood and considered in making a decision regarding the appropriateness of surgery for these patients.

Because of documented seroconversion of health-care personnel after HIV-contaminated puncture injuries<sup>4</sup> and the frequency of parenteral and surface exposure to blood and body fluids in the operating room setting, there has been extensive study of the risks to health-care personnel. Recommendations of methods to reduce the risk of HIV infection and acquired immunodeficiency syndrome (AIDS) in the practice of orthopaedics have been developed and published by the Task Force on AIDS and Orthopaedic Surgery of the American Academy of Orthopaedic Surgeons. To date, there have been 49 well-documented occupational seroconversions among health-care workers. None followed a suture-needle injury, the most common surgical percutaneous injury.<sup>4</sup> In a recent report from the CDC, zidovudine (ZDV) was shown to be effective in the prevention of seroconversion after percutaneous exposure to HIV-contaminated blood.<sup>5,6</sup> In our opinion, if the AAOS-CDC recommendations are closely followed, the risk to health-care personnel, although real, can be reduced to an acceptable level.

In addition to concern about the risk of HIV transmission in the health-care setting, surgeons have expressed concern about the complications and outcome of operations on HIV-infected patients. The early postoperative complications of greatest concern in the HIV-positive patient include sepsis and impaired healing. The late postoperative complication of primary concern is implant infection, which

some authors have speculated has increased in incidence.<sup>7-9</sup> The risk of early and late septic complications is theoretically increased because of impaired cellular and humoral immunity. The estimated magnitude of increased risk is based on a series of reports of the outcome of surgery on HIV-positive patients and is less well delineated than the theoretical basis. These clinical studies also address our ability to successfully prevent complications in the HIV-positive surgical patient. Before describing these clinical series, some of the postulated immunity-impairment mechanisms in HIV infection will be briefly reviewed.

### **Pathophysiology of Immunity Impairment**

The CD4 lymphocyte, which is responsible for cellular immunity, is the primary target cell in HIV infection. Differentiation of the B lymphocyte, responsible for humoral immunity, is indirectly impaired.<sup>10</sup> Additional derangements occur in the monocyte-macrophage cell line and in the production of interferon gamma and lymphokines, which are products of antigenically stimulated lymphocytes.<sup>10</sup>

As the disease progresses, the absolute polymorphonuclear leukocyte count drops to a level that impairs phagocytosis.<sup>11</sup> This may be further reduced by marrow-suppressing drugs such as ZDV, which are used to treat AIDS. Malnutrition, which may be the consequence of both the disease process and the administration of therapeutic medications, causes hypalbuminemia, which may further impair lymphocyte function and phagocytosis.<sup>12,13</sup>

In addition to the crucial role they play in the immune system,

CD4 lymphocytes and lymphokines are important in wound healing.<sup>14</sup> Fishel et al<sup>15</sup> documented the migration of CD lymphocyte subsets into healing wounds, which peaks at 7 days. Furthermore, in a study in rats, impairment of both cellular and humoral immunity by cyclosporin A reduced wound tensile strength to a significant degree at 10 days.<sup>16</sup>

Autoimmune dysfunction also occurs with AIDS. One manifestation of this phenomenon is platelet deficiency, which, if uncorrected, can result in excessive bleeding at surgery. Immunodeficiency-associated thrombocytopenic purpura may be the result of direction of an autoimmune globulin against platelet antigens, similar to the production of immunoglobulin G in idiopathic thrombocytopenic purpura.<sup>17</sup> It seems somewhat paradoxical that autoimmune afflictions should occur in individuals with reduced immunity, but such reactions are common among AIDS patients. Platelet deficiency is treated initially with corticosteroids and, if persistent, with splenectomy. The former further reduces host resistance to infection, and the latter is associated with an increased risk of septicemia.<sup>17,18</sup>

Several groups of researchers have studied neutrophil bactericidal capacity in HIV-positive patients. This capacity is dependent on chemotaxis, phagocytosis, and secretion of oxygen-dependent and oxygen-independent microbicides. Using cultures of *Staphylococcus aureus* as the target organism, Murphy et al<sup>19</sup> compared 90-minute bacterial survival in washed neutrophils from 19 AIDS patients, who had no active infections and were receiving no drugs, with that in washed neutrophils from 17 healthy control subjects. Bacterial survival in the

AIDS patients was significantly higher (32.5% vs 13.8%). Reduced bacterial killing against *S aureus* was also demonstrated by Ellis et al<sup>11</sup> in patients with AIDS and Kaposi's sarcoma. These two studies suggest impairment of all three leukocyte bactericidal functions—chemotaxis, phagocytosis, and secretion of microbicides—in patients with AIDS.

As a result of this complex, widespread immune system impairment, patients with advanced HIV infection have increased susceptibility to common pathogens as well as to opportunistic infections. Many of these pathogens include those commonly involved in musculoskeletal infections. Ganesh et al<sup>20</sup> have shown that the carriage rate for *S aureus* in the nose, throat, and perineum in asymptomatic HIV-positive subjects was double that in HIV-negative control subjects (49% vs 27%). Krumholz et al<sup>21</sup> reported 44 episodes of community-acquired bacteremia in 38 AIDS patients at San Francisco General Hospital. The most common infecting organisms, in descending order, were *S aureus*, *Streptococcus pneumoniae*, and *Escherichia coli*. Presenting infections included pneumonia, central-line phlebitis, cellulitis, and urinary tract infection. Only 57% of the patients were febrile, which is typical of AIDS patients with a bacterial infection, such as pyarthrosis or another orthopaedic infection. These patients often present with a minimal inflammatory response, which appears deceptively benign.

## **Surgical Complications and Outcome**

Impaired defenses to common surgical pathogens and delayed wound healing are causes for concern about the outcome of orthopaedic proce-

dures on the HIV-positive patient. A moderate number of surgical outcome studies, focusing on early complications, have been published. Very high rates of postoperative complications and mortality were found in the earlier studies, which involved general surgical procedures on patients with advanced AIDS.<sup>15,16</sup>

Wilson et al<sup>22</sup> reported the outcome of 31 general surgical procedures on AIDS patients performed between 1982 and 1985. Most of the procedures were major (e.g., thoracotomy, laparotomy, and craniotomy) and were performed on patients with advanced disease, including opportunistic infections and malignant neoplasms. The 30-day mortality rate for the 24 elective procedures was 43%; for the 7 emergent procedures, 57%. The authors believed this very high postoperative mortality rate was the result of progression of opportunistic infection, Kaposi's sarcoma, or lymphoma, as well as the fact that these patients were critically and chronically ill at a time when the capability of managing the complications of AIDS was very limited.

A second study by the same authors involved 35 major abdominal procedures performed on AIDS patients from 1984 to 1988.<sup>23</sup> The 30-day mortality rate for the 22 elective procedures was 9%; for the 13 emergent procedures, 46%. The dramatic difference in the elective mortality rates in these two studies may reflect the improvement in management of opportunistic infections and preterminal AIDS.

Later studies included asymptomatic HIV-positive patients as well as those with AIDS. Several studies of orthopaedic patients, most of them hemophiliacs, have also been published. These studies may be divided into two cate-

gories: those involving early postoperative infections (mostly in surgical wounds) and those involving late infections of hematogenous origin.

## **Early Postoperative Infections**

Diettrich et al<sup>13</sup> reported the data on a series of 120 HIV-positive patients, 56 (47%) of whom had AIDS, who underwent elective or emergent procedures between 1986 and 1990. The 30-day mortality after emergent procedures was 23% (7/30) for patients with AIDS, compared with 0% (0/24) for those who did not have AIDS. For elective procedures, it was 4% (1/26) for AIDS patients, compared with 0% (0/40) for non-AIDS patients. Of the 7 surviving patients with postoperative complications, 1 had a wound infection and 1 experienced a delay in healing; contrary to what might be expected, neither patient had AIDS. The risk of morbidity or mortality was higher if the patient had a history of opportunistic infection and a serum albumin level below 25 g/L. The results in the HIV-positive patients without AIDS—0% mortality and 4% postoperative complications—are roughly comparable to those in the HIV-negative population.

Buehrer et al<sup>24</sup> studied surgical wound-infection rates in HIV-positive and HIV-negative hemophiliacs who underwent 169 procedures, 53 of which were orthopaedic. There were two wound infections, but there was no statistically significant difference between the wound-infection rates of the HIV-positive patients (1.4%) and the HIV-negative patients (0%). No wound infections occurred after the 7 procedures performed on patients with AIDS.

Greene et al<sup>25</sup> reviewed 26 orthopaedic procedures performed on HIV-positive hemophiliacs between 1984 and 1988. There were no surgical-site infections, but there was one instance of cellulitis at the site of intravenous-line insertion. Five patients had a protracted postoperative fever, but clinical infection did not develop. The outcomes and functional results were similar to those in patients treated before 1982 who were presumed to be HIV-negative.

Ragni et al<sup>26</sup> used a mail survey of 115 hemophilia centers to study the rate of early postoperative infection after orthopaedic procedures performed on 66 HIV-positive patients with CD4 lymphocyte counts below 200 at the time of surgery. (A CD4 lymphocyte count under 200 is considered diagnostic of AIDS.) When patients with preoperative evidence of active infection were eliminated, the rate of postoperative infection was 7.5%.

In a series from Kigali, Rwanda, Hoekman et al<sup>27</sup> compared the rate of postoperative infection after open reduction and internal fixation of fractures in 171 HIV-negative patients, 26 asymptomatic HIV-positive patients, and 17 symptomatic HIV-positive patients. None of these patients had hemophilia. The surgeons did not know the patients' HIV status, and no prophylactic antibiotics were used. The infection rates were 5% in the HIV-negative group, 0% in the asymptomatic HIV-positive group, and 23% in the symptomatic HIV-positive group. As in the other studies discussed, the infecting organisms were common surgical pathogens: *S aureus* in eight cases, group A streptococci in two, *E coli* in one, and *Pseudomonas aeruginosa* in one. All infections resolved with antibiotic manage-

ment, and there were no deaths. The rate of infection in the symptomatic HIV-positive patients in this study was substantially higher than that in the survey by Ragni et al<sup>26</sup> of high-risk patients with CD4 lymphocyte counts below 200. The lack of prophylactic antibiotic therapy and other factors related to the patient population and location may have made a critical difference. The authors did not give the CD4 lymphocyte counts of the symptomatic patients, which would have allowed better correlation of the rate of infection with the degree of immune impairment. Remarkably, the rate of infection in the HIV-negative and asymptomatic HIV-positive patients, who did not receive prophylactic antibiotic therapy, was similar to that in a reported series of open fracture repair in the general population.<sup>28</sup> On the basis of other studies cited in that report, it appears likely that the symptomatic HIV-positive patients harbored more pathogens and had more severe immunity impairment, which would have made the absence of prophylactic antibiotic administration more critical.

Paiement et al<sup>29</sup> reported the data on 476 orthopaedic surgical trauma patients who underwent at least one open procedure at San Francisco General Hospital. There were 444 HIV-negative patients and 30 HIV-positive patients without AIDS. In the clean and clean-contaminated wound categories, infection occurred in 15 of the 364 HIV-negative patients but in none of the 21 HIV-positive patients. In the open-fracture category, deep infections occurred in 3 of the 80 HIV-negative patients and in 1 of the 9 HIV-positive patients. Because of the retrospective nature of this study, CD4 lymphocyte counts and other indicators of immune status were not available.

## **Late Hematogenous Infections**

There has been much speculation but few studies on the effect of HIV infection on the incidence of late prosthetic-joint infection. Two studies involving hemophiliacs have been presented at national meetings. In the first, Luck et al<sup>30</sup> studied the incidence of infection in 93 joint replacements performed in 62 hemophiliacs between 1968 and 1991. At the time of surgery, 25 patients were HIV-negative and 25 were HIV-positive; the status of the 12 patients who underwent surgery between 1978 and 1985 was unknown. There were no early postoperative infections in any of these patients. The incidence of late postoperative infection in the HIV-negative group was 8%, which is similar to the average (10%) in other studies on HIV-negative hemophiliacs.<sup>31-33</sup> This high incidence of late hematogenous prosthetic-joint infection in HIV-negative hemophiliacs may be a consequence of bacteremia from frequent intravenous self-administration of clotting-factor concentrate. The incidence of late prosthetic-joint infection in the patients known to be HIV-positive at surgery was 18%. Because of the small numbers in each group, this difference is not statistically significant but may represent a trend indicating that the already high risk of infection in HIV-negative hemophiliacs is magnified by the immune impairment caused by HIV infection. This hypothesis should not be assumed to be true for the nonhemophiliac HIV-positive patients who do not possess the other risk factors found in hemophilia.

In the second study, Unger et al<sup>34</sup> reported on 26 total knee replacements performed on hemophiliacs between 1984 and 1991

(follow-up period, 1 to 9 years). Despite the fact that all patients were HIV-positive, there were no early or late infections reported.

Teeny et al found that the incidence of spontaneous hematogenous joint infections in hemophiliacs increased significantly after HIV-1 was introduced into the donor blood pool (unpublished data, 1989). In the period between 1973 and 1980, there were 3 such infections in a stable population of 480 hemophiliacs that varied by less than 6% per year; in the subsequent 7-year period from 1981 to 1988, there were 13. In the group of hemophiliacs with CD4 lymphocyte counts less than 200, which would currently qualify for the diagnosis of AIDS, the incidence of musculoskeletal infection was 11%, compared with 1.1% in the group of all other hemophiliacs at this center. Both of these differences were statistically significant ( $P \leq 0.01$ ). All of these infections involved either arthropathic or prosthetic joints. In the six prosthetic joints, the time from implantation to infection ranged from 6 months to 15 years. As in the study by Krumholz et al,<sup>21</sup> infected joints in the HIV-positive patients with CD4 lymphocyte counts less than 200 appeared deceptively benign, and fever was usually low grade or absent.

Opportunistic infections, which are common in patients with AIDS, are very rarely causative of orthopaedic implant infection. A review of the literature revealed only one case that involved *Mycobacterium avium-intracellulare* (MAI). Mycobacterial infections, including those due to atypical strains, are common in patients with advanced HIV infection.

Hawkins et al<sup>35</sup> reported disseminated MAI infection in 53% of patients who died of AIDS at

Memorial Sloan-Kettering Cancer Center. They also reported positive blood cultures in 98% of 46 patients infected with MAI and positive cultures of bone-marrow aspirate specimens in 100% of 14 patients.

McLaughlin et al<sup>36</sup> reported the case of one patient in whom MAI infection developed in both prosthetic hips, which had demonstrated prosthetic loosening for many years. The patient had clinical AIDS at the time of apparent mycobacterial infection. The prostheses in this patient could have become infected through hematogenous seeding or from contact with adjacent bone. Loosening with hyperemic interface membrane would predispose to this complication.

Fungal infections, which are also common in HIV-positive patients, have been reported to cause prosthetic-joint infection. To the best of our knowledge, however, there have been no reports of fungal prosthetic-joint infection related to HIV infection.

## Discussion and Recommendations

On the basis of current scientific and clinical knowledge, a general philosophy or set of guidelines can be developed for elective and emergent surgery on the HIV-positive patient in various stages of disease.

Most of the clinical studies available to date do not demonstrate a greater incidence of early postoperative complications in asymptomatic HIV-positive patients than in HIV-negative patients. Furthermore, most of the orthopaedic studies and the more recent general surgery studies do not show a greater incidence of early complications in symptomatic HIV-positive

patients with CD4 lymphocyte counts above 200 who undergo elective procedures. The risk of complications after emergent surgery is consistently higher in patients with AIDS. The basic science work establishes some impairment of defenses against common orthopaedic pathogens, as well as impairment of wound healing. As the disease progresses and these impairments increase, the hazard of early complications increases. The risk of late prosthetic-implant infection, although not yet quantified, may be somewhat increased as well, especially in hemophiliacs. Implant infection by opportunistic organisms, although very rare, has been reported. In view of all these factors, special management of the HIV-positive patient undergoing surgery seems warranted. The Hemophilia Treatment Center at Orthopaedic Hospital, Los Angeles, uses a protocol that serves as the basis for the following recommendations.

If the procedure is elective, decision making about the advisability of surgery is crucial. As a result of the availability of improved reverse-transcriptase agents and third-generation protease inhibitors, it is often possible to reduce high viral loads to undetectable levels, resulting in CD4 lymphocyte count elevation. The prognosis and life expectancy for patients with AIDS have improved, making reconstructive surgery for patients who require it a reasonable consideration. After a thorough assessment of the patient's medical status, a thoughtful discussion of the risk-benefit ratio should ensue. In patients with more advanced disease, quality-of-life issues are often the patient's principal consideration. In emergent situations, like open tibial fractures, early wound debridement and

thorough irrigation are highly desirable, but decisions regarding definitive internal fixation might best await medical evaluation and stabilization.

The spectrum of disease in HIV infection is a continuum on which each patient must be positioned to properly assess risk. No single clinical factor is a reliable predictor of longevity or risk of surgical complications. Several components should be combined in determining a prognosis and assigning risk. The factors that seem to correlate best with surgical outcome in published studies are history of opportunistic infection, CD4 lymphocyte count less than 200, serum albumin concentration less than 25 g/L, and cutaneous anergy. The combination of the viral load and the CD4 lymphocyte count has recently been shown to be the best prognostic indicator. This is especially valuable in elective-surgery risk-benefit analysis.

Once a decision has been made to proceed with surgery, several steps can be taken to further reduce the risk. Some of the measures are applicable in an emergent situation; others require more time and are feasible only in elective surgery. The absolute polymorphonuclear leukocyte count should exceed 1,000; the platelet count, 60,000. When appropriate, granulocyte-stimulating factor may be used to elevate an unacceptably low white blood cell count. Platelet transfusions also may be used when needed. All patients should be carefully screened for opportunistic infections, including bacterial, mycobacterial, and fungal infections. If the patient has a treatable opportunistic infection, it should be brought under control.

Some of the drugs used to suppress HIV infection and to prevent

opportunistic infections (e.g., ZDV, didanosine [DDI], and zalcitabine [DDC]) can cause marrow suppression. The more recently developed reverse-transcriptase inhibitors, such as lamivudine (3TC) and stavudine (D4T), are not likely to do this. Many symptomatic HIV-positive patients have chronic anemia as well as drug-related anemia and may require transfusion before surgery. When clinically appropriate, marrow-suppressing drugs should be stopped a few days before surgery and resumed after the first postoperative week. Prophylactic antibiotics seem clearly indicated in this patient population. In patients with advanced HIV infection, some authors have suggested continuation of prophylactic antibiotics longer than normal, but there are no data to demonstrate efficacy.

The HIV-positive patient with a prosthetic implant may be at increased risk for late hematogenous implant infection as host defenses diminish. Regular medical attention, prophylactic antibiotics (preferably a cephalosporin) before dental work and invasive procedures, and early evaluation and treatment of possible infections are especially important in such patients.<sup>27,37-39</sup>

Many patients will require long-term venous access. Subcutaneous ports are less likely to become infected than external percutaneous catheters. Wastell et al<sup>40</sup> reported a rate of infection with Hickman catheters of 0.65 instances per 100 days. Tanner et al<sup>41</sup> found a similar rate of infection in Hickman catheters of 50%, compared with 5% for implanted subcutaneous ports placed in the upper extremity. These should be avoided whenever possible in HIV-positive patients undergoing joint replacement.

Some clinicians have raised the issue of using chronic prophylactic antibiotics in symptomatic HIV-positive patients with a joint replacement. To date, no studies have demonstrated a reduction in the rate of late infection with long-term prophylactic antibiotic administration. Long-term use of trimethoprim-sulfamethoxazole as prophylaxis against *Pneumocystis pneumonia* may offer some protection against *S aureus* infection in prosthetic joints.

## Summary

The risks of surgery on the HIV-positive patient include both early and late postoperative complications. Several general surgical and orthopaedic retrospective studies have reported the outcome of emergent and elective procedures on HIV-positive patients. These analyses generally compare the patients with early asymptomatic HIV infection with those who have clinical AIDS. The risk of early postoperative complications in the asymptomatic HIV-positive patient undergoing an orthopaedic procedure is not significantly greater than that in an HIV-negative patient. Patients with AIDS have shown an increased risk of postoperative infection in some series but not in others.

The principal concern regarding late hematogenous infection in HIV-positive orthopaedic patients is prosthetic-implant infection. The series in which this issue has been studied included only hemophiliacs. The incidence of late prosthetic-joint infection in hemophiliacs was unusually high before the HIV pandemic. Although not statistically significant, this incidence may be higher in HIV-positive hemophiliacs, especially those with advanced disease. There are no data to show

that this risk applies to the HIV-positive nonhemophilic patient with a prosthetic joint.

Decisions about elective surgery should be made on a risk-benefit

basis. Patients undergoing surgery, whether emergent or elective, should have absolute polymorphonuclear leukocyte counts above 1,000 and platelet counts above

60,000 whenever possible. Prophylactic antibiotic therapy should be used for orthopaedic procedures, and patients should be observed closely until the wound has healed.

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