

# HIV-Associated Pulmonary Hypertension: A Global Perspective

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Human immunodeficiency virus (HIV) infection is a well-recognized cause of pulmonary arterial hypertension (PAH). Worldwide, an estimated 37 million individuals are infected with HIV, and the availability of effective HIV therapy means that more of these patients are living longer and developing cardiovascular complications, including PAH. In European populations, it is estimated that 0.5% of patients with HIV infection develop moderate to severe PAH, so that HIV infection may be one of the most common causes of PAH worldwide. Untreated, the prognosis of HIV-associated PAH is particularly poor, and a large proportion of patients with HIV infection live in resource-poor regions of the world where PAH therapy is not available. In this review, the available data on epidemiology, hemodynamics, mechanisms, and therapeutic strategies for HIV-associated PAH are summarized.

The first case of human immunodeficiency virus-associated pulmonary arterial hypertension (HIV-PAH) was reported in 1987, in an HIV-infected patient who died of PAH and glomerulonephritis.<sup>1</sup> Since that time PAH has become a well-recognized complication of HIV infection. Modern treatment with antiretroviral therapy has improved survival for patients with HIV infection so that cardiovascular disease and other non-acquired immunodeficiency syndrome (AIDS) conditions are increasingly encountered as these patients live longer.<sup>2-4</sup> HIV-infected patients are more likely to develop cardiovascular disease than the general population, probably due to a combination of traditional risk factors, HIV-related inflammation, and effects of antiretroviral drugs.<sup>5</sup> Among the cardiovascular complications of HIV infection, HIV-PAH is especially severe and is associated with significant mortality.<sup>6</sup> Given the large number of HIV-infected patients worldwide, HIV-PAH could be among the most common causes of PAH. HIV-PAH may be particularly common in resource-poor countries, which bear a disproportionate burden of HIV infection and are least equipped to diagnose and manage HIV-PAH.

## EPIDEMIOLOGY

Estimates of the prevalence and incidence of HIV-PAH have varied considerably depending on the population studied and the time period of the study.<sup>7</sup> The earliest prevalence estimates of HIV-PAH were determined from a Swiss cohort of 1200 HIV-positive patients not treated with antiretroviral therapy who were evaluated with echocardiography for unexplained respiratory complaints. HIV-PAH was diagnosed in 6 patients yielding a prevalence estimate for HIV-PAH of 0.5%.<sup>8</sup> In a more recent prospective cohort study, 7648 HIV-infected patients in France were screened to identify those with unexplained dyspnea. Patients with dyspnea were then further evaluated with an echocardiogram and pulmonary artery catheterization to evaluate for PAH. The final prevalence of HIV-PAH in this study was 0.46% (95% confidence interval 0.32-0.64).<sup>9</sup> The estimated prevalence of HIV-PAH was remarkably nearly identical in the 2 cohorts despite differences in HIV therapy. The study in the French cohort is the only large study that has used pulmonary artery catheterization to diagnose PAH so that the prevalence rate of 0.5% is generally accepted to be the most accurate.

Studies in several other populations have found a much higher prevalence of echocardiographic signs of PAH. In a study performed in an American inner-city population at San Francisco General Hospital, tricuspid regurgitant jet velocity (TRV) and right atrial pressure were used to estimate pulmonary artery systolic pressure (PASP) in 196 HIV-infected subjects and 52 age-matched uninfected controls.<sup>10</sup> HIV-infected subjects had a higher PASP compared to controls with a median PASP of 27.5 mm Hg (interquartile range 22 to 32.5 mm Hg) compared to 22 mm Hg (interquartile range 18 to 25 mm Hg ( $P<0.001$ )). A PASP of greater than 30 mm Hg or 40 mm Hg was found in 35.2% of HIV patients compared to 6.6% of controls ( $P<0.001$ ), and 7.7% of HIV patients compared to 1.9% of controls ( $P=0.005$ ), respectively. After adjustment for age, gender, smoking, stimulant drug use, and intravenous drug use, HIV-infected subjects had a 5.1 mm Hg higher mean PASP and a 7-fold greater odds of having a PASP  $>30$  mm Hg ( $P<0.001$ ). Another study of 656 HIV-infected individuals from a multisite American cohort of HIV-positive patients demonstrated that among individuals with a detectable TR jet, 57% had evidence of pulmonary hypertension (PH) as defined as PASP greater than 30 mm Hg, and 7% had a PASP greater than 45 mm Hg. In this cohort, the only factor associated with elevat-

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ed PASP was current use of a ritonavir-boosted antiretroviral regimen.<sup>11</sup> A retrospective study in patients attending the National Institutes of Health HIV clinic found that 9.3% of patients had a TRV  $\geq 2.5$  m/s (translating into a PASP of 30 mm Hg) and 0.4% had a TRV  $\geq 3.0$  m/s (PASP 41 mm Hg), a finding that is more consistent with the prevalence found in the French and Swiss cohorts.<sup>6</sup> In another recent study, a randomly selected cohort of 392 HIV-positive patients attending an HIV clinic in Madrid was evaluated with echocardiography. In this study, 9.9% of patients had a TR jet over 2.8 m/sec and were considered to have PAH.<sup>12</sup>

Data about the prevalence of PAH in non-Western countries are lacking. In patients with symptoms of cardiovascular disease, the prevalence of a PASP over 35 mm Hg was reported to be 13% in Tanzania, 13% in Cameroon, and 42% in South Africa<sup>13</sup>; however, there are no estimates of the prevalence of HIV-PAH in all HIV-infected patients.

Pulmonary artery catheterization is required for making the diagnosis of PAH, so interpreting prevalence estimates of HIV-PAH from studies using echocardiography to diagnose PAH and making comparisons with the French cohort study is difficult. It is possible (and even likely) that echocardiography studies overestimate the prevalence of HIV-PAH. However, it is also possible that differences in prevalence are related

to characteristics of the population studied such as genetic susceptibility to PAH, use of stimulant drugs, or mode of HIV transmission. It is also possible that the large number of individuals with echocardiographic abnormalities but who may not meet criteria for a diagnosis of PAH represent many patients who could have early or mild forms of PAH.<sup>6,11</sup>

At the end of 2015, there were an estimated 36.7 million HIV-infected individuals worldwide.<sup>14</sup> Using the French prevalence estimate of 0.5% of patients with HIV, there may be as many as 200,000 patients with HIV infections affected by PAH worldwide.<sup>7</sup> Approximately 19 million HIV-infected individuals live in Southern and Eastern Africa, so there could be up to 95,000 cases of HIV-PAH in these resource-poor countries (Figure 1).

### PATHOGENESIS

Patients with HIV and PAH have plexogenic lesions similar to patients with other diseases associated with PAH.<sup>15</sup> Most patients with HIV infection do not develop PAH, and it remains unclear how HIV leads to the development of PAH in some HIV-infected patients.

HIV has never been shown to directly infect pulmonary vascular endothelial cells,<sup>16,17</sup> but HIV viral antigens are present in the pulmonary endothelium and may directly stimulate abnormal apoptosis, growth, and proliferation,

processes that are thought to result in PAH.<sup>18</sup> Gp120, an HIV viral protein necessary for the binding and entry of HIV into macrophages, has been shown to target human lung endothelial cells, increase markers of apoptosis, and stimulate the secretion of endothelin-1.<sup>16</sup> The negative factor (nef) antigen, critical for the maintenance of HIV viral loads and for host cell signaling interactions, has been found in multiple pulmonary and vascular cells types.<sup>19</sup> Primates infected with a simian immunodeficiency virus expressing HIV nef protein develop lesions resembling plexiform lesions, and co-localization of HIV-1 nef has been demonstrated in pulmonary artery endothelial cells of HIV-infected individuals with PAH, but not in uninfected individuals or in individuals with idiopathic PAH.<sup>19,20</sup> Certain genetic mutations in HIV viral antigens may predispose to the development of HIV-PAH. In HIV virus taken from a cohort of HIV-infected patients with and without PAH, specific mutations in the nef protein were associated with a 12-fold increased risk of HIV-PAH.<sup>21</sup>

Bone morphogenic protein receptor 2 (*BMPR-2*) mutations, associated with familial PAH, result in decreased signaling through *BMPR-2*.<sup>22</sup> The HIV-1 tat protein (transcriptional transactivator) represses *BMPR-2* gene expression in human macrophages in vitro, interfering with BMP-*BMPR-2* transcriptional regulation.<sup>22</sup> Exogenous tat protein has

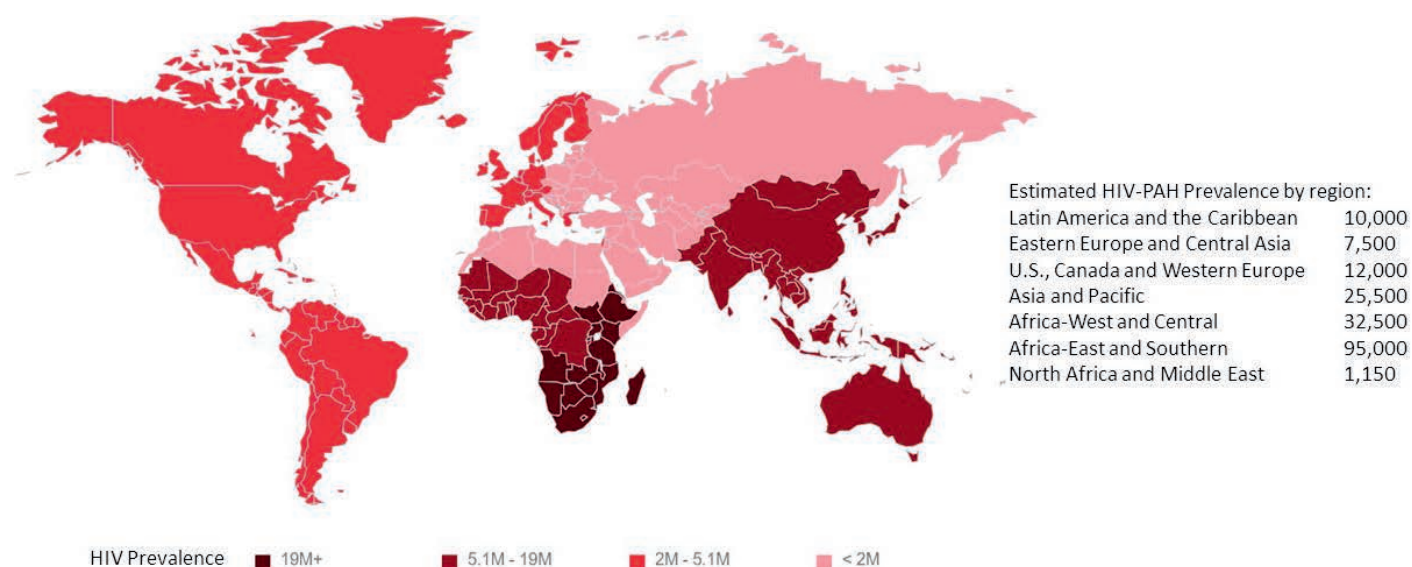


Figure 1: Prevalence of HIV infection at the end of 2015, and estimated prevalence of HIV-PAH. Modified from <http://aidsinfo.unaids.org>. Accessed March 3, 2017.

also been shown to activate endothelial cells, resulting in the release of growth factors,<sup>22</sup> supporting the hypothesis that HIV viral proteins could induce aberrant endothelial function, leading to PAH.

HIV infection induces a chronic inflammatory state and persistent immune activation and dysregulation<sup>23</sup> that could indirectly induce the release of proinflammatory cytokines and growth factors that have been invoked in the development of PAH.<sup>24</sup> Sputum inflammatory markers and activated CD8+ T cells have been associated with elevated PASP.<sup>25</sup> Increased expression of platelet-derived growth factor, a potent stimulus of smooth muscle cell and fibroblast growth and migration, has also been noted in lung tissue from patients with HIV-associated PAH.<sup>17</sup> Similarly, vascular endothelial growth factor-A induces vascular permeability and endothelial cell proliferation and is produced by T cells infected by HIV in vivo.<sup>26</sup>

Not all patients with HIV develop HIV-PAH, so it has been suggested that an additional insult or “second hit” is required in addition to HIV infection for PAH to develop.<sup>27</sup> Stimulant drug use has been proposed as one possible “second hit” because it is more common in patients with HIV-PAH.<sup>10</sup> Additional support for this hypothesis comes from a study showing that plexiform lesions develop in simian immunodeficiency virus-infected macaques also treated with intravenous morphine.<sup>28</sup>

## SURVIVAL

Survival estimates for HIV-PAH are imprecise and have varied overtime because they are derived from limited data and have potentially been affected by the availability of therapies for HIV and PAH. Survival reported for patients with HIV-PAH has consistently been worse than either HIV infection or idiopathic PAH alone (Figure 2).<sup>29,30</sup>

The first study of PAH-HIV, a prospective cohort study of 19 HIV-PAH patients compared to 19 patients with HIV-infected controls, was published in 1997, prior to the wide availability of antiretroviral therapy.<sup>29</sup> Survival in HIV-PAH was 58%, 32%, and 21% at 1, 2, and 3 years, markedly worse than

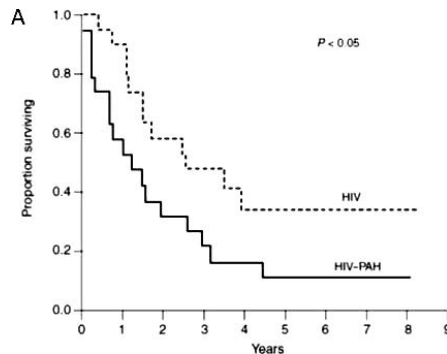


Figure 2: A. Kaplan-Meier plot demonstrating the probability of survival in patients with HIV infection and PAH compared to matched HIV-infected controls without PAH prior to the modern era of antiretroviral and PAH-specific therapy. Reprinted with permission of the American Thoracic Society. Copyright © 2017 American Thoracic Society. Opravil M, Pechere M, Speich R, et al. HIV-associated primary pulmonary hypertension. A case control study. *Swiss HIV Cohort Study. Am J Respir Crit Care Med.* 1997;155(3):990-995. The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society.

controls (Figure 2). A lower CD4 lymphocyte count and the diagnosis of PAH were associated with worse survival.

The most recent data on survival of patients with HIV-PAH come from the French cohort. This series includes 77 patients with HIV-PAH evaluated between 2000 and 2008, and managed with modern therapy for HIV and PAH.<sup>31</sup> On univariate analysis, a history of right-sided heart failure, baseline New York Heart Association (NYHA) functional class IV, cardiac index less than 2.8 L/min per m<sup>2</sup>, detectable HIV viral load, and CD4 count less than 200 were associated with poor survival. In multivariate analysis, a low cardiac index and CD4 count remained associated with worse survival. Overall survival was 88%, 72%, and 63% at 1, 3, and 5 years, significantly better than prior series. In patients who received PAH-specific therapy, survival was 72% compared to 66% in those who did not.

## CLINICAL PRESENTATION AND DIAGNOSIS

Presenting complaints of HIV-PAH are the same as those for patients with idiopathic PAH. Symptoms are often nonspecific and insidious so that they are attributed to other complications

of HIV or HIV itself. The time from presentation to diagnosis is often long, from 6 months to 2 years. In a series of patients diagnosed with HIV-PAH prior to the year 2000, the most common presenting symptom was progressive shortness of breath (85%), followed by pedal edema (30%), nonproductive cough (19%), fatigue (13%), presyncope or syncope (12%), and chest pain (7%).<sup>15</sup> Physical examination may be unremarkable, but in some cases typical findings of right-sided heart failure and volume overload are apparent.<sup>15</sup>

Although PAH is more common in HIV-infected patients, it remains a rare disease and routine screening with echocardiography for PAH in asymptomatic HIV-infected patients has not been shown to be a useful or cost-effective practice.<sup>32</sup> The French cohort study demonstrated the utility of a strategy to screen for symptoms of dyspnea of unclear etiology among HIV patients followed by an echocardiogram and pulmonary artery catheterization. Unexplained dyspnea or other symptoms or signs of right heart failure should prompt consideration for pulmonary artery catheterization even if PASP is not elevated on the echocardiogram. This may be particularly true in HIV-infected patients (Figure 3). In the San Francisco General Hospital cohort, echocardiographic estimates of PASP were inaccurate in 19.7% of cases, and

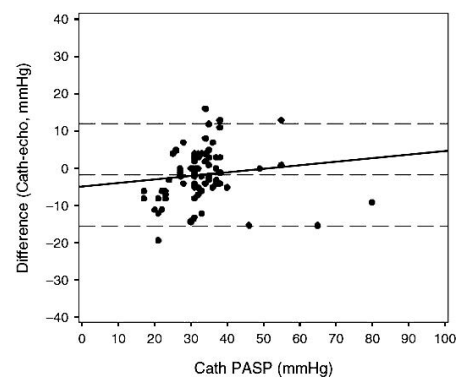


Figure 3: Bland-Altman analysis demonstrating lack of agreement between the Doppler echocardiogram-estimated PASP and right heart catheterization-measured PASP. Reproduced with permission from Selby VN, Scherzer R, Barnett CF, et al. Doppler echocardiography does not accurately estimate pulmonary artery systolic pressure in HIV-infected patients. *AIDS.* 2012;26(15):1967-1969.



echocardiography missed the diagnosis of HIV-PAH in 1 out of 3 patients.<sup>33</sup>

HIV patients may have a variety of comorbid conditions that could also predispose to PH and/or PAH, making it important that patients undergoing evaluation for suspected HIV-PAH undergo testing to exclude other causes of PAH and PH according to current recommendations.<sup>34</sup>

## TREATMENT

### *Antiretroviral Treatment*

Current guidelines recommend that all HIV-infected patients be treated with antiretroviral agents regardless of CD4 T-cell count and viral load.<sup>35,36</sup> Therefore, all patients with HIV-PAH should, if possible, be treated with antiretroviral therapy. It remains unclear, however, if antiviral therapy in and of itself is useful to treat PAH in patients with HIV-PAH.

Two large retrospective studies showed a reduced incidence of HIV-PAH after antiretroviral treatment became available.<sup>7,37</sup> Data from the Swiss cohort study showed that individuals with HIV-PAH diagnosed after 1995 had slightly improved survival compared to those diagnosed before this time. Additionally, it was noted that higher CD4 cell counts was associated with a lower incidence of HIV-PAH.<sup>31</sup> These findings have been interpreted to mean that antiretroviral therapy may prevent the development of and effectively treat HIV-PAH. The evidence for this conclusion remains poor, however, and antiretroviral therapy alone is not an adequate therapy for patients who develop HIV-PAH.

A small French cohort compared patients with HIV-PAH, 50 treated with PAH therapy and antiretrovirals, and 27 treated with antiretrovirals alone. In this study, exercise tolerance as assessed by 6-minute walk distance (6MWD) improved in HIV-PAH patients treated with antiretroviral therapy alone; however, antiretroviral therapy alone did not result in an improvement in hemodynamics.<sup>31</sup>

### *Conventional PAH Therapy*

As in all patients with PAH, volume overload should be treated with diuretics

and hypoxemia should be treated with supplemental oxygen. A favorable long-term response to oral calcium channel blockers has been reported only rarely in patients with HIV-PAH,<sup>31</sup> so that this therapy is generally not recommended. In fact, the role of vasodilator testing in HIV-PAH has been questioned, and recent guidelines do not explicitly recommend this procedure in associated forms of PAH, including HIV.<sup>34</sup>

### *PAH-Specific Therapy*

Survival in retrospective cohort studies suggests that survival in patients treated with PAH-specific therapy in addition to antiretroviral therapy is improved compared to patients not treated with PAH-specific therapy.<sup>31</sup> Few studies of PAH therapy have enrolled patients with HIV-PAH so that treatment decisions for HIV-PAH patients must be extrapolated from studies in other PAH populations.<sup>38</sup> HIV-PAH treatment is particularly challenging secondary to the potential for significant drug interactions between HIV and PAH medications and adverse effects of PAH medications. Due to the high costs of PAH medications, complex delivery systems, and intensive monitoring required, they are still rarely available to patients in resource-poor environments such as Southern and Eastern Africa, where HIV-PAH may be most common.

### *Phosphodiesterase Inhibitors*

Beneficial effects of phosphodiesterase inhibitors in patients with HIV-PAH have been reported in small series and case reports.<sup>39,40</sup> Ritonavir and other protease inhibitors are inhibitors of cytochrome P450 CYP3A4 and CYP2C9, which are important in the metabolism of sildenafil and tadalafil. Marked increases in sildenafil levels have been observed during coadministration with indinavir,<sup>41</sup> saquinavir, and ritonavir<sup>42</sup> so that some guidelines consider this combination to be contraindicated. However, increased sildenafil levels have not been associated with hypotension or adverse effects in pharmacokinetic studies,<sup>42</sup> and successful coadministration of ritonavir and sildenafil in HIV-PAH patients has been reported.<sup>43</sup> Tadalafil levels are less affected by ritonavir, and guide-

lines suggest only close monitoring of tadalafil therapy is initiated. Because of the relatively low cost, ease of administration, and limited adverse effects, these therapies are often first-line treatment for HIV-PAH.

### *Endothelin Receptor Antagonists*

The endothelin receptor antagonist bosentan has been specifically studied in patients with HIV-PAH. The BREATHE-4 trial was a prospective study of 16 HIV-PAH patients treated with bosentan for 16 weeks. NYHA classification was improved by at least 1 class in 14 patients, cardiac index improved by 39%, mean pulmonary arterial pressure decreased by 21%, and 6MWD improved by 91±60 meters. In another study of 59 patients treated with bosentan for a median of 29 weeks, there were improvements in symptoms, exercise tolerance, and hemodynamic parameters.<sup>44</sup> In both studies, bosentan was well tolerated. Because of potential drug interactions, treatment with bosentan requires initiating low-dose therapy that may be titrated up to full dose with careful monitoring for adverse effects and liver function test abnormalities.<sup>45</sup>

Ambrisentan has not been studied specifically in patients with HIV-PAH, but it does not have the same potential drug interactions with antiretroviral medications, which makes it simpler to use in patients with HIV-PAH.<sup>46</sup> Macitentan has not been specifically studied in HIV-PAH.

### *Prostacyclin Analogues*

Improvements in hemodynamics and exercise tolerance have been observed in small series of patients treated with intravenous and subcutaneous prostanoids. In one report, 6 patients with HIV-PAH were treated with intravenous epoprostenol for 12 to 47 months. Acute improvements in pulmonary artery pressure, cardiac index, and pulmonary vascular resistance (PVR) persisted at the time of repeat right heart catheterization.<sup>47</sup> NYHA classification also improved. In another study, 3 patients with severe HIV-PAH were treated with 1 year of subcutaneous treprostinil. All patients had improvement in NYHA

functional class, increased 6MWD by at least 75 meters (baseline 313–500), and improvement in hemodynamics.<sup>48</sup> Intravenous and subcutaneous prostanoid treatment, however, is challenging to use because it requires close follow-up, and patient management of an intravenous or subcutaneous catheter may not be desirable in HIV-infected patients at risk for catheter-related infection and injection drug use.

Inhaled prostanoids offer a useful alternative to intravenous and subcutaneous delivery methods. The effects of inhaled iloprost were reported in a study of 8 patients with severe HIV-PAH. Hemodynamics following initial iloprost treatment improved with a 31% reduction in PVR and a 21% increase in cardiac index. Four of those patients were treated with iloprost for at least 6 months with an improvement in NYHA functional class and improved 6MWD from 331±21 to 471±40 meters. Treprostinil is another inhaled prostanoid with the advantage of reduced dosing frequency. HIV-PAH patients were included in the TRIUMPH study of treprostinil that demonstrated improved exercise tolerance when treprostinil was added to baseline oral therapy.<sup>50</sup> The number of HIV-PAH patients, however, was too small for meaningful analysis.

In our practice, we frequently initiate inhaled prostanoid therapy—usually treprostinil—in patients who remain symptomatic despite maximal oral therapy or as a first-line agent in patients with severe symptoms at the time of presentation. We avoid catheter-based therapies in this population given the challenges of managing the therapy, risk of infection, and risk of the catheter being used for illicit drug administration, which is common in our patient population.

## CONCLUSION

The number of individuals with HIV infection continues to increase, so that HIV-PAH may become one of the most common causes of PAH worldwide. Mortality from HIV-PAH without treatment is high; however, treatments for PAH are expensive and many require complex delivery systems and monitoring. Additional research is needed to

better understand why HIV-infected individuals develop PAH and to introduce new therapies that will be accessible to more patients.

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