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Antiretroviral Therapy in AIDS Patients with Tuberculosis

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Abstract

Tuberculosis associated with HIV infection continues to be an important problem throughout the world. Since the advent of HAART, the medication of HIV-infected patients who have to receive concomitant treatment for tuberculosis has become a difficult task. The two main problems faced by clinicians include the significant pharmacokinetic interactions between rifamycins, a cornerstone in antituberculosis therapy, and protease inhibitors and nonnucleoside reverse transcriptase inhibitors, which are essential components of antiretroviral combination regimens, as well as the best moment to initiate antiretroviral therapy in patients with tuberculosis. The therapy of choice for patients with no previous antiretroviral experience includes an antituberculous regimen with rifampin and an efavirenz-based antiretroviral regimen. No dose adjustments of these drugs seem to be necessary. Nevirapine can be an alternative to efavirenz in this situation. For patients who cannot take efavirenz, either due to resistance or intolerance, rifabutin and a boosted protease inhibitor can be coadministered, with the necessary dose adjustments. No definite recommendations can be given regarding the optimal timing of antiretroviral therapy, but a delay of two months after initiation of antituberculosis therapy would be advisable and seems to be safe in most patients. **(AIDS Reviews 2006;8:115-24)**
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Key words

HIV. Tuberculosis. Protease inhibitors. Nonnucleoside reverse transcriptase inhibitors. Rifampin. Rifabutin.

Introduction

Treatment of HIV-infection in the setting of active tuberculosis (TB) has been, and continues to be, a difficult task in clinical practice. In contrast to other opportunistic infections associated with HIV-infection, the advent of HAART has somehow complicated the management of HIV-associated TB. It is true that the incidence of TB has decreased in countries where antiretroviral (ARV) therapy is readily available and can be administered in routine clinical practice[1,2] but, for patients who develop TB at any time during the course of HIV infection, the administration of ARV therapy poses important challenges.

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Several important issues have emerged, mostly related to the potential interactions between some ARV drugs, protease inhibitors (PI) and nonnucleoside reverse transcriptase inhibitors (NNRTI), and the rifamycins[3-5]. Also important from a clinical point of view is the optimal timing of administration of HAART in relation with the anti-TB treatment[6,7]. It is clear that anti-TB drugs have to be administered immediately after the diagnosis is made, but there is debate on the best moment to initiate ARV therapy.

HIV-infected patients who develop TB usually have a low CD4+ count and have a clear indication for ARV therapy. However, simultaneous initiation of anti-TB and ARV therapy is highly problematic due to the high pill burden which complicates adherence, an increased risk of drug-related toxicity in the first months of therapy, the development of unfavorable drug interactions and, finally, an increased risk of appearance of the immune reconstitution inflammatory syndrome[8,9]. For this reason, several authors and guidelines have recommended withholding the initiation of HAART for the first two months of anti-TB therapy[8]. There is little information on

the risk that such a delay may entail in the clinical progression of patients with advanced immunodeficiency.

The aim of this review is to update the state-of-the-art concomitant treatment of TB and HIV infection. Before focusing on specific matters related to ARV treatment, we will briefly review certain general considerations of TB treatment in HIV-infected patients that should be taken into account.

Treatment of tuberculosis in HIV-infected patients

Anti-TB treatment should be started under founded clinical suspicion of TB or after visualization of acid-fast bacilli in stained clinical samples. Currently available data show that regimes recommended for HIV-negative individuals are equally effective in HIV-infected patients. Furthermore, no greater ratio of therapeutic failure or relapse has been documented, except in areas with a high incidence of TB disease in the general population where reinfection may be common.

Before the introduction of combined ARV treatment including NNRTI or PI, the recommended anti-TB regimen was isoniazid (300 mg/d) plus rifampin (600 mg/d) and pyrazinamide (25 mg/kg/d). If resistance to isoniazid is suspected, ethambutol (15 mg/kg/d) should be added[10]. In HIV-infected patients, rifapentine should not be given in the continuation phase of treatment. Intermittent regimens (two or three weekly doses) should be used cautiously, especially in highly immunosuppressed patients. No available data exist indicating that some forms of TB (disseminated, osteoarticular, meningitis) require routine addition of a fourth drug, although some authors recommend it.

With respect to the duration of anti-TB treatment, the optimal length is not known, but the recommendation is six to nine months with isoniazid and rifampin, plus pyrazinamide during the first two months. Probably in patients with a better immune situation, the regime could be shortened to six months. Studies that demonstrated superiority of a regimen of nine or twelve months were carried out in highly immunosuppressed patients. In cases where isoniazid or rifampin could not be given, treatment should be continued for 12-18 months.

Regarding toxicity, some studies have documented a high frequency of adverse events of anti-TB treatment in HIV-infected patients. However, in most cases such adverse events (hypertransaminasemia, cutaneous reactions) do not warrant the modification or interruption of the regimen. Moreover, some prospective studies have shown that the incidence of adverse events is not higher in HIV-infected subjects when compared to HIV-negative ones.

The risk of therapeutic failure, transmission of the infection to contacts, and development of resistance on due to the lack of adherence to anti-TB treatment, account for the need for guaranteeing an adequate compliance with the prescribed regimen. The implementation of directly observed therapy programs is recommended, although their universal introduction is probably more feasible in closed institutions such as penitentiary centers. Several studies have demonstrated the high efficacy of directly observed therapy programs in achieving the pursued objectives of adequate TB treatment[11].

Pharmacokinetic interactions between antituberculous and antiretroviral drugs

General considerations

The only anti-TB agents with significant drug interactions with ARV drugs are rifamycins (mainly rifampin, but also rifabutin), which are among first-line drugs used in the treatment of TB. These compounds are enzyme inducers, and one of the systems they interfere with is cytochrome P450 (CYP), specifically its CYP3A4 isoenzyme member, involved in the liver metabolism of two families of ARV drugs, NNRTI and PI. As a consequence of the CYP induction, the metabolism of NNRTI and PI is accelerated and their plasma levels lowered with the subsequent risk of lack of efficacy or resistance induction due to subtherapeutic levels. This interaction is significant and has led to the initial recommendation of avoiding the concomitant use of rifampin with NNRTI and PI[3,4]. The effect is slightly different for rifabutin as it induces CYP to a lesser extent, so the effects on the plasma levels of NNRTI and PI may not have clinical relevance.

On the other hand, rifamycins are also metabolized by means of CYP, which in turn is inhibited by PI, leading to increased plasma levels of the former and a correspondingly higher risk of toxicity. This effect is more acute for rifabutin, requiring proportional dose adjustment when coadministered with PI.

Given the different degrees of interaction with antituberculous drugs, the available data will be reviewed separately for the different families of ARV drugs.

Nucleoside reverse transcriptase inhibitors (NRTI)

In general, the interaction between NRTI and anti-TB drugs is scarce. Currently available NRTI do not have

important interactions with rifampin. Absorption of ethambutol can be reduced by didanosine and the administration of both drugs must be done separately. The new enteric-coated didanosine tablets are no longer buffered and probably do not interact with ethambutol or isoniazid[12].

For different reasons, isoniazid may have potential interactions with abacavir, didanosine, stavudine, and zalcitabine that have to be taken into account when these drugs have to be administered together. Increases in the area under the curve (AUC) of isoniazid and abacavir on account of the inhibition of alcohol-dehydrogenase and UDP-glucuronyltransferase enzymes can be observed[13]. It is recommended, as well, that isoniazid be administered at least two hours before didanosine. The coadministration of isoniazid and other drugs with a similar neurotoxic profile (zalcitabine, stavudine, didanosine) could increase the risk of peripheral neuropathy.

Because of its low pill burden and lack of significant interaction with rifampin or other anti-TB drugs, a fixed dose combination of abacavir/lamivudine/zidovudine has been proposed as an alternative therapy among patients coinfected with HIV and TB. In a clinical trial performed in Tanzania[14], treatment-naive patients (n = 70) with smear-positive pulmonary TB and documented HIV infection were randomized to receive early (two weeks) or delayed (eight weeks) abacavir/lamivudine/zidovudine relative to the start of anti-TB therapy[14]. This fixed-dose combination was tolerated in > 90% of subjects and significant increases in CD4+ cell counts were observed over 48 weeks[14]. Thus, the triple-nucleoside regimen of abacavir/lamivudine/zidovudine could be a reasonable option for HIV-infected patients who have TB. It must be taken into account, however, that current guidelines for initial treatment of HIV-infected patients consider the triple-NRTI regimen of abacavir/lamivudine/zidovudine as an alternative only when a preferred regimen cannot be used.

Protease inhibitors (boosted and unboosted with ritonavir)

As previously stated, rifamycins are associated with significant drug interactions with PI because of their effects as inducers of the hepatic cytochrome P450 (CYP3A4) enzyme system. Despite these interactions, a rifamycin should be included whenever possible in the TB treatment regimen in HIV-infected patients receiving ARV agents.

Table 1. Pharmacokinetic interactions between rifamycins and protease inhibitors

Effect of rifamycins on protease inhibitors plasma levels		
	Rifampin	**Rifabutin**
Indinavir	↓ 89%	↓ 32%
Nelfinavir	↓ 82%	↓ 32%
Ritonavir	↓ 35%	–
Saquinavir	↓ 80%	↓ 40%
Amprenavir	↓ 81%	↓ 14%
Atazanavir	↓ 80%	No change
Lopinavir/r	↓ 75%	↓ 15%
Effect of protease inhibitors on rifabutin plasma levels		
		Rifabutin
Indinavir		x 2
Nelfinavir		x 2
Ritonavir		x 4
Saquinavir		x 1.5
Amprenavir		x 2
Atazanavir		x 2.5
Lopinavir/r		x 3

Interaction with rifampin

Plasma drug levels of PI are significantly reduced in the presence of rifampin, and concomitant therapy with PI and rifampin is generally not recommended. Since the beginning of the HAART era it was clear that unboosted PI could not be coadministered with rifampin due to the pharmacokinetic interaction (Tables 1 and 2). Only ritonavir could be administered with rifampin given the smaller decrease of ritonavir plasma levels. A small clinical trial showed good clinical, immunologic, and virologic outcome in patients treated with an anti-TB regimen containing rifampin and a ritonavir-containing ARV therapy[15]. The significant pill burden and the toxicity associated with full-dose ritonavir makes this possibility impractical nowadays.

The high plasma levels that are achieved after boosting most PI with small doses of ritonavir could sustain therapeutic levels of the drug even after the interaction with rifampin. This hypothesis, however, was proved to be erroneous. Pharmacokinetic studies performed to

Table 2. Coadministration of rifamycins and antiretroviral drugs for the concomitant treatment of tuberculosis and HIV-infection

Drug	Administration with rifabutin	Administration with rifampin	Comments
Nonnucleoside reverse transcriptase inhibitors			
Delavirdine	No	No	
Nevirapine	Possibly	Yes	Pharmacokinetic data and observational studies No adjustment dose is needed with rifampin
Efavirenz	Possibly	Yes	Pharmacokinetic data and clinical trials No adjustment dose is needed with rifampin Increase the rifabutin dose
Protease inhibitors			
Saquinavir/ritonavir	Yes	No	Increased toxicity with rifampin (clinical data) Decrease the rifabutin dose to 150 mg/d x 2-3/week
Ritonavir	Yes	Yes	Decrease the rifabutin dose to 150 mg/d No need of dose adjustment with rifampin (clinical data)
Indinavir	Yes	No	Decrease the rifabutin dose to 150 mg/d (clinical data) Increase indinavir dose to 1000 mg/8 h
Nelfinavir	Yes	No	Decrease the rifabutin dose to 150 mg/d (clinical data) Increase nelfinavir dose to 1000 mg/8 h
Fosamprenavir/ritonavir	Yes	No	Decrease the rifabutin dose to 150 mg/d (only PK data)
Atazanavir/ritonavir	Yes	No	Decrease the rifabutin dose to 150 mg thrice weekly (only PK data)
Lopinavir/ritonavir	Yes	No	Clinical studies on the coadministration with rifampin are ongoing Decrease the rifabutin dose to 150 mg/d (only PK data)

PK: Pharmacokinetic.

date with ritonavir-boosted PI have shown that no drug in the family (indinavir, saquinavir, lopinavir, fosamprenavir, atazanavir, tipranavir) can be coadministered with rifampin, and the combination should be avoided[16-19]. In addition, some of the combinations are more toxic than expected, as is the case for saquinavir/ritonavir or lopinavir/ritonavir.

The coadministration of lopinavir/ritonavir and rifampin is still being explored. There is some limited experience in healthy volunteers (n = 22) using rifampin (600 mg/24h x 10 days) with lopinavir/ritonavir. At the standard dose of lopinavir/ritonavir (three capsules/12h) a 75% decrease in the AUC of lopinavir was observed. The administration of higher doses of ritonavir (additional 300 mg 2/d; i.e. lopinavir/ritonavir 400/400 mg/12h) or of lopinavir/ritonavir (800/200 mg/12h) offset the rifampin-inducing activity of lopinavir[19]. However, minimum concentration (C_{min}) of lopinavir in this study was not equivalent to that of standard of lopinavir/ritonavir dosing without rifampin, suggesting that an adjusted-dose lopinavir/ritonavir regimen may, in some cases, not be capable of completely compensating for the accelerated metabolism of lopinavir by the latter. Of note, 28% of subjects discontinued because of increases in liver function tests. After this study, it was strongly recommended that when rifampin and lopinavir/ritonavir are coadministered, drug therapeutic measurements and a close monitoring of liver function tests be performed[19]. The safety and efficacy of this combination is still under evaluation.

Interaction with rifabutin

As an alternative to rifampin, rifabutin is a weaker inducer of cytochrome P450 (CYP3A4). According to the results of pharmacokinetic studies and limited clinical experience, rifabutin can be coadministered with PI, although dosage adjustments have to be considered (Tables 1 and 2). The interaction between these drugs has been extensively evaluated in both unboosted and boosted PI[20-28].

Coadministration of rifabutin and indinavir induces an increase of 204% in the AUC of rifabutin, and a decrease of 32% in the AUC of indinavir[20]. These changes are explained by the inhibitor effect of indinavir and the inducer action of rifabutin over the CYP3A4. Rifabutin-induced toxicity should be monitored. The clinical experience with this combination is limited but favorable[21]. The appropriate dose adjustment is as follows: indinavir 1000 mg/8h + rifabutin 150 mg/d or 300 mg x 3/week[20,21].

Coadministration of rifabutin and nelfinavir creates a 32% decrease in the AUC of nelfinavir, and a 207% increase in the AUC of rifabutin[22]. These changes are explained by the inhibitor effect of nelfinavir and the inducer action of rifabutin over the CYP3A4. The appropriate dose adjustment is as follows: nelfinavir 1000 mg/8h + rifabutin 150 mg/d or 300 mg x 3/week.

Coadministration of saquinavir (hard-gel or soft-gel capsules) and rifabutin is contraindicated because the therapeutic efficacy of saquinavir is reduced[23,24]. Rifabutin may be used with saquinavir only if it is boosted with ritonavir.

Ritonavir increases the AUC of rifabutin fourfold (from 1938 to 8362 ng/h/ml) and its metabolite desacetyl-rifabutin 35-fold (from 165 to 6289 ng/h/ml)[12]. The sum of the mean AUC of rifabutin and its metabolite increased nearly sevenfold. Therefore, it has been recommended that the dosage of rifabutin be reduced to 150 mg every other day or 150 mg x 3/week.

The coadministration of fosamprenavir/ritonavir and rifabutin requires reducing rifabutin to 150 mg/48h. In an open-label, randomized, cross-over study performed in healthy volunteers (n = 15), the potential interaction between rifabutin and fosamprenavir/ritonavir was evaluated in a steady state phase[25]. The subjects received rifabutin 300 mg/24h x 13 days, followed by rifabutin 150 mg/48h + fosamprenavir/ritonavir 700/100 mg/12h x 14 days. The AUC and maximum concentration (C_{max}) of rifabutin were similar in both study periods. The AUC of 25-O-desacetyl-rifabutin, a metabolite of rifabutin, increased tenfold in the presence of fosamprenavir/ritonavir. However this product represents a small amount of total rifabutin[25].

In one study performed in healthy volunteers (n = 14), lopinavir/ritonavir (400/100 mg/12h x 10 days) increased threefold the AUC of rifabutin (300 mg/24h x 10 days) and 5.7-fold the AUC of rifabutin plus its metabolites (25-O-desacetyl-rifabutin)[26]. Rifabutin (150 mg/24h x 10 days) did not alter the pharmacokinetic parameters of lopinavir/ritonavir [20]. Rifabutin dose must be decreased to 150 mg every other day or 150 mg x 3/week when coadministered with lopinavir/ritonavir.

When rifabutin (150 mg/24h) was coadministered with atazanavir (dosage: 400 mg/24h) the AUC of atazanavir did not change, but it was increased two- and threefold when doses were atazanavir 600 mg/24h or atazanavir/ritonavir 400/100 mg/24h, respectively[22]. The AUC of rifabutin was similar in the three groups, but 2.5-fold greater than that obtained with the standard dose of rifabutin (300 mg/24h). This suggests that rifabutin must be reduced to less than 150 mg/24h when coadministered with atazanavir, with no variations in the atazanavir dose[27].

The coadministration of tipranavir/ritonavir and rifabutin was evaluated in a group of healthy volunteers (n = 24) who received rifabutin (single dose of 150 mg) or in combination with tipranavir/ritonavir 500/200 mg/12h in different multiple doses[28]. Rifabutin increased the C_{min} of tipranavir by 16%, but no significant changes in AUC or C_{max} were observed. However, the AUC of rifabutin increased threefold and the C_{max} 70%. Significant increases in its active metabolite (25-O-desacetyl-rifabutin) were also observed (AUC by 20-fold and C_{max} threefold). Four subjects abandoned the study due to elevations in the liver function tests (n = 3) or severe rash[28].

Nonnucleoside reverse transcriptase inhibitors (NNRTI) (Tables 2 and 3)

Nevirapine

According to different pharmacokinetic studies and reports, the administration of rifampin results in a decrease in the plasma levels of nevirapine of 37-58%[29]. However, nevirapine is characterized by a high therapeutic index. With the usual dose of 400 mg/d, the C_{min} in the steady state is 4.5 ± 1.9 µg/ml, high above the usual IC_{50} for the drug (0.0025-0.025 µg/ml)[30]. Thus, sufficient drug levels to inhibit the virus are present in plasma even after the most significant interaction found with rifampin, although some authors have recommen-

Table 3. Pharmacokinetic interactions between rifamycins and nonnucleoside reverse transcriptase inhibitors

	Rifampin	Rifabutin
Nevirapine	↓ 37%	No change
Efavirenz	↓ 26%	↓ 16%

ded close monitoring of nevirapine plasma concentration when the two drugs are given concomitantly[31]. Moreover, two clinical studies have shown that the interaction between rifampin and nevirapine led to a reduction of about 20% in nevirapine plasma levels, with no significant impact on the virologic effect of the drug[32,33].

The efficacy and safety of the coadministration of nevirapine and rifampin was evaluated in an observational study[34]. In this study, 32 patients received anti-TB therapy consisting of rifampin 600 mg/d for nine months (in all cases in combination with isoniazid plus pyrazinamide during the first two months) and an ARV regimen that included nevirapine 400 mg/d (in all cases in combination with two NRTI). Special attention was paid to a potentially increased risk of toxicity, but the development of liver toxicity or skin rash was not higher for the combination than when the drugs were given separately. All the patients were clinically and microbiologically cured of their TB at the end of therapy, and no relapses were observed after a median follow-up of six months. HIV-RNA decreased a median of 4.1 log copies/ml (from 4.4 to < 2.3 log), with 74% of the patients reaching undetectable HIV-RNA. The CD4+ count increased from 121 to 284 cells/mm^3, with a median increase of 116 cells/mm^3.

Although a prospective clinical trial may be warranted, according to data available to date nevirapine can be included in an ARV regimen to treat HIV-infected patients newly diagnosed with TB who receive rifampin (Table 2).

Efavirenz

Efavirenz is the ARV drug most extensively evaluated in association with anti-TB drugs. Significant pharmacokinetic and clinical information has been generated with both rifampin and rifabutin that is presented separately.

Interaction with rifampin

The first data on the pharmacokinetic interactions between efavirenz and rifampin were presented in 1998[35]. Researchers from DuPont Pharmaceuticals presented a two-week study carried out in 12 healthy volunteers. Coadministration of rifampin 600 mg and efavirenz 600 mg, both in a once-daily regimen, showed a significant reduction of efavirenz peak concentration (from 15.1 to 11.7 mM) and AUC (from 224 to 151 μM.h) compared to efavirenz administered alone. The authors found this reduction significant and proposed adjusting the efavirenz dose when administered with rifampin. It was also shown that rifampin plasma levels were not modified when given together with efavirenz.

The first study to evaluate the pharmacokinetic interaction between efavirenz and rifampin in HIV-infected patients with TB was carried out in Spain by López Cortés, et al.[36]. This work confirmed a significant reduction in efavirenz plasma levels (mean reduction > 20% for trough and peak values and AUC) and the absence of effect of efavirenz on rifampin plasma levels. The main contribution of this study was, however, the finding that efavirenz pharmacokinetic parameters correlated with the dose per weight administered. In patients < 50 kg body weight (BW) the usual dose of efavirenz 600 mg reaches adequate plasma levels despite the coadministration of rifampin, but in patients > 50 kg BW only doses of efavirenz 800 mg/d would guarantee plasma levels similar to those obtained when administering efavirenz without rifampin. According to these results the authors recommended increasing the efavirenz dose to 800 mg/d when administered with rifampin. This recommendation had a great impact on clinical practice and has been incorporated in most guidelines.

Likewise, it has motivated further studies regarding the evaluation of efavirenz 800 mg/d with concomitant anti-TB treatment. In this regard, a study carried out in Thailand compared 600 and 800 mg of efavirenz, combined with stavudine and lamivudine, given to two groups of 42 patients with TB receiving rifampin[37]. No differences were found in the median efavirenz plasma levels of both groups, nor in the percentage of either patients with subtherapeutic levels (defined as < 1 mg/l) or with levels associated with greater toxicity (> 4 mg/l). As an added clinical value they found that at 24 weeks of follow-up the time to virologic success was similar in both therapeutic groups. In their opinion efavirenz 600 mg was enough to treat Thai patients receiving concomitant rifampin, although they draw attention to the fact that the same recommendation could be of no value for patients with higher BW.

A second study evaluating the administration of efavirenz 800 mg was done in nine English patients, all of

them with BW > 50 kg[38]. Seven of these patients developed serious central nervous system toxicity associated to high levels of efavirenz (median > 11 g/dl). Consequently the authors question the convenience of initiating treatment with high doses of efavirenz in any patient and they propose drug monitoring in this setting. They also suggest that given that all patients but one that developed toxicity were of African origin a polymorphism in CYP2B6 could be responsible for the event.

In summary, the pharmacokinetic studies done with efavirenz and rifampin allow the conclusion that both drugs could clearly be coadministered in the concomitant treatment of HIV infection and TB. The 600 mg dose is adequate for people with a low BW (< 50 kg) and it seems enough for patients with BW > 50 kg. The excess of toxicity observed with the 800 mg dose in one of the studies would argue against the routine use of the high dose, even in patients with BW > 50 kg.

Efficacy and toxicity of the efavirenz and rifampin combination

The first report that provided data on this matter was an observational study carried out in India[39]. The authors compared the clinical and immunologic evolution as well as toxicity in two groups of patients: those receiving efavirenz 600 mg/d plus rifampin for TB treatment (n = 126) *versus* patients treated without rifampin with other opportunistic infections (n = 129). No data relative to the patients' BW are given, nor is the virologic response evaluated. The CD4+ increase after nine months of treatment was similar for both groups: 275 and 295 cells/mm^3, respectively. The central nervous system alterations were more frequent in the group not taking rifampin (20 *vs.* 13%), although this difference was not statistically significant. Hepatic toxicity was more frequent in the group with concomitant TB treatment.

Later, a Brazilian group (Pedral-Sampaio, et al.) published an open, single-arm study evaluating the coadministration of efavirenz 600 mg/d with a standard anti-TB treatment (isoniazid, rifampin and pyrazinamide)[40]. Forty-nine patients (mean BW 51 kg; baseline viral load 5.6 logs; CD4+ count 101 cells/mm^3) were included and followed up for at least 24 months. At the end of the follow-up the mean viral load was 1.4 log and the CD4+ count 326 cells/mm^3. Based on their experience, the authors recommend the 600 mg/d of efavirenz dose for the simultaneous administration with rifampin, considering that the 800 mg dose does not provide extra efficacy and could add toxicity.

The last study analyzing the evolution of patients concomitantly treated with efavirenz and rifampin is a continuation of the Thai study comparing 600-800 mg of efavirenz, the pharmacokinetic results of which had been previously published. On this occasion they showed the virologic and immunologic evolution at 48 weeks of treatment[41]. Undetectable viral load was achieved by 91 and 87% of patients receiving 600 and 800 mg of efavirenz, respectively. Immune restoration was also identical for both treatment groups (p = 0.93) and no differences between groups with respect to toxicity were observed. Once again, the researchers were in favor of the 600 mg dose of efavirenz for the treatment of patients receiving concomitant rifampin, although they were cautious with the extrapolation of their conclusion to populations with higher BW.

The available clinical studies confirm the efficacy and safety of the coadministration of efavirenz and rifampin for the concomitant treatment of HIV infection and TB. The results seem to support unanimously the 600 mg dose in this context. It must be taken into account that most studies (three out of four) are observational and non-comparative, and the majority (three out of four, including the only randomized one) have been carried out in patients with low BW. Taking together the pharmacokinetic and clinical data it seems highly probable that efavirenz 600 mg would be enough for its administration together with rifampin.

Interaction with rifabutin

Initial studies of the interaction between efavirenz and rifabutin showed the absence of a significant effect. Thus, no efavirenz dose adjustment is required. Since efavirenz could act as enzymatic inductor of CYP it is recommended to increase the rifabutin dose to 450-600 mg. A study done in 20 patients treated with two day per week regimes confirmed the lack of pharmacokinetic interaction significantly affecting efavirenz levels. The 300 mg dose of rifabutin did not seem to reach the expected pharmacokinetic range, endorsing the need to increase its administration to 450 mg[42]. The results have been confirmed in a more recent study in which adequate plasma levels were obtained when rifabutin was given at a dose of 600 mg in combination with efavirenz 600 mg[43].

Studies showing clinical efficacy and toxicity of the concomitant administration of efavirenz and rifamycins are scarce. The contribution of some of them is limited to the valuable aforementioned pharmacokinetic data, and only a few of them have reported the clinical evolu-

tion of the patients. In the above-mentioned studies the patient follow-up was very limited, but during this period the CD4+ count increase and the viral load decrease were both significant[42,43].

Other available data belong to a prospective study evaluating the combination of ARV drugs with rifabutin[44]. Among 169 patients included, 59 received a regimen containing efavirenz. Although specific data relative to this subgroup of patients are not stated, the significant increase in CD4+ counts and decrease in viral load, and especially the decreased mortality of patients receiving rifabutin for the TB treatment while having to take ARV drugs, is highlighted.

Antituberculous treatment recommendations in HIV-infected patients

Due to the complexity of the described interactions, and considering the lack of clinical trial data for most combinations, recommendations and guidelines have been issued on the combination of anti-TB and ARV drugs[45-47]. Taking into account such recommendations together with the pharmacokinetic and clinical data reviewed, the following anti-TB and ARV regimens could be considered:

a) Regimens including rifampin.
- Anti-TB drugs and doses: isoniazid, rifampin, pyrazinamide ± ethambutol, at the usual dose. These could also be administered two or three days per week at the adequate dose.
- ARV drugs:
  - NRTI: any of them at the usual dose.
  - NNRTI: efavirenz (600 mg/d) is the first-choice drug, but nevirapine (200 mg/12 h) could be used as an alternative[33,34,36,40,47].
  - PI: only ritonavir can be coadministered with rifampin[4,15].

A three-drug regimen consisting of two NRTI plus an NNRTI is the preferred option. A combination of three NRTI is an attractive alternative, given the lack of interactions with the rifamycins, but the lower efficacy of these regimens precludes its use in patients with TB.

b) Regimens without rifampin.
- Including rifabutin:
  - Anti-TB drugs and doses: isoniazid, rifabutin, pyrazinamide ± ethambutol. Rifabutin dose should be adjusted (reduced if combined with PI, increased if combined with efavirenz).
  - ARV drugs:
    NRTI: any of them.
    NNRTI: nevirapine and efavirenz.
    PI: any of them.
- No rifamycins used:
  - Anti-TB drugs and doses: isoniazid, pyrazinamide, ethambutol ± streptomycin, at the usual doses.
  - ARV drugs: any of them.

Optimal timing of administration of ARV therapy in patients with tuberculosis

The best moment to initiate ARV therapy in HIV-infected patients with TB is certainly among the most frequently discussed issues, and no satisfactory clinical evidence has been provided so far for solving this question.

Treatments for TB and for HIV infection share some disadvantageous characteristics. Both are complex therapies that include combinations of at least three drugs with an important pill burden that can be associated with suboptimal compliance. Frequent adverse events are also common with both treatments. A number of these adverse events (mainly rash and liver toxicity) can be caused both by anti-HIV and anti-TB therapies. In addition, the concomitant administration of anti-TB and ARV therapies is associated with a high risk of development of the immune reconstitution inflammatory syndrome (IRIS). The administration of HAART within the first two months of initiation of anti-TB treatment has been found to be an independent predictor of IRIS in HIV-infected patients with TB[9]. Taken together, these arguments have led to the current clinical practice of delaying ARV therapy as much as possible in patients who initiate treatment for TB. Fear of immunologic or even clinical worsening due to the delay in administering ARV therapy counterbalance this approach in patients with severe immunosuppression.

No clinical study has been published so far that directly evaluates the best strategy. In a retrospective, multicenter study we showed that delaying the initiation of ARV therapy for two months was not associated with an increased risk of clinical progression of HIV infection. Indeed, deferred ARV therapy was not a predictor of clinical progression, even in patients with a low CD4+ cell count. Patients with a CD4+ cell count > 200 at the moment of TB diagnosis could delay ARV therapy even until anti-TB therapy was completed. In a multivariate analysis, clinical progression and death in HIV-patients with TB were associated with the degree of immunosuppression but not with the timing of administration of ARV drugs[48].

Despite the lack of clinical data, some recommendations can be made. When possible, therapy for HIV should be given concomitantly with anti-TB treatment. Only those with no or mild immunosuppression (i.e. CD4+ > 400 cells/mm^3) could be maintained off ARV therapy during the full course of treatment for TB. On the other hand, delaying ARV drugs for a reasonable period of time (two months) in patients who have to initiate therapy will not place the patient at increased risk of progression and may have substantial advantages.

Clinical decisions, however, must be guided by the particular situation of a given patient, especially in those most severely immunosuppressed. Some authorities have recommended that the delay in starting therapy should be proportional to the CD4+ count, suggesting no delay or a delay of up to two weeks in patients with CD4+ < 100 cells/mm^3, one month for those with CD4+ 100-200 cells/mm^3, and two months only for those with CD4+ > 200 cells/mm^3.

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