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Tenofovir DF/emtricitabine and efavirenz combination therapy for HIV infection in patients treated for tuberculosis: the ANRS 129 BKVIR trial

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Background: HIV-infected patients with TB need simplified, effective and well-tolerated antiretroviral regimens.

Methods: The French ANRS 129 BKVIR open trial evaluated the once-daily tenofovir DF/emtricitabine and efavirenz combination, started within 12 weeks after TB treatment initiation, in antiretroviral-naive HIV-1-infected patients. Success was defined as an HIV-1 RNA <50 copies/mL and TB cure at 48 weeks.

Results: TB was confirmed microbiologically (90%) or histologically (10%) in 69 patients (71% male; median age 43 years; 54% born in Africa). The median time between TB treatment initiation and antiretroviral therapy was 8 weeks (range 1–22 weeks). At baseline, median HIV-1 RNA was 5.4 $\log_{10}$ copies/mL and median CD4 cell count 74 cells/mm^3. In the ITT analysis, combined success at week 48 was achieved in 57/69 patients (83%, 95% CI 74–92). Twelve patients did not achieve virological success, and TB was not cured in one of them. Among the 47 patients who fully adhered to the strategy, the success rate was 96% (95% CI 90–100) and was not affected by low rifampicin and isoniazid serum concentrations. Forty-nine serious adverse events were reported in 31 patients (45%), and 11 led to antiretroviral drug interruption. All adverse events resolved. The immune reconstitution inflammatory syndrome occurred in 23 patients (33%, 95% CI 22–44), and was associated with a low baseline BMI ($P=0.03$) and a low haemoglobin level ($P=0.02$).

Conclusion: These results support the use of tenofovir DF/emtricitabine and efavirenz combination therapy for HIV infection in patients with TB.

Introduction

Co-infection with *Mycobacterium tuberculosis* and HIV is a major public health problem worldwide,[1] and TB is the most common AIDS-defining illness in many countries. An estimated 1.37 million new cases of TB occur each year in HIV-infected patients, mostly in Africa, and 25% of TB-related deaths involve HIV-infected patients. In addition, there is very limited decrease in TB incidence among patients having CD4 <50 cells/mm^3 on a combination ART (cART) regimen.[2] Numerous pharmacokinetic interactions and

additive toxicities have been reported between TB drugs and cART[3–6] and the risk of an immune reconstitution inflammatory syndrome (IRIS) has been well documented.[7,8] Finally, the need for close long-term adherence to both cART and TB therapy calls for simplified cART regimens.[9,10]

The ANRS 129 BKVIR non-comparative pilot trial was designed to evaluate the efficacy and safety of once-daily tenofovir DF/emtricitabine and efavirenz, prescribed as a first-line combination <12 weeks after starting antituberculous drugs in patients co-infected with HIV and TB. This trial also assessed rifampicin and isoniazid pharmacokinetics and the potential impact on TB outcome.

Patients and methods

Study design and population

The ANRS 129 BKVIR study was a multicentre, non-comparative, nationwide trial. HIV-1-infected, antiretroviral-naive adults were eligible if they had confirmed TB and had been treated with antituberculous drugs for <12 weeks before inclusion. Patients had to be affiliated to the healthcare system and were not eligible if they had HIV-2 or group O infection or active cancer, were pregnant or breastfeeding, or had creatinine clearance <60 mL/min, haemoglobin <8 g/dL, neutrophils <750/mm^3, platelets <50000/mm^3, or any liver enzyme value >3-fold higher than the upper normal limit.

All the patients gave their written informed consent and the protocol was approved by an ethics committee (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale Paris Necker, France, number 05-06-09) and by the Agence Française de Sécurité Sanitaire des Produits de Santé. The trial conformed to the Declaration of Helsinki. This trial is registered with ClinicalTrials.gov (identifier: NCT00115609).

Study treatments

At week 0, all the patients started a once-daily cART regimen combining tenofovir DF (300 mg/day)/emtricitabine (200 mg/day) and efavirenz (800 mg/day if also treated with rifampicin, otherwise 600 mg/day). Antitubercular treatment was managed by the study investigators according to the standard of care (intensive phase followed by a continuation phase with duration depending on TB localization).

Primary and secondary outcome measures

The primary endpoint was a combination of HIV-1 RNA <50 copies/mL and TB cure at week 48 ('combined success'). The choice of a combined outcome was based on a real-life approach, taking into account difficulties of compliance to multiple drugs. TB was considered 'probably cured' if all TB-attributed signs resolved and 'certainly cured' when, in addition, at least two sputum smears were negative (if TB had been diagnosed microscopically) or if culture was negative (in patients with positive culture at baseline). Secondary endpoints included changes in the plasma HIV-1 RNA level and CD4+ T cell count, changes in the HIV-1 DNA level, TB cure at week 48, adherence to treatment, pharmacokinetics of TB drugs, safety and IRIS.

Local laboratories measured HIV-1 RNA and CD4+ T cells at the screening visit, baseline (week 0) and weeks 4, 8, 12, 24, 36 and 48. HIV-1 DNA was measured in peripheral blood mononuclear cells at weeks 0, 24 and 48.[11] Drug susceptibility testing (DST) was performed in each centre by using the proportion method, on either solid (Löwenstein–Jensen) or liquid (MGIT) medium. DST quality was assessed by an external quality assessment programme using proficiency testing organized by the National Reference Laboratory. The average agreement rates for isoniazid and rifampicin DST were >90%.

Efavirenz plasma concentrations were measured at week 2 in patients treated with rifampicin. Concentrations were considered sub-therapeutic if <1 mg/L and supra-therapeutic if >4 mg/L. Rifampicin and isoniazid trough and 2 h concentrations were measured at weeks 2, 8, 12 and 24 by liquid chromatography.[12] Low 2 h concentrations were defined as <8 mg/L for rifampicin and <3 mg/L for isoniazid, and very low 2 h concentrations as <4 mg/L for rifampicin and <2 mg/L for isoniazid.[13,14]

TB was evaluated by the investigators according to national guidelines. The severity of clinical and laboratory abnormalities was graded with the Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (ANRS) scale.

Events Review Committee

An Events Review Committee (ERC) reviewed TB diagnoses and cures, as well as adverse events related or not related to the study drugs. IRIS cases were reviewed and classified.[15,16] IRIS was also classified as definite, probable or ruled out.

Statistical analysis

Based on the literature available at the set-up of the trial, the success rate at week 48 was expected to be at least 55%. One hundred patients were required to ensure that the precision of the estimated success rate (two-sided 95% CI) would be at least 10%. The primary analysis was conducted on an ITT basis and included all enrolled patients, regardless of whether or not the study treatment was prematurely discontinued. Missing HIV-1 RNA values were classified as treatment failures in the primary efficacy analysis. The primary endpoint was also analysed separately among patients who fully adhered to the trial strategy and among patients who did not comply with the therapeutic strategy.

Differences in continuous variables were assessed using the Wilcoxon rank-sum test. The cumulative incidence of events was estimated using the Kaplan–Meier method, from week 0 onwards.

Risk factors for IRIS were identified by logistic regression. Baseline characteristics with P values of $\leq$0.25 in univariable analysis were included in the multivariable model. Variables retained in the multivariable model were those associated with IRIS at a P value of $\leq$0.05.

All statistical analyses were performed with SAS software version 9.1.3 service pack 2 (SAS institute Inc., Cary, NC, USA). Drug concentrations were analysed with JMP version 5.0.1.2 (SAS institute Inc., Cary, NC, USA).

Results

From December 2005 to December 2008, 85 patients were screened, 70 were enrolled and 69 were analysed (one patient had no French healthcare coverage). Despite extension of the inclusion period, recruitment of the 100 participants needed was not achieved because of the lack of healthcare coverage in migrants with TB in France.

Four patients did not complete follow-up (one patient developed lymphoma and three were lost to follow-up) (Figure 1).

Baseline characteristics at cART initiation

The time between diagnosis of HIV infection and cART initiation was <3 months in 40 patients (58%). TB and HIV infections were diagnosed simultaneously in 71% of cases.

Extrapulmonary TB was found in 64 patients (93%). Samples were acid-fast bacilli-positive in 48 patients (70%). TB was confirmed by culture in 60 patients (87%), histology (tuberculous

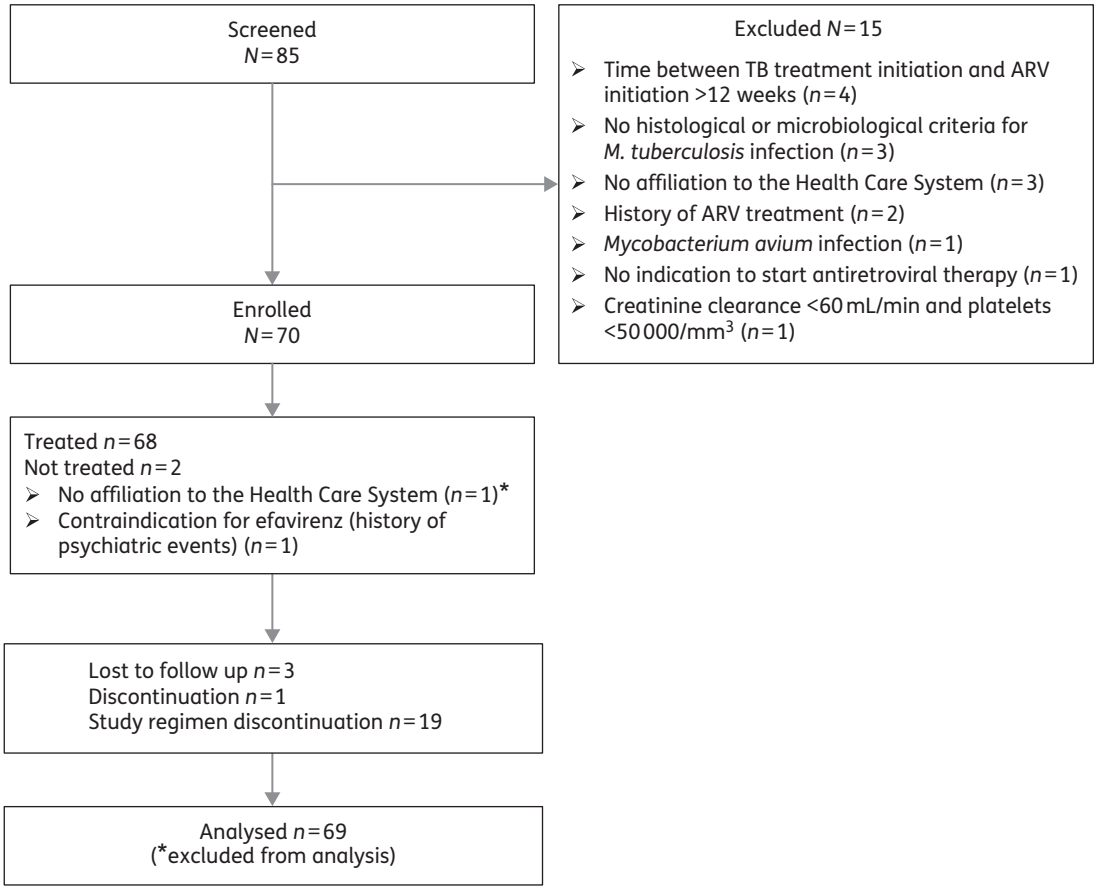

Figure 1. Trial flow chart, ANRS 129 BKVIR trial, France, 2005–08.

granuloma with or without necrosis) in 7 patients (10%) and other techniques in 2 patients (3%). The median baseline CD4+ T cell count was 159 (IQR 137–223) and 70 cells/mm^3 (IQR 20–142) in patients with isolated pulmonary TB and patients with other TB sites, respectively (Table 1).

Sixty-two patients (90%) received rifampicin and 7 received other antituberculous drugs (3 because of rifampicin resistance and 4 for other reasons).

Fifty-six (81%) received efavirenz at 800 mg/day and 11 efavirenz at 600 mg/day (most of them not receiving rifampicin); 2 patients did not receive efavirenz (1 lost to follow-up and 1 treated with lopinavir because efavirenz was contraindicated).

Main outcomes

In the ITT analysis, combined success (HIV-1 RNA <50 copies/mL and TB cure at week 48) was achieved in 57/69 patients (83%, 95% CI 74–92). TB cure at week 48 was considered definite in 49 patients (71%, 95% CI 60–82) and probable in 19 patients. The median duration of TB treatment was 11 months (IQR 9–12). Fifty-seven patients (83%) took TB treatment continuously, while 12 patients interrupted at least one drug. Combined success was obtained in 8 of 9 patients with TB drug resistance. The remaining patient was lost to follow-up at week 48 but was considered cured at the last visit. Among the 47 patients who fully adhered to the trial strategy, combined success was achieved in 45 cases (96%, 95% CI 90–100). Twenty-two patients did not comply perfectly with the strategy, because of adverse events related to the study drugs (n=12), virological failure/resistance (n=5), voluntary withdrawal (n=3) or other causes (n=2).

The reasons for failure were HIV-1 RNA >50 copies/mL at week 48 in 12 patients (17%) and TB treatment failure in 1 of them (this patient was lost to follow-up at week 0). Six patients had HIV-1 RNA >400 copies/mL at the last visit, including three patients who discontinued cART.

Virological outcome

Median HIV-1 RNA load fell from 5.4 to 2.6 $\log_{10}$ copies/mL between weeks 0 and 4, and by a median of 3.5 $\log_{10}$ copies/mL between weeks 0 and 48 (IQR −4.2 to −2.9). Plasma HIV-1 RNA was <50 copies/mL in 53%, 79% and 88% of patients at weeks 12, 24 and 48, respectively, with no difference between the two efavirenz dosages (Figure 2a). One virological failure due to acquired resistance to lamivudine and efavirenz was observed. Median HIV-1 DNA values fell from 3.3 to 2.7 $\log_{10}$ copies/mL between weeks 0 and 48, with a median decrease of 0.6 $\log_{10}$ copies/mL (IQR −1.0 to −0.3).

The median increase in the CD4+ T cell count between weeks 0 and 48 was 150 cells/mm^3 (IQR 94–289) (Figure 2b) and was similar in patients with isolated pulmonary TB and those with TB at other sites.

Table 1. Baseline demographic and clinical characteristics of the 69 patients enrolled in the ANRS 129 BKVIR trial, France, 2005–2008

Baseline demographic and clinical data	Values
Median age, years (IQR)	43 (34–52)
Males, *n* (%)	49 (71)
Birthplace, *n* (%)	
sub-Saharan Africa	37 (54)
France	16 (23)
other countries	16 (23)
Time between arrival in France and TB diagnosis in years ($N=53$), median (IQR)	8 (4–19)
Mode of HIV infection, *n* (%)	
heterosexual	52 (75)
homo/bisexual male	11 (16)
other	6 (9)
HBV serology, *n* (%) ($N=66$)	
HBsAg positive	7 (11)
anti-HBc-positive and/or anti-HBs positive	37 (56)
negative	22 (33)
HCV serology, *n* (%) ($N=68$)	
positive	5 (7)
negative	63 (93)
Body weight, kg, median (IQR)	63 (56–73)
BMI, kg/m^2, median (IQR)	21.5 (19.6–24.3)
CD4 T cells/mm^3, median (IQR)	74 (23–159)
CD4 T cells (%), median (IQR)	8 (3–14)
CD8 T cells/mm^3, median (IQR)	555 (399–910)
CD8 T cells (%), median (IQR)	65 (57–76)
Ratio CD4 T cells/CD8 T cells, median (IQR)	0.11 (0.05–0.22)
HIV-1 RNA, $\log_{10}$ copies/mL, median (IQR)	5.4 (4.9–5.9)
TB localization, *n* (%)	
isolated pulmonary	5 (7)
pulmonary and extrapulmonary	52 (76)
isolated extrapulmonary	12 (17)
Result of AFB detection for pulmonary TB ($N=57$), *n* (%)	
positive	34 (60)
positive culture	33 (97)
negative	23 (40)
positive culture	17 (74)
Elements of diagnosis, *n* (%)	
positive culture	60 (87)
histology	7 (10)
other	2 (3)[a]
TB drug resistance, $n=60$ (%)	
no resistance	51 (85)
streptomycin resistance	4 (7)
isoniazid + rifampicin resistance	2 (3)
isoniazid resistance	2 (3)
rifampicin resistance	1 (2)

AFB, acid-fast bacilli; HBV, hepatitis B virus; HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen; HBc, hepatitis B core.
[a]Both patients had a microscopically positive sputum smear plus positive *M. tuberculosis* PCR in one case and a positive Quantiferon test in the other case.

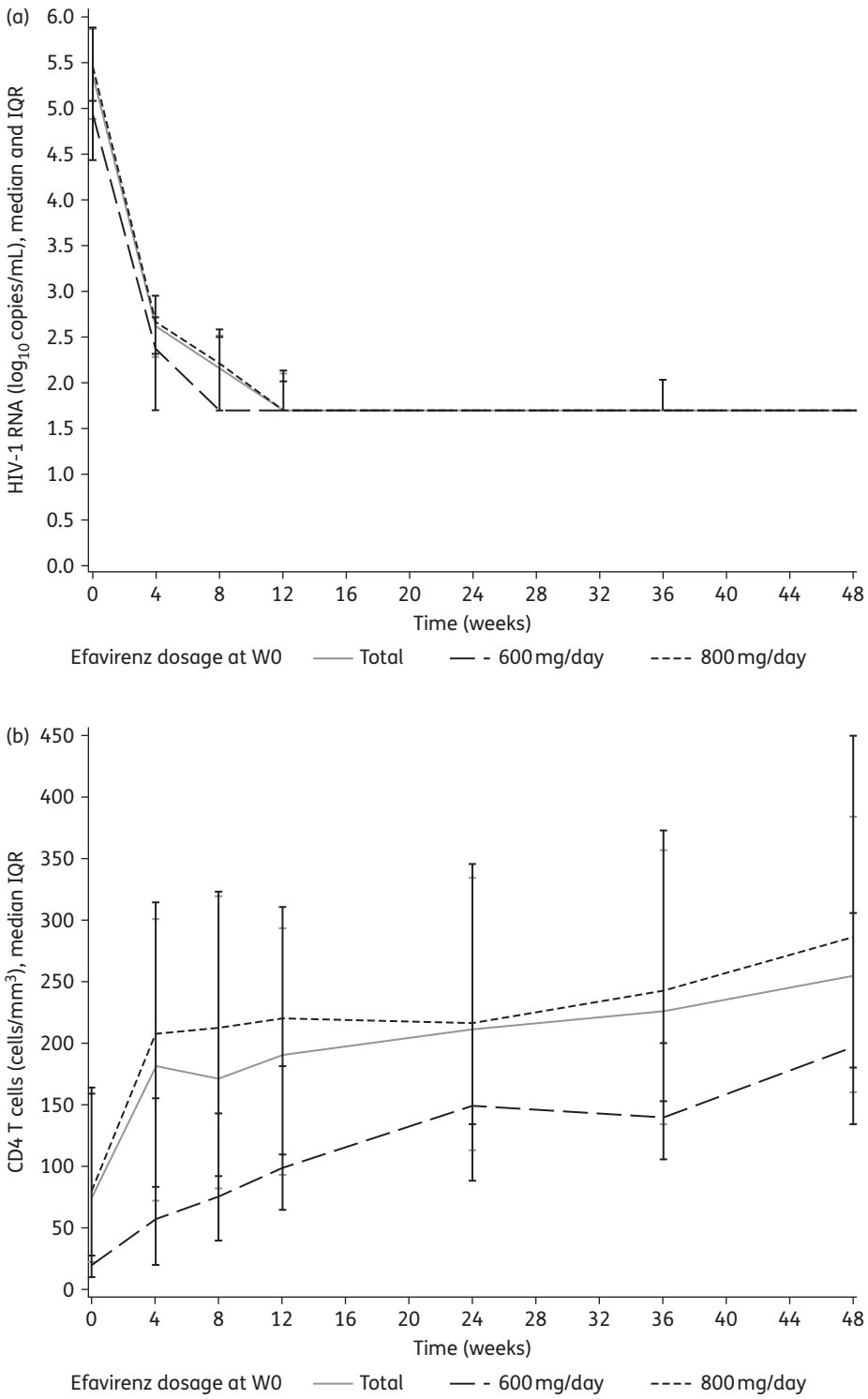

Figure 2. (a) Change in median HIV-1 RNA (log_{10} copies/mL). (b) CD4+ T cell count from week 0 to week 48, ANRS 129 BKIVR trial, France, 2005–08.

Adverse events and safety

Sixty-eight patients (99%) experienced at least one adverse event, including at least one serious adverse event in 31 patients (45%), the latter being attributed to the study drugs in 23 patients. Among a total of 49 serious adverse events (24 related to study drugs), 11 led to discontinuation of one or both antiretroviral drugs, comprising 4 liver-related events, 4 cases of renal failure, 2 psychiatric events and 1 case of fever with abdominal pain. All

Table 2. Adverse events and relationship with efavirenz, ANRS 129 BKVIR trial, France, 2005–08

	Type of adverse event, *n* (%)				
Events	neurological (43)	hepatic (12)	cutaneous (19)	other (205)	Total (279)
Serious adverse event	5 (12)	9 (75)	1 (5)	39 (19)	54 (19)
Adverse event related to efavirenz	35 (81)	7 (58)	3 (16)	32 (16)	77 (28)
maximum dosage of efavirenz: 600 mg/day	5 (14)	0 (0)	1 (33)	4 (13)	10 (13)
maximum dosage of efavirenz: 800 mg/day	30 (86)	7 (100)	2 (67)	28 (88)	67 (87)
Adverse event leading to efavirenz withdrawal	7 (20)	4 (57)	0 (0)	3 (9)	14 (18)

Table 3. Isoniazid and rifampicin 2 h and trough concentrations (mg/L), ANRS 129 BKVIR trial, France, 2005–08

	Isoniazid		Rifampicin	
	2 h	trough	2 h	trough
Samples, *n*	201	198	175	169
Patients, *n*	63	63	56	56
Median	3.0	0.1[a]	4.3	0.1[a]
Interquartile range	1.5–4.6	0.1[a]–0.2	2.3–7.4	0.1[a]–0.4
Minimum–maximum	0.1[a]–12.7	0.1[a]–6.1	0.1*–16.9	0.1[a]–11.7

[a]Limit of quantification.

were considered related to the study drugs by the investigator and the sponsor and all resolved during the trial. No patient died.

The adverse events were neurological ($n=43$, 16%), cutaneous ($n=19$, 7%) or hepatic ($n=12$, 4%). Seventy-seven adverse events were considered by the investigator as related to efavirenz (71 clinical, 6 biological). Clinical adverse events related to efavirenz occurred after a median of 26 days (first quartile 6 days). Eighty-one percent of neurological and 58% of hepatic adverse events were considered related to efavirenz (Table 2). Among the 19 patients who discontinued the study regimen, 9 (47%) did so because of efavirenz intolerance (initial dosage 800 mg/day in eight cases, 600 mg/day in one case). These latter adverse effects occurred after a median of 26 days (IQR 16–116) and comprised four neuropsychiatric events, three hepatic events, one case of gynaecomastia and one of IRIS. At the time of efavirenz withdrawal, three of the patients concerned were receiving 600 mg/day.

All seven renal adverse events (four serious) were attributed to tenofovir.

Among the 277 recorded adverse events, 33 (12%) were attributed to TB agents, including 9 hepatic events and 1 cutaneous event.

Impact of the initial efavirenz dosage and therapeutic monitoring

Among the 37 patients receiving efavirenz at 800 mg/day plus rifampicin at week 0 and for whom efavirenz serum concentrations were available at week 2, values were within, above and below the therapeutic range in 26 (71%), 9 (24%) and 2 (5%) patients, respectively. The two patients receiving efavirenz at 600 mg/day plus rifampicin both had efavirenz serum concentrations within the therapeutic range at week 2. Week 2 efavirenz serum concentrations did not differ between patients of African origin and other patients. The increase in the CD4+ T cell count between baseline and week 48 was 209 (IQR 10–357) and 150 cells/mm^3 (IQR 96 to 230), respectively, in patients with efavirenz plasma concentration >4 mg/L at week 2 ($n=11$) and patients with lower concentrations ($n=34$).

Among the 26 patients who experienced neurological adverse effects related to efavirenz, 14, 7 and 2 patients had week 2 serum efavirenz concentrations within, above and below the therapeutic range, respectively, while 3 patients had no available values. Among the nine patients with high efavirenz concentrations at week 2, eight (89%) experienced a related adverse event (neurological, hepatic and cutaneous events in seven, two and one, respectively).

Serial serum concentrations of rifampicin and isoniazid

Rifampicin concentrations at 2 h were often below the expected range of C_{max} values (Table 3): almost 75% of samples were below the expected range and 50% were <4 mg/L (data not shown). Median 2 h rifampicin concentrations differed significantly between week 2 (6.0 mg/L; IQR 3.6–8.8) and week 12 (3.8 mg/L; IQR 0.9–6.0, $P<0.03$) (Figure 3a) and were significantly lower in males (4.0 mg/L, IQR 2.3–6.1) than in females (6.0 mg/L, IQR 1.7–9.2) ($P<0.04$) (Figure 3b). Neither the degree of immune deficiency nor body weight influenced TB drug pharmacokinetics. Almost 50% of 2 h isoniazid serum concentrations were below the therapeutic range (data not shown), but low concentrations of TB drugs were not associated with TB treatment failure.

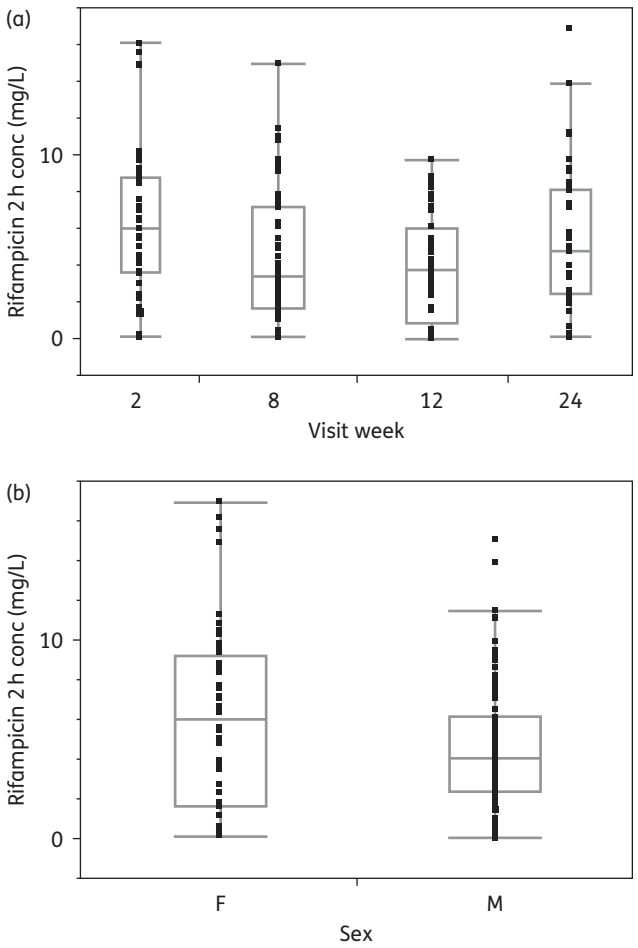

Figure 3. (a) Median rifampicin 2 h concentrations at each protocol visit and (b) according to gender [male (M); female (F)]. Error bars indicate the range of concentrations and boxes represent the IQRs. ANRS 129 BKIVR trial, France, 2005–08.

IRIS

Twenty-three patients (33%) had IRIS (95% CI 22–44), 19 cases being considered 'definite' according to the French, INSHI (International Network for the Study of HIV IRIS) and ERC classifications. Discrepancies among the three classifications were noted in the remaining four cases.

Five episodes (22%) were considered serious (two cases of acute renal failure, two cerebral tuberculomas with seizures or intracranial hypertension, and one case of segmental bronchus compression), and 12 patients (52%) required steroid therapy. The median time between cART initiation and the onset of IRIS was 8 days (IQR 5–14). In multivariate analysis, a higher BMI (OR=0.84 per additional unit, 95% CI 0.71–0.98, P=0.03) and a higher haemoglobin level (OR=0.66 per additional unit, 95% CI 0.45–0.95, P=0.02) were protective against IRIS (Table 4).

Discussion

In the ANRS 129 BKVIR trial, 83% of HIV-infected patients with TB were successfully treated, with tuberculosis cure and HIV viral control at week 48. Our findings thus support UK, EACS (European AIDS Clinical Society) and WHO recommendations advocating first-line tenofovir DF/emtricitabine and efavirenz combination therapy for antiretroviral-naive HIV-infected patients receiving TB drugs.[3,17]

Previous studies of efavirenz combined with other nucleoside analogues have also given encouraging results.[18–23] Subsequent studies favoured efavirenz rather than nevirapine co-administration with rifampicin.[6] Given the deleterious pharmacokinetic interaction between rifampicin and efavirenz,[24] we initially prescribed efavirenz at 800 mg/day. However, 50% of patients who discontinued the study regimen did so because of efavirenz intolerance, mostly at 800 mg/day, in keeping with British data.[25] The optimal efavirenz dosage for use in combination with rifampicin remains a matter of heated debate. One study showed that ethnicity and low body weight influenced efavirenz concentrations.[26] Earlier studies of slim Thai patients failed to show differences in efavirenz concentrations or efficacy when used with rifampicin.[20,21] In South Africa, efavirenz at 600 mg/day plus rifampicin was associated with wide variations in efavirenz concentrations and with neurological adverse effects in up to 50% of patients but resulted in good virological outcomes.[27] A more recent study showed that efavirenz concentrations did not decrease after adding rifampicin when 600 mg/day dosage was used, while they increased when 800 mg/day dosage was used.[28] Our data support recommendations advocating efavirenz at 600 mg/day for co-administration with rifampicin, but efavirenz at 800 mg/day remains an option for patients weighing >60 kg,[3,4] who tend to have lower efavirenz concentrations.[29] A higher risk of treatment failure was found when the efavirenz dose was not adjusted to body weight,[30] but the recent STRIDE study showed no benefit of weight-based dosing.[31] The tenofovir DF/emtricitabine and efavirenz combination tested here, although associated with a high rate of well-known adverse effects (partially due to close observation in the hospital setting), appears to be an acceptable option. Other options, such as nevirapine-containing regimens, could also be acceptable.[32]

We found low concentrations of both rifampicin (75% of patients) and isoniazid (50% of patients) in these HIV-infected patients with TB. In four earlier studies, around three-quarters of patients had rifampicin concentrations <8 mg/L (<4 mg/L in around one-third of cases).[33–36] In three studies, around 50% of patients had isoniazid concentrations <3 mg/L.[33,35,36] Of note, we found no influence of body weight on rifampicin concentrations, contrary to a recent study of South African patients.[33] Two former studies and the present study showed lower rifampicin concentrations in male patients.[33,37] Surprisingly, isoniazid plasma levels were also low, whereas HIV serostatus is supposed to have little or no effect on isoniazid concentrations.[38–40] We found that low rifampicin and isoniazid serum concentrations did not affect TB treatment efficacy. Likewise, Chideya *et al.*[41] and Burhan *et al.*[42] only found a relationship between low pyrazinamide concentrations and poorer outcome in Botswana and Indonesia, respectively. Together, these data suggest that routine monitoring of isoniazid and rifampicin concentrations is not mandatory for HIV-infected patients with TB, even though low drug exposure is predictive of poor clinical outcome in all-comer patients with tuberculosis.[43]

Twelve percent of adverse events were attributed to TB drugs, including 9/12 hepatic and 1/19 cutaneous events, although it should be noted that recording only started at the time of inclusion and that early TB drug-related adverse effects were therefore

Table 4. Analysis of factors associated with the occurrence of IRIS, ANRS 129 BKVIR trial, France, 2005–08

	Univariate analysis		Multivariate analysis: initial model		Multivariate analysis: final model	
Variable	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, years (per additional year)	1.015 (0.972–1.061)	0.498				
BMI, kg/m^2 (per additional kg/m^2)	0.859 (0.735–1.004)	0.056	0.901 (0.741–1.095)	0.296	0.835 (0.711–0.981)	0.028
Lymph node TB (yes vs no)	1.575 (0.487–5.090)	0.448				
Disseminated TB (yes vs no)	2.533 (0.735–8.730)	0.141	1.319 (0.179–9.691)	0.786		
Number of organs affected by TB (per additional organ affected)	1.299 (1.008–1.672)	0.043	1.233 (0.815–1.865)	0.321		
Time (days) between start of TB drugs and cART (per additional day)	0.974 (0.950–0.999)	0.039	0.993 (0.964–1.023)	0.636		
Time (weeks) between start of TB drugs and cART (<4 vs ≥ 8)	2.625 (0.484–14.24)	0.263				
Time (weeks) between start of TB drugs and cART (4–8 vs ≥ 8)	3.000 (0.998–9.020)	0.263				
Haemoglobin, g/dL (per additional g/dL)	0.707 (0.502–0.996)	0.047	0.791 (0.511–1.225)	0.294	0.655 (0.453–0.946)	0.024
Total lymphocytes/mm^3 (per additional cell/mm^3)	0.999 (0.999–1.000)	0.238	1.001 (0.998–1.004)	0.493		
Calcaemia, mmol/L (per additional mmol/L)	0.107 (0.002–6.495)	0.286				
Creatinine, μmol/L (per additional μmol/L)	0.959 (0.923–0.997)	0.032	0.976 (0.935–1.018)	0.258		
CD4 T cells/mm^3 (per additional cell/mm^3)	0.996 (0.991–1.001)	0.165	1.002 (0.993–1.010)	0.724		
CD4 T cell percentage (per additional %)	0.986 (0.926–1.049)	0.648				
CD8 T cells in cells/mm^3 (per additional cell/mm^3)	0.999 (0.998–1.000)	0.168	0.997 (0.994–1.001)	0.186		
CD8 T cell percentage (per additional %)	1.025 (0.988–1.063)	0.187	1.059 (0.995–1.126)	0.070		
Ratio CD4/CD8 (per additional unit)	1.093 (0.114–10.49)	0.939				
HIV-1 RNA, $\log_{10}$ copies/mL (per additional $\log_{10}$ copies/mL)	2.256 (1.038–4.901)	0.040	1.994 (0.725–5.480)	0.181		

missed. The hepatic toxicity of TB drugs is increased by HIV infection[5] and adds to that of NNRTIs.[19,23,44]

Our results are consistent with those of trials in which at least 90% of surviving TB patients had an undetectable viral load after 1 year of efavirenz combined with nucleoside inhibitors.[45–47]

Using consensus definitions[8,15] we observed a high rate (33%) of paradoxical but not unmasking IRIS,[8,48] one-fifth of cases being considered serious. This is in the upper range of values reported in the literature.[16,49–52] Such a high rate of paradoxical IRIS based on systematic notification strongly suggests that the frequency of subacute IRIS is underestimated in poorer countries, at least outside of clinical trials; for example, the Camelia study showed that IRIS occurred in 26% of HIV-infected patients with TB.[53] A recent meta-analysis suggested that IRIS occurs in 16% of HIV-infected patients with TB.[54] A similarly high concordance between expert opinions, INSHI-2008 and French-2004 IRIS definitions was recently found by Manosuthi *et al.*,[16] but not in other studies.[7,52]

In all HIV-infected patients with active TB, cART is recommended to be initiated in the 2 weeks after TB treatment initiation when CD4+ T cell count is <50 cells/mm^3.[4,45,46,55] Half of our patients started cART within 8 weeks after TB treatment initiation and the median time between cART initiation and IRIS onset was 8 days. Only a low BMI and a low haemoglobin level were independently associated with the occurrence of IRIS. We recently showed that early CD4+ T cell activation was predictive of IRIS in the same cohort of patients.[56] Early cART introduction, a low baseline CD4+ T cell count, extrapulmonary TB, high viral load at cART initiation and good immunological and virological responses to cART have been shown elsewhere to be risk factors for IRIS.[16,31,49–51,53,54,57,58]

Finally, we believe that the smaller sample size did not affect the conclusion as the success rate was far higher than expected. Indeed, the confidence interval of 83% ranged from 74% to 92% (i.e. a precision of 9%) and the lower bound (74%) is higher than the estimated upper bound of a confidence interval of 55% with a precision of 10% (i.e. 65%).

In conclusion, our results support the use of tenofovir DF/emtricitabine/efavirenz (600 mg/day) as first-line therapy for HIV infection in patients with tuberculosis.

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Transparency declarations

None to declare.

References

1 Aaron L, Saadoun D, Calatroni I *et al*. Tuberculosis in HIV-infected patients: a comprehensive review. *Clin Microbiol Infect* 2004; **10**: 388–98.

2 del Amo J, Moreno S, Bucher HC *et al*. Impact of antiretroviral therapy on tuberculosis incidence among HIV-positive patients in high-income countries. *Clin Infect Dis* 2012; **54**: 1364–72.

3 European AIDS Clinical Society. *Guidelines Version 6.0. Octobre 2011*. Brussels: EACS, 2011. http://apps.who.int/medicinedocs/en/d/Js19813en/.

4 Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. Washington: Department of Health and Human Services, 2013. https://aidsinfo.nih.gov/guidelines.

5 Lanternier F, Dalban C, Perez L *et al*. Tolerability of anti-tuberculosis treatment and HIV serostatus. *Int J Tuberc Lung Dis* 2007; **11**: 1203–9.

6 Manosuthi W, Sungkanuparph S, Tantanathip P *et al*. A randomized trial comparing plasma drug concentrations and efficacies between 2 nonnucleoside reverse-transcriptase inhibitor-based regimens in HIV-infected patients receiving rifampicin: the N2R Study. *Clin Infect Dis* 2009; **48**: 1752–9.

7 Haddow LJ, Moosa MY, Easterbrook PJ. Validation of a published case definition for tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS* 2010; **24**: 103–8.

8 Meintjes G, Lawn SD, Scano F *et al*. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis* 2008; **8**: 516–23.

9 Onyebujoh PC, Ribeiro I, Whalen CC. Treatment options for HIV-associated tuberculosis. *J Infect Dis* 2007; **196** Suppl 1: S35–45.

10 Nachega JB, Parienti JJ, Uthman OA *et al*. Lower pill burden and once-daily antiretroviral treatment regimens for HIV infection: a meta-analysis of randomized controlled trials. *Clin Infect Dis* 2014; **58**: 1297–307.

11 Rouzioux C, Melard A, Avettand-Fenoel V. Quantification of total HIV1-DNA in peripheral blood mononuclear cells. *Methods Mol Biol* 2014; **1087**: 261–70.

12 Boffito M, Tija J, Reynolds HE *et al*. Simultaneous determination of rifampicin and efavirenz in plasma. *Ther Drug Monit* 2002; **24**: 670–4.

13 Peloquin CA, Jaresko GS, Yong CL *et al*. Population pharmacokinetic modeling of isoniazid, rifampin, and pyrazinamide. *Antimicrob Agents Chemother* 1997; **41**: 2670–9.

14 Alsultan A, Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis: an update. *Drugs* 2014; **74**: 839–54.

15 French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. *AIDS* 2004; **18**: 1615–27.

16 Manosuthi W, Van Tieu H, Mankatitham W *et al*. Clinical case definition and manifestations of paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS* 2009; **23**: 2467–71.

17 Pozniak AL, Coyne KM, Miller RF *et al*. British HIV Association guidelines for the treatment of TB/HIV coinfection 2011. *HIV Med* 2011; **12**: 517–24.

18 Jack C, Lalloo U, Karim QA *et al*. A pilot study of once-daily antiretroviral therapy integrated with tuberculosis directly observed therapy in a resource-limited setting. *J Acquir Immune Defic Syndr* 2004; **36**: 929–34.

19 Patel A, Patel K, Patel J *et al*. Safety and antiretroviral effectiveness of concomitant use of rifampicin and efavirenz for antiretroviral-naive patients in India who are coinfected with tuberculosis and HIV-1. *J Acquir Immune Defic Syndr* 2004; **37**: 1166–9.

20 Manosuthi W, Sungkanuparph S, Thakkinstian A *et al*. Efavirenz levels and 24-week efficacy in HIV-infected patients with tuberculosis receiving highly active antiretroviral therapy and rifampicin. *AIDS* 2005; **19**: 1481–6.

21 Manosuthi W, Kiertiburanakul S, Sungkanuparph S *et al*. Efavirenz 600 mg/day versus efavirenz 800 mg/day in HIV-infected patients with tuberculosis receiving rifampicin: 48 weeks results. *AIDS* 2006; **20**: 131–2.

22 Boulle A, Van Cutsem G, Cohen K *et al*. Outcomes of nevirapine- and efavirenz-based antiretroviral therapy when coadministered with rifampicin-based antitubercular therapy. *JAMA* 2008; **300**: 530–9.

23 Shipton LK, Wester CW, Stock S *et al*. Safety and efficacy of nevirapine- and efavirenz-based antiretroviral treatment in adults treated for TB-HIV co-infection in Botswana. *Int J Tuberc Lung Dis* 2009; **13**: 360–6.

24 Lopez-Cortes LF, Ruiz-Valderas R, Viciana P *et al*. Pharmacokinetic interactions between efavirenz and rifampicin in HIV-infected patients with tuberculosis. *Clin Pharmacokinet* 2002; **41**: 681–90.

25 Brennan-Benson P, Lyus R, Harrison T *et al*. Pharmacokinetic interactions between efavirenz and rifampicin in the treatment of HIV and tuberculosis: one size does not fit all. *AIDS* 2005; **19**: 1541–3.

26 Stohr W, Back D, Dunn D *et al*. Factors influencing efavirenz and nevirapine plasma concentration: effect of ethnicity, weight and co-medication. *Antivir Ther* 2008; **13**: 675–85.

27 Friedland G, Khoo S, Jack C *et al*. Administration of efavirenz (600 mg/day) with rifampicin results in highly variable levels but excellent clinical outcomes in patients treated for tuberculosis and HIV. *J Antimicrob Chemother* 2006; **58**: 1299–302.

28 Orrell C, Cohen K, Conradie F *et al*. Efavirenz and rifampicin in the South African context: is there a need to dose-increase efavirenz with concurrent rifampicin therapy? *Antivir Ther* 2011; **16**: 527–34.

29 Manosuthi W, Sungkanuparph S, Tantanathip P *et al*. Body weight cut-off for daily dosage of efavirenz and 60-week efficacy of efavirenz-based regimen in human immunodeficiency virus and tuberculosis coinfected patients receiving rifampin. *Antimicrob Agents Chemother* 2009; **53**: 4545–8.

30 Villar J, Sanchez P, Gonzalez A *et al*. Use of non-nucleoside analogues together with rifampin in HIV patients with tuberculosis. *HIV Clin Trials* 2011; **12**: 171–4.

31 Luetkemeyer AF, Rosenkranz SL, Lu D *et al*. Relationship between weight, efavirenz exposure, and virologic suppression in HIV-infected patients on rifampin-based tuberculosis treatment in the AIDS Clinical Trials Group A5221 STRIDE Study. *Clin Infect Dis* 2013; **57**: 586–93.

32 Bonnet M, Bhatt N, Baudin E *et al*. Nevirapine versus efavirenz for patients co-infected with HIV and tuberculosis: a randomised non-inferiority trial. *Lancet Infect Dis* 2013; **13**: 303–12.

33 McIlleron H, Rustomjee R, Vahedi M *et al*. Reduced antituberculosis drug concentrations in HIV-infected patients who are men or have low weight: implications for international dosing guidelines. *Antimicrob Agents Chemother* 2012; **56**: 3232–8.

34 Perlman DC, Segal Y, Rosenkranz S *et al*. The clinical pharmacokinetics of rifampin and ethambutol in HIV-infected persons with tuberculosis. *Clin Infect Dis* 2005; **41**: 1638–47.

35 Fahimi F, Tabarsi P, Kobarfard F *et al*. Isoniazid, rifampicin and pyrazinamide plasma concentrations 2 and 6 h post dose in patients with pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2013; **17**: 1602–6.

36 Bhatt NB, Barau C, Amin A *et al*. Pharmacokinetics of rifampin and isoniazid in tuberculosis-HIV-coinfected patients receiving nevirapine- or efavirenz-based antiretroviral treatment. *Antimicrob Agents Chemother* 2014; **58**: 3182–90.

37 Kwara A, Cao L, Yang H *et al*. Factors associated with variability in rifampin plasma pharmacokinetics and the relationship between rifampin concentrations and induction of efavirenz clearance. *Pharmacotherapy* 2014; **34**: 265–71.

38 Conte JE, Golden JA, Kipps JE *et al*. Effect of sex and AIDS status on the plasma and intrapulmonary pharmacokinetics of rifampicin. *Clin Pharmacokinet* 2004; **43**: 395–404.

39 Wilkins JJ, Langdon G, McIlleron H *et al*. Variability in the population pharmacokinetics of isoniazid in South African tuberculosis patients. *Br J Clin Pharmacol* 2011; **72**: 51–62.

40 Holland DP, Hamilton CD, Weintrob AC *et al*. Therapeutic drug monitoring of antimycobacterial drugs in patients with both tuberculosis and advanced human immunodeficiency virus infection. *Pharmacotherapy* 2009; **29**: 503–10.

41 Chideya S, Winston CA, Peloquin CA *et al*. Isoniazid, rifampin, ethambutol, and pyrazinamide pharmacokinetics and treatment outcomes among a predominantly HIV-infected cohort of adults with tuberculosis from Botswana. *Clin Infect Dis* 2009; **48**: 1685–94.

42 Burhan E, Ruesen C, Ruslami R *et al*. Isoniazid, rifampin, and pyrazinamide plasma concentrations in relation to treatment response in Indonesian pulmonary tuberculosis patients. *Antimicrob Agents Chemother* 2013; **57**: 3614–9.

43 Pasipanodya JG, McIlleron H, Burger A *et al*. Serum drug concentrations predictive of pulmonary tuberculosis outcomes. *J Infect Dis* 2013; **208**: 1464–73.

44 Hoffmann CJ, Charalambous S, Thio CL *et al*. Hepatotoxicity in an African antiretroviral therapy cohort: the effect of tuberculosis and hepatitis B. *AIDS* 2007; **21**: 1301–8.

45 Abdool Karim SS, Naidoo K, Grobler A *et al*. Integration of antiretroviral therapy with tuberculosis treatment. *N Engl J Med* 2011; **365**: 1492–501.

46 Blanc FX, Sok T, Laureillard D *et al*. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med* 2011; **365**: 1471–81.

47 Grinsztejn B, De Castro N, Arnold V *et al*. Raltegravir for the treatment of patients co-infected with HIV and tuberculosis (ANRS 12 180 Reflate TB): a multicentre, phase 2, non-comparative, open-label, randomised trial. *Lancet Infect Dis* 2014; **14**: 459–67.

48 Manabe YC, Breen R, Perti T *et al*. Unmasked tuberculosis and tuberculosis immune reconstitution inflammatory disease: a disease spectrum after initiation of antiretroviral therapy. *J Infect Dis* 2009; **199**: 437–44.

49 Colebunders R, John L, Huyst V *et al*. Tuberculosis immune reconstitution inflammatory syndrome in countries with limited resources. *Int J Tuberc Lung Dis* 2006; **10**: 946–53.

50 Michailidis C, Pozniak AL, Mandalia S *et al*. Clinical characteristics of IRIS syndrome in patients with HIV and tuberculosis. *Antivir Ther* 2005; **10**: 417–22.

51 Lawn SD, Myer L, Bekker LG *et al*. Tuberculosis-associated immune reconstitution disease: incidence, risk factors and impact in an antiretroviral treatment service in South Africa. *AIDS* 2007; **21**: 335–41.

52 Haddow LJ, Easterbrook PJ, Mosam A *et al*. Defining immune reconstitution inflammatory syndrome: evaluation of expert opinion versus 2 case definitions in a South African cohort. *Clin Infect Dis* 2009; **49**: 1424–32.

53 Laureillard D, Marcy O, Madec Y *et al*. Paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome after early initiation of antiretroviral therapy in a randomized clinical trial. *AIDS* 2013; **27**: 2577–86.

54 Muller M, Wandel S, Colebunders R *et al*. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. *Lancet Infect Dis* 2010; **10**: 251–61.

55 Havlir DV, Kendall MA, Ive P *et al*. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med* 2011; **365**: 1482–91.

56 Chakrabarti LA, Boucherie C, Bugault F *et al*. Biomarkers of CD4+ T-cell activation as risk factors for tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS* 2014; **28**: 1593–602.

57 Luetkemeyer AF, Kendall MA, Nyirenda M *et al*. Tuberculosis immune reconstitution inflammatory syndrome in A5221 STRIDE: timing, severity, and implications for HIV-TB programs. *J Acquir Immune Defic Syndr* 2014; **65**: 423–8.

58 Naidoo K, Yende-Zuma N, Padayatchi N *et al*. The immune reconstitution inflammatory syndrome after antiretroviral therapy initiation in patients with tuberculosis: findings from the SAPiT trial. *Ann Intern Med* 2012; **157**: 313–24.