Timing of antiretroviral therapy in Cambodian hospital after diagnosis of tuberculosis: impact of revised WHO guidelines

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Objective To determine if implementation of 2010 World Health Organization (WHO) guidelines on antiretroviral therapy (ART) initiation reduced delay from tuberculosis diagnosis to initiation of ART in a Cambodian urban hospital.

Methods A retrospective cohort study was conducted in a nongovernmental hospital in Phnom Penh that followed new WHO guidelines in patients with human immunodeficiency virus (HIV) and tuberculosis. All ART-naïve, HIV-positive patients initiated on antituberculosis treatment over the 18 months before and after guideline implementation were included. A competing risk regression model was used.

Findings After implementation of the 2010 WHO guidelines, 190 HIV-positive patients with tuberculosis were identified: 53% males; median age, 38 years; median baseline CD4+ T-lymphocyte (CD4+ cell) count, 43 cells/μL. Before implementation, 262 patients were identified; 56% males; median age, 36 years; median baseline CD4+ cell count, 59 cells/μL. With baseline CD4+ cell counts ≤ 50 cells/μL, median delay to ART declined from 5.8 weeks (interquartile range, IQR: 3.7–9.0) before to 3.0 weeks (IQR: 2.1–4.4) after implementation ($P < 0.001$); with baseline CD4+ cell counts > 50 cells/μL, delay dropped from 7.0 (IQR: 5.3–11.3) to 3.6 (IQR: 2.9–5.3) weeks ($P < 0.001$). The probability of ART initiation within 4 and 8 weeks after tuberculosis diagnosis rose from 23% and 65%, respectively, before implementation, to 62% and 90% after implementation. A non-significant increase in 6-month retention and antiretroviral substitution was seen after implementation.

Conclusion Implementation of 2010 WHO recommendations in a routine clinical setting shortens delay to ART. Larger studies with longer follow-up are needed to assess impact on patient outcomes.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

Tuberculosis remains one of the major causes of death in patients infected with the human immunodeficiency virus (HIV) in resource-limited settings.[1] Initiating antiretroviral therapy (ART) during the treatment of tuberculosis has been shown to reduce mortality across a wide range of CD4+ T-lymphocyte (CD4+ cell) counts better than waiting until completion of antituberculosis treatment.[2] However, in programmes in low-resource settings, ART uptake is often poor or treatment is delayed.[3–8] The 2010 revision of the World Health Organization (WHO) guidelines for ART in low-resource settings, which recommend ART in HIV-positive patients with tuberculosis, irrespective of CD4+ cell count, has been a major step forward. According to these guidelines ART should be initiated as soon as the antituberculosis therapy is tolerated, which could be as early as two weeks but ideally not more than eight weeks after the start of treatment.[9] These revised guidelines were followed by the publication of three clinical trials comparing early and late ART initiation (2–4 weeks versus 8–12 weeks after commencing antituberculosis treatment).[10–12] Overall, these studies demonstrated that early ART can be safely implemented and that it is associated with a survival benefit mainly concentrated among individuals with baseline CD4+ cell counts of < 50 cells/μL.[13]

Several factors could preclude the implementation of these revised guidelines in routine clinical settings in resource-limited areas. First, good integration of tuberculosis and HIV care programmes, which has proved challenging, is required.[14–18] Operational issues or non-compliance with the guidelines at the level of the health care system or provider could delay ART initiation.[19] Second, the rates of early death and loss to follow-up before ART initiation are usually higher in programme settings than in controlled study settings.[6,20–25] Third, early initiation in routine care may be delayed by the management of co-morbid conditions and opportunistic infections.

Several recent studies have reported the impact of integrating tuberculosis and HIV services on improved and accelerated ART uptake.[26–36] However, there has been no formal evaluation of the operational feasibility and impact of the revised WHO guidelines on the timing of ART initiation within routine clinical settings. The main objective of this study was to assess the change in time to ART initiation following the implementation of the 2010 WHO ART guidelines in a programmatic setting in a resource-limited area. The secondary objective was to monitor trends in HIV infection treatment outcomes (retention on ART) and toxicity-driven antiretroviral drug substitutions. In this operational study, no reliable data on the occurrence of the immune reconstitution inflammatory syndrome could be obtained.

Methods

Study design and population

In March 2003, Sihanouk Hospital Centre of Hope started providing comprehensive HIV care free of charge in Phnom Penh, Cambodia, as part of the national ART programme. Patients presenting at this nongovernmental hospital come from both rural and urban areas (around 50% each) and are almost universally poor. We conducted a retrospective cohort study with a before–after design. We included in the study all ART-naïve HIV-positive adults who initiated antituberculosis treatment as inpatients or outpatients over the 18 months that preceded and the 18 months that followed the implementation of the 2010 WHO guidelines in June 2010. The pre-

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implementation period extended from 1 December 2008 to 31 May 2010 and the post-implementation period, from 1 June 2010 to 30 November 2011. Before June 2010 the hospital had followed the 2006 WHO guidelines.

Organization of tuberculosis and HIV care

The tuberculosis and HIV care clinics were located within close vicinity of each other in the hospital. Over 3000 adult patients on ART were in follow-up at the HIV clinic; an average of around 1400 individuals were screened annually for tuberculosis at the tuberculosis clinic. All patients with HIV infection were routinely screened for tuberculosis, and testing for HIV was proposed to all cases diagnosed with tuberculosis. Details of the organizational setup are given in Box 1 and Fig. 1.

Tuberculosis screening and diagnosis

The tools for tuberculosis diagnosis available in our setting included microscopy to check for acid-fast bacilli in sputum smears and lymph node fine needle aspirates, chest radiography and abdominal ultrasound (Box 1 and Fig. 1). Tuberculosis screening and diagnostic algorithms recommended by the WHO and the national tuberculosis programme were used throughout the study period.[37,38] Tuberculosis was diagnosed according to WHO criteria for smear-positive pulmonary tuberculosis, smear-negative pulmonary tuberculosis or extrapulmonary tuberculosis.[37,38]

All patients diagnosed with tuberculosis were evaluated for ART eligibility. As explained earlier, up to May 2010, the 2006 WHO ART guidelines were used;[39] following a revision of the Cambodian national guidelines the 2010 WHO ART guidelines were implemented beginning on 1 June 2010. Clinicians were instructed to initiate ART early on, irrespective of CD4+ cell count, and ideally two weeks after initiation of antituberculosis treatment.[9] Before implementation, the rationale and required changes in patient flow and organization were discussed with the entire team in charge of tuberculosis and HIV services (Box 2).

Antiretroviral initiation and monitoring

Programme details, including toxicity monitoring and outcome data of the ART programme in the Sihanouk Hospital Centre of Hope have been published before (Fig. 1).[21,40–43] All medical care was provided by physicians, supported by a team of nurses and adherence counsellors. From early 2010 on, patient tracing was reinforced by systematically telephoning patients not presenting at their scheduled visit. This resulted in gradual improvements in outcome ascertainment over the study period. Patients not presenting at the hospital for a period of 6 months without additional information were considered lost to follow-up.

Box 1. **Overview of care activities at the tuberculosis and HIV care clinics**

Tuberculosis clinic

- Tuberculosis diagnostic workup (by tuberculosis care physician) of cases referred with possible tuberculosis
- Immediate referral of tuberculosis cases for HIV testing and same-day enrolment in HIV care if HIV-positive
- Tuberculosis daily observed treatment and support; monitoring of side-effects
- Recording of detailed tuberculosis information (screening, diagnosis, treatment)

HIV clinic

- Tuberculosis screening (by HIV care physician)
- HIV care programme enrolment (sputum smear microscopy, additional tests as indicated)
- Tuberculosis symptom screening at every clinical encounter
- Pre-ART initiation (sputum smear microscopy and routine chest X-ray)
- IPT if tuberculosis ruled out (since March 2011)
- Diagnostic work-up if tuberculosis suspected in HIV-positive individuals (sputum collected at tuberculosis clinic)
- Tuberculosis treatment decision (HIV care physician with input from tuberculosis physician as required)
- Electronic recording of clinical information (including on tuberculosis) for all HIV-positive individuals

Factors enhancing coordination/integration of tuberculosis and HIV activities

- Localized in close vicinity in the same hospital and within the same department
- Joint multidisciplinary meetings (logistical, operational, medical topics)
- Joint staff trainings
- Well defined role of tuberculosis and HIV clinic staff in tuberculosis- and HIV-related activities
- Key information on HIV infection and tuberculosis cases collected in a single database

ART, antiretroviral therapy; HIV, human immunodeficiency virus; IPT, isoniazid preventive therapy.

Data collection

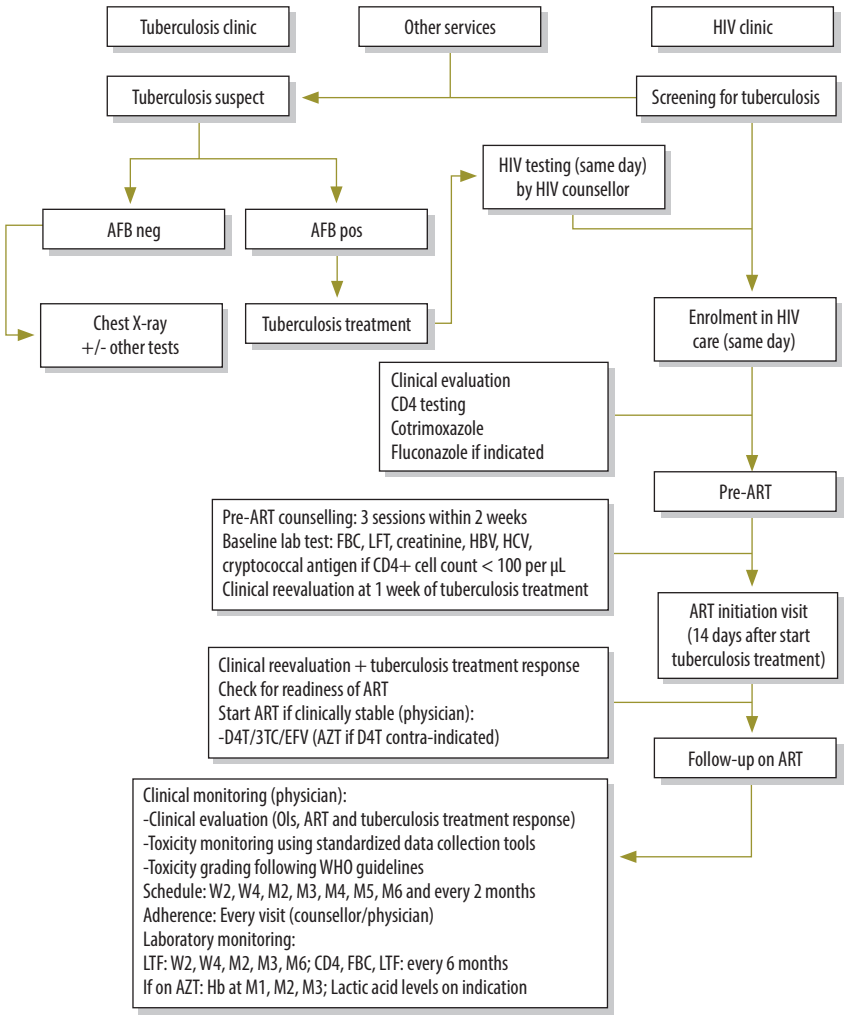
At the onset of the ART programme, structured clinical records, data collection tools and a database were developed.[21] Clinical, laboratory and treatment data, including data on tuberculosis diagnosis and treatment, were collected and stored electronically every day. Physicians were trained to conduct standardized patient assessment using the hospital guidelines and protocols. Quality control of the stored data was performed at regular intervals. For this study, data were extracted from this database. Data were cross-checked against HIV clinical records and tuberculosis registers.

Statistical analysis

The main outcome was the time from the diagnosis of tuberculosis to ART initiation and the probability of starting ART within the 8-week period immediately following the diagnosis. Secondary outcomes included overall programme retention (i.e. the proportion of patients retained on ART) six months after the diagnosis of tuberculosis and the proportion with toxicity-related antiretroviral drug substitution six months after ART initiation.

Baseline patient characteristics before and after implementation were described and compared using χ^2 or Fisher's exact tests for categorical variables and the Wilcoxon rank-sum test for continuous variables. Follow-up time was censored at the earliest of the following: ART initiation, death, loss to follow-up, transfer-out, or end of study period. Among individuals initiating ART, we calculated the median and interquartile

Fig. 1. **Organization of tuberculosis and HIV care activities and initiation and monitoring of antiretroviral therapy (ART), Cambodia, December 2008 to November 2011**



AFB, acid-fast bacilli; AZT, zidovudine; D4T, stavudine; EFV, efavirenz; FBC, full blood count; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; 3TC, lamivudine; LFT, liver function tests; M, month; OI, opportunistic infection; W, week; WHO, World Health Organization.

range (IQR) of the time in weeks from the diagnosis of tuberculosis to ART initiation before and after implementation of the new WHO guidelines, stratified by baseline CD4+ cell count. We compared pre- and post-implementation values using the Wilcoxon test. To visualize the effect of guideline implementation, we calculated the median ART delay per quartile and plotted it on a graph (Fig. 2). We used Kaplan–Meier methods to estimate the cumulative incidence of ART initiation at 2, 4 and 8 weeks after the diagnosis of tuberculosis among those initiating ART. In a secondary analysis, we calculated the overall probability of initiation of ART among all individuals diagnosed with tuberculosis, whether or not they ever initiated ART. In case of competing risks (ART initiation precluded by death), standard survival methods can provide biased estimates.[44,45] Consequently, we used a competing risks proportional hazards regression model to identify independent factors associated with probability of ART initiation.[44,45] We modelled the effect of the implementation of revised WHO guidelines on time to ART initiation after a diagnosis of tuberculosis was modelled over three time periods: < 2 weeks, 2–6 weeks and > 6 weeks after the diagnosis. In addition, the following factors were considered for inclusion in the model: age, sex, type of tuberculosis (extrapulmonary or pulmonary), point of entry into care (HIV or tuberculosis care programme) and CD4+ cell count when tuberculosis was diagnosed. Starting from the full model, a stepwise selection process was performed. Associations in the model were reported as subhazard ratios (sHR). The proportional-hazards assumption was tested graphically and formally using Schoenfeld residuals. The cumulative incidence of starting ART, with death before ART (pre-ART death) as a competing risk, was calculated as well. In sensitivity analysis, we treated a combined end-point consisting of pre-ART death and loss to follow-up as a competing event (i.e. we assumed that individuals who were lost to follow-up before initiating ART had died).

We performed logistic regression to look for an association between implementation of the revised WHO guidelines and secondary outcomes. Additional covariates such as sex, age, body weight at the time when tuberculosis was diagnosed, type of tuberculosis, and point of entry into care were considered potential confounders for inclusion. For retention on ART as outcome, we selected a priori for inclusion in the model the CD4+ cell count and body weight at the time of the diagnosis of tuberculosis; for drug substitution as outcome, we selected a priori sex, age and CD4+ cell count at the time of the diagnosis of tuberculosis. We analysed the data using STATA version 11 (STATACorp LP, College Station, United States of America). The level of significance was set at $P < 0.05$.

Ethical issues

Since the launch of the HIV care programme, clinical data have been routinely collected for purposes of programme monitoring and evaluation and research activities. Patients were requested to give written informed consent to store and use the data. The data collection and informed consent procedures were approved by the Institutional Review Board of the Institute of Tropical Medicine, Antwerp, Belgium, and the Institutional Review Board of the Sihanouk Hospital Centre of Hope.

Results

Patient characteristics

The post-implementation group consisted of 190 patients. Before revised guideline implementation, 262 patients with tuberculosis and HIV co-infection were identified. Both groups were com-

Box 2. **Implementation of early initiation of antiretroviral therapy (ART) in patients with tuberculosis and HIV co-infection: organizational aspects**

Communication: platforms for discussion, planning and dissemination of information (general)

- Weekly medical department meeting (tuberculosis and HIV physicians)
- Monthly multidisciplinary meeting of key HIV and tuberculosis care staff to discuss logistical and managerial issues
- Monthly multidisciplinary operational meeting with the entire HIV and tuberculosis care team
- Daily educational activities for HIV patients attending the HIV clinic

Preparation of implementation

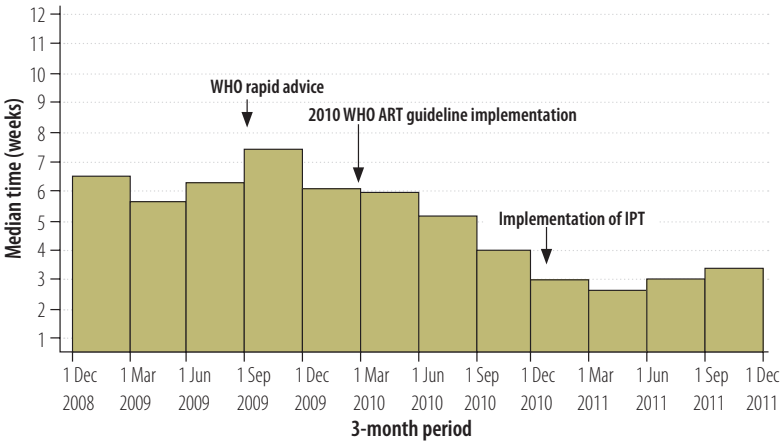
- Required changes in patient flow discussed during above-mentioned meetings: key changes consisted of more rapid pre-ART counselling and fast-tracking for ART initiation
- No concurrent changes in tuberculosis case-finding strategies or tuberculosis and HIV care clinic organizational set-up (staffing, HIV/tuberculosis service delivery model) were made
- Starting date of implementation fixed

Monitoring

- Within each service, supervisors monitored adherence to the implementation during their routine (clinical) work as part of their continuous monitoring of all guidelines and practices
- Operational challenges with implementation could be raised by the staff during above-mentioned team meetings

HIV, human immunodeficiency virus.

Fig. 2. **Evolution of time to initiation of antiretroviral therapy (ART), pre- and post-implementation of the 2010 WHO guidelines, December 2008 to November 2011**



IPT, isoniazid preventive therapy; WHO, World Health Organization.

parable except that individuals in the post-implementation group were older, on average, and that a smaller proportion of them were already enrolled in HIV care before being diagnosed with tuberculosis (Table 1).

Delay to initiation of antiretroviral therapy

Among patients initiating ART, the median time to ART initiation after the diagnosis of tuberculosis declined from over 6 weeks before implementation to just over 3 weeks after implementation (Table 2). Significant decreases in time to ART initiation were seen in analysis of subgroups based on baseline CD4+ cell count, type of tuberculosis, sex and point of entry into care. Pre-implementation, 23% and 65% of individuals initiating ART did so by the end of week 4 and the end of week 8 after being diagnosed with tuberculosis, respectively (Fig. 3). These proportions increased to 62% and 90% after implementation. The post-implementation period was marked by a progressive and sustained decline in delay to ART initiation (Fig. 2).

Probability of initiating antiretroviral therapy

We calculated the overall probability of starting ART by a certain week for all individuals diagnosed with tuberculosis and we treated pre-ART death as a competing risk (Table 3). The estimated probability of starting ART by weeks 2, 4 and 8 after the diagnosis of tuberculosis increased respectively from 0.8%, 19.5% and 58.0% before implementation, to 3.9%, 51.8% and 78.8% after implementation. The probability of initiating ART by week 8 after the diagnosis of tuberculosis, on the assumption that individuals lost to follow-up had died, was 51.1% and 72.1% pre- and post-implementation, respectively.

Competing risk regression modelling

Both in unadjusted and adjusted analyses, the implementation effect was restricted to the 2- to 6-week period after the diagnosis of tuberculosis, with an adjusted sHR of 2.60 (95% CI: 1.87–3.62). We found an adjusted sHR of 2.44 when pre-ART loss to follow-up was considered on the assumption that individuals lost to follow up had died (Table 4). In addition, a CD4+ cell count of ≤ 50 cells/μL and enrolment in HIV care before the diagnosis of tuberculosis were independently associated with an increased probability of ART initiation by a given week after diagnosis. The delay before ART initiation was longer among cases of smear-negative pulmonary tuberculosis than among cases of extrapulmonary tuberculosis.

Secondary outcomes

Six months after the diagnosis of tuberculosis, the proportion of patients who had died or were lost to follow-up before and after implementation of revised WHO guidelines were 24.0% and 24.2%, respectively (Fig. 4). The proportion retained and on ART increased from 68% pre-implementation to 73% after implementation (adjusted OR: 1.37; 95% CI: 0.85–2.19; *P*: 0.197). The incidence of toxicity-driven antiretroviral substitution by the end of the sixth month after ART initiation was 10.3% (27/262) during the pre-implementation period and 11.0% (21/190) in the post-implementation period (adjusted OR: 1.18; 95% CI: 0.55–2.18, *P*-value 0.796). The most common adverse reactions were hepatitis (17 reports), central nervous

Table 1. **Baseline characteristics of individuals with tuberculosis and HIV co-infection, pre- and post-implementation of the 2010 WHO ART guidelines, Cambodia, December 2008 to November 2011**

Characteristic	Before[a] (*n* = 262)	After[b] (*n* = 190)	*P*
Sex, no. (%)			
Female	115 (43.9)	89 (46.8)	0.534
Male	147 (56.1)	101 (53.2)	
Age (years), median (IQR)	36 (30.2–41.7)	38 (31.8–44.7)	0.022
≤ 35, no. (%)	125 (47.7)	72 (37.9)	0.038
> 35, no. (%)	137 (52.3)	118 (62.1)	
Body weight (kg); (*n* = 443)	46 (41–52)	46 (40–53)	0.681
> 50, no. (%)	161 (61.9)	119 (65.0)	0.505
≤ 50, no. (%)	99 (38.1)	64 (35.0)	
CD4+ cell count (cells/μL) at tuberculosis diagnosis, median (IQR)	59 (18–168)	43 (20.0–162.5)	0.572
> 50, no. (%)	130 (49.6)	82 (43.2)	0.096
≤ 50, no. (%)	104 (39.7)	94 (49.5)	
Missing, No. (%)	28 (10.7)	14 (7.4)	
Type of tuberculosis, no. (%)			
Extrapulmonary	135 (51.5)	92 (48.4)	0.753
Smear-positive pulmonary	55 (21.0)	40 (21.1)	
Smear-negative pulmonary	72 (27.5)	58 (30.5)	
Enrolled in HIV care before tuberculosis diagnosis, no. (%)			
No	107 (40.1)	125 (65.8)	< 0.001
Yes	155 (59.2)	65 (34.2)	
Initiated on ART, no. (%)			
Total	210 (80.1)	152 (80.0)	0.978
Within 6 months after tuberculosis diagnosis	197 (75.2)	151 (79.5)	0.286

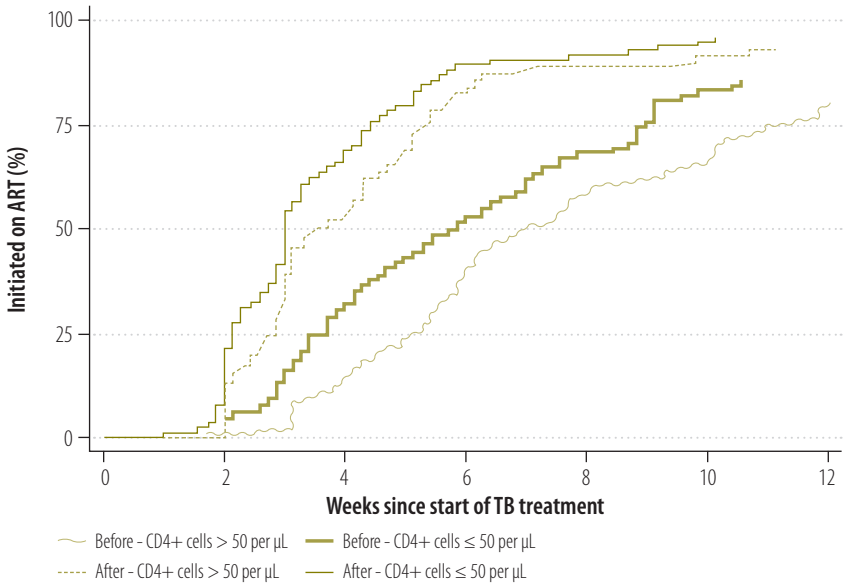
ART, antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range; WHO, World Health Organization.
[a] December 2008 to May 2010.
[b] June 2010 to November 2011.

Table 2. **Time (weeks) between the diagnosis of tuberculosis and initiation of antiretroviral therapy (ART) pre- and post-implementation of the 2010 WHO ART guidelines, Cambodia, December 2008 to November 2011**

Parameter	Median in weeks from tuberculosis diagnosis to ART (IQR)		
	Before (*n* = 210)	After (*n* = 152)	*P*
CD4+ cell count (cells/μL) at start of antituberculosis treatment			
All	6.3 (4.1–10.0)	3.1 (2.4–5.1)	< 0.001
> 50	7.0 (5.3–11.3)	3.6 (2.9–5.3)	< 0.001
≤ 50	5.8 (3.7–9.0)	3.0 (2.1–4.4)	< 0.001
Sex			
Female	6.3 (3.9–10.0)	4.0 (2.6–5.1)	< 0.001
Male	5.8 (3.4–9.6)	2.8 (2.0–4.3)	< 0.001
Age (years)			
≤ 35	3.1 (2.6–5.3)	3.1 (2.1–5.0)	< 0.001
> 35	6.1 (3.1–10.0)	3.0 (2.0–4.8)	< 0.001
Body weight (kg)			
> 50	5.3 (2.8–9)	3.0 (2.0–4.7)	< 0.001
≤ 50	6.1 (3.9–9.9)	3.0 (2.0–4.3)	< 0.001
Type of tuberculosis			
Extrapulmonary	6.7 (4.3–9.9)	3.0 (2.3–4.6)	< 0.001
Smear-positive pulmonary	6.6 (4.6–10.0)	3.1 (2.6–4.4)	< 0.001
Smear-negative pulmonary	5.6 (3.6–9.8)	4.3 (2.4–5.9)	< 0.001
Enrolled in HIV care before tuberculosis diagnosis			
No	6.9 (5.1–10.0)	3.0 (2.2–4.8)	< 0.001
Yes	5.9 (3.7–10.0)	3.1 (2.0–5.0)	< 0.001

HIV: human immunodeficiency virus; IQR, interquartile range; WHO, World Health Organization.

Fig. 3. **Time to initiation of antiretroviral therapy (ART) after diagnosis of tuberculosis, pre- and post-implementation of the 2010 WHO guidelines, Cambodia, December 2008 to November 2011**



TB, tuberculosis; WHO, World Health Organization.
Kaplan–Meier graph with data stratified according to CD4+ cell count at time of tuberculosis diagnosis.

system toxicity (15 reports) and skin rash (10 reports).

Discussion

Clinical trials are pivotal in identifying novel therapeutic approaches. However, the impact of any approach depends on its effective implementation in routine clinical services. We assessed the impact of the revised WHO guidelines on ART initiation after a diagnosis of tuberculosis in patients with HIV infection attending an urban nongovernmental hospital. After implementation of the new guidelines, ART delays were substantially shortened and initiation of ART occurred earlier on average. Non-significant increases in retention on ART and in ART toxicity were also noted. Our findings support the safety and feasibility of initiating ART early in real-life settings, even in a patient population with advanced HIV infection. To the best of our knowledge, this study is among the first formal and

Table 3. **Overall probability of initiation of antiretroviral therapy (ART) up to week 8 after the diagnosis of tuberculosis, pre- and post-implementation of the 2010 WHO ART guidelines, by CD4+ cell count and competing risk assumption, Cambodia, December 2008 to November 2011**

CD4+ cell count (cells/µL)	Probability of ART initiation, % (95% CI)		
	At 2 weeks	At 4 weeks	At 8 weeks
Pre-ART death as competing risk			
Pre-implementation			
Overall	0.8 (0.1–2.7)	19.5 (14.8–24.8)	58.0 (51.4–64.1)
> 50	0.8 (0.1–3.9)	11.9 (7.1–18.3)	53.4 (44.2–61.7)
≤ 50	1.0 (0.1–5.0)	29.2 (20.5–38.5)	64.2 (53.7–72.9)
Post-implementation			
Overall	3.9 (1.7–7.5)	51.8 (44.2–58.9)	78.8 (72.0–84.2)
> 50	0.0 (0–2.8)	45.8 (34.6–56.4)	79.0 (68.1–86.6)
≤ 50	7.6 (3.3–14.2)	60.9 (50.0–70.1)	84.6 (75.3–90.7)
Pre-ART death and loss to follow-up as competing risks			
Pre-implementation			
Overall	0.8 (0.1–2.5)	17.6 (13.2–22.4)	51.1 (44.9–57.0)
> 50	0.8 (0.1–3.8)	11.5 (6.8–17.7)	50.1 (41.9–59.0)
≤ 50	0.9 (0.1–4.7)	26.9 (18.8- 35.7)	58.6 (48.6–67.4)
Post-implementation			
Overall	3.6 (1.6–7.1)	47.9 (40.6–54.8)	72.1 (65.1–77.9)
> 50	0.0 (0–4.4)	43.9 (33.0–54.2)	74.4 (63.5–82.5)
≤ 50	7.4 (3.3–13.9)	58.5 (47.9–67.7)	80.8 (71.3–87.5)

CI, confidence interval; WHO, World Health Organization.

Table 4. **Competing risk regression modelling of time from the diagnosis of tuberculosis to initiation of antiretroviral therapy (ART) among all individuals diagnosed with tuberculosis ($n = 452$), pre- and post-implementation of the 2010 WHO ART guidelines, Cambodia, December 2008 to November 2011**

Parameter	sHR (95% CI)	Adjusted sHR[a] (95% CI)	Adjusted sHR (LTFU = death) (95% CI)
Pre-implementation	Ref	Ref	Ref
Post-implementation			
Time (weeks) from tuberculosis diagnosis			
< 2	0.75 (0.45–1.25)	0.97 (0.57–1.66)	0.76 (0.46–1.23)
2–6	2.45 (1.79–3.65)	2.60 (1.87–3.62)	2.44 (1.79–3.33)
> 6	0.93 (0.59–1.47)	1.08 (0.69–1.69)	1.43 (0.92–2.22)
CD4+ cell count (cells/μL) at tuberculosis diagnosis			
> 50	Ref	Ref	Ref
≤ 50	1.46 (1.11–1.91)	1.44 (1.17–1.76)	1.32 (1.07–1.63)
Missing	0.59 (0.23–1.55)	0.26 (0.10–0.66)	0.13 (0.06–0.30)
Type of tuberculosis			
Extrapulmonary	Ref	Ref	Ref
Smear-positive pulmonary	1.20 (0.91–1.59)	0.97 (0.73–1.29)	0.87 (0.65–1.15)
Smear-negative pulmonary	0.87 (0.61–1.22)	0.76 (0.59–0.98)	0.77 (0.60–1.00)
Enrolled in HIV care before tuberculosis diagnosis			
No	Ref	Ref	Ref
Yes	1.16 (0.89–1.52)	1.31 (1.06–1.63)	1.25 (1.00–1.59)

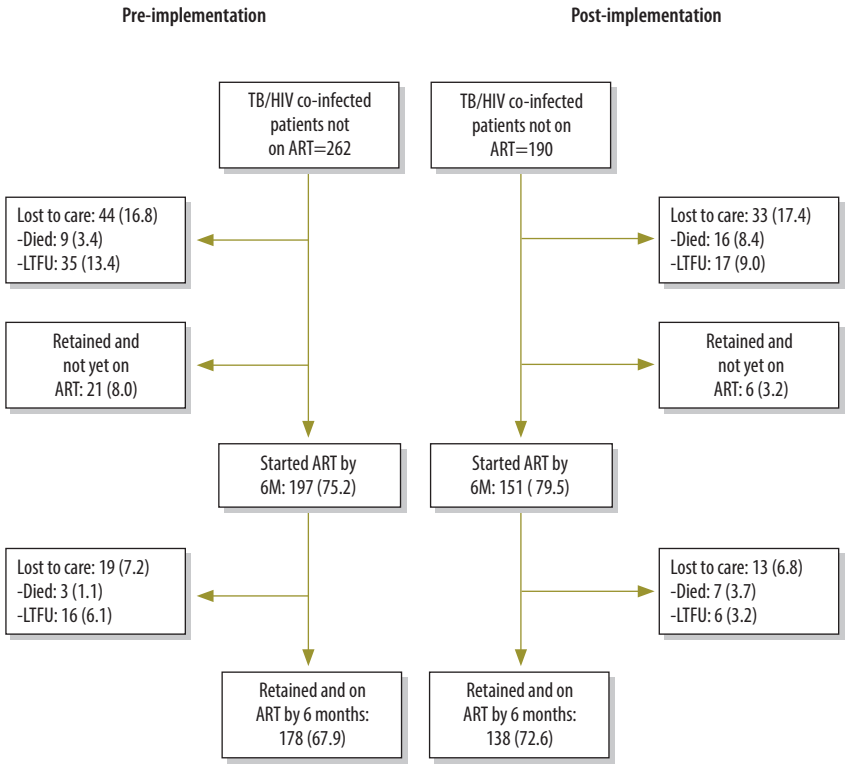
CI, confidence interval; HIV, human immunodeficiency virus; LTFU, loss to follow-up; Ref, reference; sHR, subhazard ratio; WHO, World Health Organization.
[a] Starting from the full model, a stepwise selection process was followed. Covariates were retained in the model if their removal/inclusion induced a change of > 10% in the measure of effect of the main exposure or if they were significantly associated with the outcome in the adjusted analysis.

explicit evaluations of these guidelines in such settings.

The before–after study design has limitations; factors not accounted for in the model could have contributed to shortening the time to ART initiation. Following WHO and national guidelines, beginning in March 2011 our programme changed its tuberculosis screening criteria for HIV-positive patients and implemented isoniazid preventive therapy.[46] Concurrent with the national scaling-up of ART services, a gradual reduction in enrolment of HIV patients was seen from early 2009 on, and proportionally fewer cases of tuberculosis were diagnosed within the HIV care programme after implementation of the revised WHO guideline. The overall reduced burden of co-infection with HIV and tuberculosis and/or the detection of tuberculosis at a less advanced stage after revised guideline implementation could have made it easier to initiate ART earlier. However, no waiting lists for ART were observed during the study period. Furthermore, the overall burden of work in the clinics remained constant throughout, and patient characteristics were fairly similar before and after implementation. It is possible that dissemination of the WHO rapid advice (November 2009) before the publication of the 2010 WHO guidelines sensitized HIV and tuberculosis care physicians and resulted in their initiating ART earlier before the guidelines were officially implemented. Although all these factors may have been influential, the rapid and sustained reduction in the time to ART initiation following implementation of the revised WHO guidelines suggests that this was the main factor contributing to the reduction.

An increasing number of studies from routine services in resource-limited settings have reported increased and expedited ART uptake,[26–35] especially after the introduction of a package of interventions aiming at achieving integration of tuberculosis and HIV care. These studies generally precede the 2010 WHO ART guidelines. Median ART delays of 7 and 11 weeks in Uganda and South Africa, respectively, were still observed after integration in recent studies.[29,32] An interesting aspect of our study is that early ART initiation was implemented as a single intervention, without major concurrent changes in the tuberculosis/HIV service delivery model. This makes it possible to better quantify the effect of the revised guidelines and to demonstrate their impact when coordination of tuberculosis/HIV activities is fairly well organized. In this regard, the increase we observed in ART initiation by week 4, from 23% to 62% after the 2010 WHO guidelines were implemented, is encouraging. As expected, the time between the diagnosis of tuberculosis and ART initiation was shorter for individuals who had enrolled in HIV care before being diagnosed with tuberculosis. Increased HIV testing and enrolment in HIV care would also provide opportunities for enhanced tuberculosis case-finding and prevention through timely ART initiation. Since reducing the burden of tuberculosis and HIV co-infection will require a range of collaborative activities

Fig. 4. **Patient flowchart and outcomes for tuberculosis patients on antiretroviral therapy (ART), 6 months (6M) after the diagnosis of tuberculosis, Cambodia, December 2008 to November 2011**



HIV, human immunodeficiency virus; LTFU, lost to follow-up; TB, tuberculosis.
Note: The values in the figure represent absolute patient numbers followed by percentages within parentheses. Adult ART-naïve patients with tuberculosis and co-infection with HIV were recruited in the 18 months before and after the implementation of the 2010 World Health Organization guidelines on ART initiation. "Lost to care" refers to patients that either died or were defined as LTFU.

involving tuberculosis and HIV services, WHO has recently re-emphasized the need to provide quality-assured, integrated preventive, diagnostic and treatment services for both tuberculosis and HIV infection.[47]

Several questions remain to be explored. Although improved patient outcomes have been reported with increased and expedited ART uptake,[47] the survival benefit of initiating ART early (within 2–4 weeks of tuberculosis treatment) for individuals with advanced HIV infection has not been demonstrated yet in routine practice. We observed a non-significant increase in patient retention, but since death ascertainment among losses to follow-up improved over time owing to active tracing of patients by telephone, meaningful comparison of mortality could not be made. Future studies should aim for longer patient follow-up and larger samples to assess the impact on overall patient outcomes. Additional relevant information would include data on the immune reconstitution inflammatory syndrome, drug toxicity associated with antituberculosis agents, and treatment adherence. We note that ART toxicity occurred frequently over the entire study period. Of interest, two recent, relatively small clinical trials in Ethiopia and Thailand did not show a survival benefit with earlier ART initiation.[48,49] How the clinical benefit of initiating ART earlier varies across patient populations and programme settings remains to be defined.

After the implementation of the revised WHO guidelines, around 30% of the individuals with advanced HIV infection still initiated ART more than 4 weeks after being diagnosed with tuberculosis. Moreover, many others were lost to care soon after the diagnosis and before initiating ART, and the same has been noted in other programmes.[6,20,24] Additional operational research focusing on the underlying causes of ART delay in such patients could reveal the programmatic adjustments needed to achieve higher rates of early ART initiation. More information on outcomes, reasons for early losses to care and possible barriers to ART would be valuable as well.[23,50]

This study has several limitations. They include the retrospective design, the use of programme data, and the possibility of residual confounding. Tuberculosis might have been missed or falsely diagnosed in some patients. However, the study, which reflects routine service delivery in resource-limited settings, served the purpose of assessing operational feasibility and changes in ART delay in the period after the implementation of WHO's revised guidelines. Moreover, it revealed a higher proportion of cases of extrapulmonary tuberculosis than other studies. The latest WHO recommendations have been slightly modified and now allow for ART delays beyond 2 weeks in patients with less advanced HIV infection.[47] The study was restricted to a single, well-staffed and well-functioning urban hospital where HIV and tuberculosis care services were hosted on the same premises. Consequently, our findings might not apply to settings with less coordination of tuberculosis and HIV care activities. Additional data on operational feasibility from a wide range of clinical settings would be valuable, especially in a context of referrals between ART and tuberculosis clinics widely separated from each other geographically or in settings with poor integration of tuberculosis and HIV care services.[5,18,47]

Conclusion

The implementation of the 2010 WHO guidelines on ART initiation in patients with tuberculosis was associated with a substantial shortening of the time from tuberculosis diagnosis to ART initiation and with an increased probability of ART initiation by week 8 after the tuberculosis diagnosis. Additional factors associated with a shorter time to ART initiation included a baseline CD4+ cell count of ≤ 50 cells/μL and enrolment in

HIV care before being diagnosed with tuberculosis. Although these findings support the operational feasibility of implementing the revised guidelines in routine clinical services, larger studies in different settings and with long-term outcome data are warranted. ■

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ملخص

توقيت العلاج بمضادات الفيروسات القهقرية في إحدى مستشفيات كمبوديا بعد تشخيص السل: أثر المبادئ التوجيهية المنقحة لمنظمة الصحة العالمية

الغرض تحديد ما إذا كان تنفيذ المبادئ التوجيهية لمنظمة الصحة العالمية لعام 2010 بشأن بدء العلاج بمضادات الفيروسات القهقرية قد أدى إلى تقليل التأخير من تشخيص السل إلى بدء العلاج بمضادات الفيروسات القهقرية في إحدى المستشفيات الحضرية في كمبوديا.

الطريقة تم إجراء دراسة أترابية استرجاعية في مستشفى غير حكومي في بنوم بنه باتباع المبادئ التوجيهية الجديدة لمنظمة الصحة العالمية فيما يخص المرضى المصابين بفيروس العوز المناعي البشري والسل. وتم إدراج جميع المرضى البسطاء للعلاج بمضادات الفيروسات القهقرية والمرضى الإيجابيين لفيروس العوز المناعي البشري الذين بدأوا العلاج المضاد للسل على مدار الثمانية عشر شهراً السابقة لتنفيذ المبادئ التوجيهية والتالية له. وتم استخدام نموذج ارتداد أخطار تنافسي.

النتائج بعد تنفيذ المبادئ التوجيهية لمنظمة الصحة العالمية لعام 2010، تم تحديد 190 مريضاً إيجابياً لفيروس العوز المناعي البشري مصابين بالسل: 53 ٪ ذكور؛ متوسط العمر 38 سنة؛ متوسط خط الأساس لإحصاء الخلايا اللمفاوية التائية المساعدة (CD4+) هو 43 خلية/ميكرولتر. وقبل التنفيذ، تم تحديد 262 مريضاً؛ 56 ٪ ذكور؛ متوسط العمر 36 سنة؛ متوسط خط الأساس لإحصاء الخلايا اللمفاوية التائية المساعدة (CD4+) هو 59 خلية/ ميكرولتر. وعند انخفاض إحصاءات الخلايا اللمفاوية التائية المساعدة (CD4+) عند خط الأساس عن 50 خلية/ ميكرولتر، انخفض متوسط تأخير العلاج بمضادات الفيروسات القهقرية من 5.8 أسبوعاً (النطاق بين الشريحتين الربعيتين: من 3.7 إلى 9.0) قبل التنفيذ إلى 3.0 أسابيع بعده (النطاق بين الشريحتين الربعيتين: من 2.1 إلى 4.4) (الاحتمال <0.001)؛ إحصاءات الخلايا اللمفاوية التائية المساعدة (CD4+) عند خط الأساس >50 خلية/ ميكرولتر، انخفض التأخير من 7.0 (النطاق بين الشريحتين الربعيتين: من 5.3 إلى 11.3) إلى 3.6 (النطاق بين الشريحتين الربعيتين: من 2.9 إلى 5.3) أسبوعاً (الاحتمال <0.001). وارتفعت احتمالية بدء العلاج بمضادات الفيروسات القهقرية في غضون أربعة وثمانية أسابيع بعد تشخيص السل من 23 ٪ و65 ٪، قبل التنفيذ إلى 62 ٪ و90 ٪ بعده، على التوالي. ولوحظ بعد التنفيذ زيادة غير كبيرة في إبقاء العلاج لمدة الستة أشهر والاستعاضة بمضادات الفيروسات القهقرية.

الاستنتاج يؤدي تنفيذ توصيات منظمة الصحة العالمية لعام 2010 في البيئة السريرية الروتينية إلى اختزال فترة تأخير العلاج بمضادات الفيروسات القهقرية. ولابد من إجراء دراسات أوسع ذات متابعة أطول لتقييم الأثر على حصائل المرضى.

摘要

柬埔寨医院结核病诊断后进行抗逆转录病毒治疗的时机：世卫组织指导方针修订版的影响

目的 确定实施2010 年世界卫生组织（WHO）有关抗逆转录病毒治疗（ART）的指导方针是否可以减少柬埔寨城市医院从结核病诊断到开始抗逆转录病毒治疗的延迟。

方法 在金边一家对携带艾滋病毒（HIV）的结核病病人贯彻新的世界卫生组织指导方针的非政府医院进行了回顾性队列研究。将在指导方针实施前后各18 个月开始结核病防治的所有未接受过ART治疗且HIV呈阳性的患者都包括在内。使用竞争风险回归模型。

结果 在实施2010 年世界卫生组织的指导方针后，确认了190 名患有结核病的艾滋病毒阳性患者：53%为男性，中位年龄为38 岁；中位基线CD4+ T淋巴细胞（CD4+细胞）计数为43 个细胞/μL。在实施前，确认了262 名患者，56% 为男性，中位年龄为36 岁，中位基线CD4+细胞计数为59 个细胞/μL。在基线CD4+细胞计数小等于50 个细胞/μL时，ART中位延迟从实施之前的5.8 周（四分位距，IQR：3.7-9.0）下降到实施之后的3.0 周（IQR：2.1-4.4）（P <0.001）；在基线CD4+细胞计数大于50个细胞/μL时，延迟从7.0 周（IQR：5.3-11.3）下降到3.6 周（IQR：2.9-5.3）（P <0.001）。在结核病诊断之后开始ART的几率分别从实施之前的23%和65%上升至实施之后的62%和90%。在实施之后的6 个月保持治疗和抗逆转录病毒替代治疗中出现不明显的增加。

结论 在常规临床设施中实施2010 年世界卫生组织的建议缩短了ART延迟。要评估其对患者治疗效果的影响，需要进行后续更长期、更大规模的研究。

Résumé

Calendrier du traitement antirétroviral dans un hôpital cambodgien après le diagnostic de la tuberculose: impact des lignes directrices révisées de l'OMS

Objectif Déterminer si la mise en œuvre des lignes directrices 2010 de l'Organisation mondiale de la Santé (OMS) relatives à la mise en œuvre du traitement antirétroviral (TAR) a réduit le délai entre le diagnostic de la tuberculose et la mise en œuvre du TAR dans un hôpital cambodgien urbain.

Méthodes Une étude de cohorte rétrospective a été effectuée dans un hôpital non gouvernemental de Phnom Penh, appliquant les nouvelles lignes directrices de l'OMS, auprès de patients atteints du virus d'immunodéficience humaine (VIH) et de la tuberculose. Ont été inclus tous les patients VIH-positifs, n'ayant pas bénéficié auparavant d'un TAR, ayant entamé un traitement antituberculeux au cours des 18 mois avant et après la mise en œuvre des lignes directrices. Un modèle de régression à risques concurrents a été utilisé.

Résultats Après la mise en œuvre des lignes directrices 2010 de l'OMS, 190 patients séropositifs atteints de la tuberculose ont été identifiés: 53% d'hommes; âge médian: 38 ans; nombre médian de lymphocytes T CD4+ (cellule CD4+): 43 cellules/µL. Avant la mise en œuvre, 262 patients ont été identifiés; 56% d'hommes; âge médian: 36 ans; nombre médian de cellules CD4+: 59 cellules/µL. Avec un nombre médian de cellules CD4+ ≤ 50 cellules/µL, le délai médian avant le TAR est passé de 5,8 semaines (intervalle interquartile, IIQ: 3,7 à 9) avant, à 3.0 semaines (IIQ: 2,1 à 4,4) après la mise en œuvre *(P* <0,001); avec un nombre médian de cellules CD4+ > 50 cellules/µL, le délai est passé de 7.0 (IIQ: 5,3 à 11,3) à 3,6 semaines (IIQ: 2,9 à 5,3) *(P* <0,001). La probabilité de mise en œuvre du TAR dans les 4 à 8 semaines suivant le diagnostic de la tuberculose est passée de 23% et 65%, respectivement, avant la mise en œuvre, à 62% et 90% après la mise en œuvre. Une augmentation non significative de la rétention à 6 mois et de substitution antirétrovirale a été observée après la mise en œuvre.

Conclusion La mise en œuvre des lignes directrices 2010 de l'OMS dans un contexte clinique de routine raccourcit le délai avant la mise en œuvre du TAR. Des études plus importantes, avec un suivi plus long, seront nécessaires pour évaluer l'impact sur les patients.

Резюме

Сроки проведения антиретровирусной терапии в камбоджийской больнице после постановки диагноза туберкулеза: влияние нового Руководства ВОЗ

Цель Определить, способствовала ли реализация Руководства Всемирной организации здравоохранения по проведению антиретровирусной терапии (АРТ) (2010 г.) сокращению временной задержки от постановки диагноза туберкулеза до проведения АРТ в камбоджийской городской больнице.

Методы Было проведено проспективное когортное исследование в негосударственной больнице в Пномпене, в которой придерживались нового Руководства ВОЗ при лечении больных вирусом иммунодефицита человека (ВИЧ) и туберкулезом. В исследование были включены все ВИЧ-положительные пациенты, не проходившие курс АРТ, направленные на противотуберкулезное лечение в течении 18 месяцев до и после реализации Руководства. В исследовании использовалась модель регрессии конкурирующих рисков.

Результаты После реализации Руководства ВОЗ от 2010 г. были выявлены 190 ВИЧ-положительных пациентов с туберкулезом: 53% мужчин, средний возраст – 38 лет, среднее исходное число CD4+ Т-лимфоцитов (клеток CD4+) – 43 клетки/мкл. До реализации были выявлены 262 пациента: 56% мужчин, средний возрастной показатель – 36 лет, среднее исходное число клеток CD4+ – 59 клеток/мкл. При исходном количестве клеток CD4+ ≤ 50 клеток/мкл., средняя временная задержка до проведения АРТ уменьшилась с 5,8 недель (межквартильный диапазон, МКД: 3,7–9,0) до реализации Руководства до 3,0 недель (МКД: 2,1–4,4) после реализации (*P* < 0,001); при исходном количестве клеток CD4+ > 50 клеток/мкл., временная задержка сократилась с 7,0 (МКД: 5,3–11,3) до 3,6 (МКД: (2,9–5,3), недель (*P*< 0,001). Вероятность проведения АРТ в течении четырех и восьми недель после постановки диагноза туберкулеза повысилась с 23% и 65% соответственно (до реализации Руководства ВОЗ от 2010 г.), до 62% и 90% соответственно (после реализации). После реализации наблюдалось незначительное повышение в шестимесячной ретенции.

Вывод Реализация рекомендаций ВОЗ от 2010 г. в обычных клинических условиях сокращает временную задержку до проведения АРТ. Для оценки влияния на результаты лечения пациентов необходимо проведение масштабных исследований с длительным периодом наблюдения.

Resumen

La coordinación de la terapia antirretroviral en un hospital camboyano tras el diagnóstico de tuberculosis: el impacto de las directrices revisadas de la OMS

Objetivo Determinar si la puesta en práctica de las directrices de la Organización Mundial de la Salud (OMS) para el año 2010 acerca de la iniciación de la terapia antirretroviral (TAR)redujo la demora desde el diagnóstico de tuberculosis hasta el inicio de la TAR en un hospital urbano de Camboya.

Métodos Se llevó a cabo un estudio de cohorte retrospectivo en un hospital no gubernamental de Phnom Penh que siguió las directrices nuevas de la OMS en pacientes con el virus de la inmunodeficiencia humana (VIH) y tuberculosis. Se incluyeron todos los pacientes seropositivos que no recibieron TAR y que iniciaron un tratamiento contra la tuberculosis durante los 18 meses antes y después de la puesta en práctica de las directrices. Se utilizó un modelo de regresión de riesgos competitivos.

Resultados Tras la puesta en práctica de las directrices OMS para el año 2010, se identificaron 190 pacientes seropositivos con tuberculosis: el 53% de ellos, varones, edad media de 38 años y un recuento de LT CD4+ (células CD4+) como punto de partida con una mediana de 43 células/µL. Antes de la puesta en práctica, se identificaron 262 pacientes;

el 56% de ellos, varones; edad media de 36 años y un recuento de células CD4+ como punto de partida con una mediana de 59 células/µL. Con los recuentos de células CD4+ de ≤ 50 células/µL como punto de partida, la demora media hasta la TAR disminuyó de 5,8 semanas (rango intercuartílico: 3,7–9,0) antes, a 3,0 semanas (rango intercuartílico: 2,1–4,4) tras la implementación ($P < 0,001$); con los recuentos de células CD4+ inferiores a 50 células/µL como punto de partida, la demora bajó de 7,0 (rango intercuartílico: 5,3–11,3) a 3,6 (rango intercuartílico: 2,9–5,3) semanas ($p < 0,001$). La probabilidad de iniciar TAR entre 4 y 8 semanas tras el diagnóstico de tuberculosis aumentó del 23% y el 65%, respectivamente, antes de la implementación, hasta el 62% y el 90% después de la misma. Tras la implementación se observó un aumento no significativo de la retención a 6 meses, así como de la sustitución antirretroviral.

Conclusión La puesta en práctica de las recomendaciones de la OMS para el año 2010 en un entorno clínico habitual acorta la demora hasta el inicio de la TAR. Son necesarios estudios más amplios con seguimientos mayores para evaluar el impacto sobre los resultados en los pacientes.

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