Dialogues in Health 2 (2023) 100120

Contents lists available at ScienceDirect

Dialogues in Health

journal homepage: www.elsevier.com/locate/dialog

The effect of the Universal Test and Treat policy uptake on CD4 count testing and incidence of opportunistic infections among people living with HIV infection in Cameroon: a retrospective analysis of routine data

C.E. Bekolo [a,b,*], S.A. Ndeso [b], C.P. Gougue [a], L.L. Moifo [a], N. Mangala [c], P. Tchendjou [d], E. Mboh [e], J. Ateudjieu [a], N. Tendongfor [b], D.S. Nsagha [b], G.E. Halle-Ekane [f], S.P. Choukem [g]

[a] Department of Public Health, Faculty of Medicine and Pharmaceutical Sciences, University of Dschang, Dschang, Cameroon
[b] Department of Public Health and Hygiene, Faculty of Health Sciences, University of Buea, Buea, Cameroon
[c] Department of Gynaecology and Obstetrics, University of Douala, Douala, Cameroon
[d] Elizabeth Glaser Pediatric AIDS Foundation, EGPAF Yaounde, Yaounde, Cameroon
[e] Cameroon Baptist Convention Health Services, Bamenda, Cameroon
[f] Department of Obstetrics and Gynaecology, University of Buea, Buea, Cameroon
[g] Department of Internal Medicine and Specialities, Faculty of Medicine and Pharmaceutical Sciences, University of Dschang, Dschang, Cameroon

ARTICLE INFO

Keywords:
HIV
Universal test and treat
CD4 testing
Opportunistic infections
Cameroon

ABSTRACT

Background: Cameroon adopted and started implementing in 2016, the 'universal test and treat' (UTT) guidelines to fast-track progress towards the 95-95-95 ambitious targets to end the HIV epidemic. UTT has shown inconsistent results elsewhere and has not yet been assessed in Cameroon. We aimed to evaluate the effectiveness of this novel approach on the quality of care and health outcomes of people living with HIV (PLHIV).

Methods: A retrospective cohort design was conducted at The Nkongsamba Regional Hospital, using routine clinical service delivery data to measure uptake levels of UTT and CD4 testing, and to compare the incidence of opportunistic infections (OI) between PLHIV initiated on ART based on the "Universal Test and Treat" strategy and those initiated on ART based on the standard deferred approach between 2002 and 2020. Kaplan Meier plots and log-rank tests were used to compare OI events between the pre-UTT and post-UTT eras. The Cox regression model was used to screen for factors independently associated with the risk of acquisition of OI.

Results: The uptake of UTT ranged from 39.1% to 92.8% while baseline CD4 count testing reduced drastically from 89.4% to 0.4% between 2016 to 2020 respectively. The median delay in ART initiation declined significantly from 21 days (IQR: 9 – 113) in the pre-UTT era to the same day of diagnosis (IQR: 0 – 2) in the UTT era ($p < 0.001$). The incidence of all OI events reported was over five times higher during the UTT era than in the pre-UTT era [aHR = 5.55 (95% CI: 3.18 – 9.69), $p < 0.001$].

Conclusion: The UTT policy has been effectively rolled out and has contributed to improved access to rapid and immediate ART initiation, but a higher incidence of OIs was observed with a rollback of baseline CD4 testing. We advocate for a return to routine baseline CD4 measurement to identify PLHIV who should benefit from interventions to prevent OIs for optimal outcomes under the UTT approach.

List of abbreviations

(a)HR	(adjusted) Hazard ratio
95% CI	95% Confidence Interval
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
CD4	Cluster of Designation 4
CPT	Cotrimoxazole prevention therapy
CrAg	Cryptococcal antigen
HIV	Human Immunodeficiency Virus
IPT	Isoniazid prevention therapy
LF-LAM	Lateral flow- lipoarabinomannan
OI	Opportunistic infection
PLHIV	People living with HIV
TB	Tuberculosis
UTT	Universal test and treat

* Corresponding author at: PO Box 96, Dschang, Cameroon.
E-mail address: cavin.bekolo@univ-dschang.org (C.E. Bekolo).

http://dx.doi.org/10.1016/j.dialog.2023.100120
Received 15 December 2022; Received in revised form 5 February 2023; Accepted 23 February 2023
Available online 26 February 2023

1. Introduction

The human immunodeficiency virus (HIV) continues to be a major global public health problem, having claimed 36.3 million lives out of the 79.3 million people infected with HIV since the start of the epidemic [1,2]. There is no cure for HIV infection. However, with increasing access to effective treatment and care, HIV infection has been turned from a rapidly fatal infection to a manageable chronic health condition, enabling people living with HIV to lead long and healthy lives. At the end of 2020, a record 27.5 million people living with HIV were receiving antiretroviral therapy (ART) worldwide representing a more than three-fold increase since 2010 [2,3]. This steady scale-up of ART has in turn driven down new HIV infections and global deaths from AIDS (acquired immune deficiency syndrome)-related illnesses to record low levels of 1.50 and 0.68 million people, respectively [2]. As deaths decline faster than new HIV infections, the number of people living with HIV has risen to over thirty-eight million. The global decline in AIDS-related mortality has largely been driven by progress in sub-Saharan Africa, particularly Eastern and Southern Africa (ESA), which is home to 55% of the world's people living with HIV. AIDS-related mortality decreased by 43% since 2010 in ESA, reflecting the rapid pace of treatment scale-up in the region owing to strong domestic and international investment [2,4]. Unfortunately, HIV responses in Western and Central Africa (WCA) continue to trail the rest of sub-Saharan Africa. There were 37% fewer new HIV infections in the WCA region in 2020 compared with 2010 showing steady progress, but far short of the 75% reduction agreed upon by the United Nations (UN) General Assembly [2]. Consequently, the incidence-to-prevalence ratio in the region has changed little since 2010: it stood at 0.06 in 2017, twice as high as the epidemic transition benchmark of 0.03 [2,5]. A priority issue facing the WCA region is the extremely low coverage of antiretroviral therapy particularly among children thus the need to bring the region to focus in the fight against the AIDS pandemic.

In response to this slow progress on the path towards reaching the 95-95-95 ambitious targets aimed at ending the AIDS epidemic by 2030, a regional catch-up plan has been implemented in the WCA region since 2016 [6,7]. In their 2016-2018 catch-up plan, Cameroon with an HIV prevalence of 2.7% (500000 PLHIV), adopted and started implementing the 'universal test and treat (UTT) approach to fast-track progress towards the 95-95-95 targets [8,9]. Through this universal test and treat approach, ART initiation immediately after HIV diagnosis is recommended irrespective of the CD4 + T-cell count by the 2016 World Health Organization (WHO) consolidated guidelines on the use of antiretroviral medicines for treating and preventing HIV infection [7]. According to this policy change, CD4 cell counts are no longer recommended as a requirement to decide when to start ART; and for patients stable on ART, CD4 cell counts are no longer needed to monitor the response to treatment where HIV viral load testing is available on the other hand. Nevertheless, CD4 remains the best measurement of a patient's immune and clinical status, and the risk of opportunistic infections, and supports diagnostic decision-making, particularly for patients with advanced HIV disease. Considering the UTT policy, the role of CD4 testing has become more restricted to baseline testing, returning to its original purpose as an essential tool in the assessment of disease progression in patients and, most importantly, in the timely screening, prophylaxis and proper management of patients with life-threatening opportunistic infections (OI). WHO recommends that HIV programmes should retain the capacity to perform CD4 cell count at baseline to assist in identifying patients with advanced immune depression who need to start cotrimoxazole prophylaxis to prevent morbidity and mortality from a variety of bacterial, fungal, and protozoan opportunistic infections. Similarly, CD4 count at baseline is mandatory to identify patients with CD4 < 100 cells/mm^3 who should be screened for cryptococcal antigen (CrAg) and the urine lateral flow-lipoarabinomannan (LF-LAM) assay to assist in the diagnosis of cryptococcal meningitis and tuberculosis (TB) respectively [10]. CrAg, LF-LAM, and other screening tools are being rolled out to support the timely detection of AIDS-defining infections. Yet as healthcare providers are pressured to initiate ART on the same day of HIV diagnosis or as quickly as possible to achieve the second 95, they are ignoring baseline CD4 testing. Phasing out CD4 count testing may lead to suboptimal outcomes than expected under UTT because it would fail to timely detect and offer a special package of care for (asymptomatic) PLHIV with severe immune deficiency who are at a higher risk of opportunistic infections and immune reconstitution syndrome (IRIS) shortly after starting ART [10,11]. The likely consequences of waiving baseline CD4 count measurement coupled with the rapid expansion of antiretroviral because of rapid UTT uptake is expected to increase the incidence of ART-driven "unmasked" subclinical infections like tuberculosis [12,13]. High incidence rates of notified TB under ART in poor-resource countries were observed; these cases of TB were likely to include both undiagnosed pre-existing TB at ART initiation and subclinical TB developing during the immune reconstitution inflammatory syndrome [14].

Implementing the Test and Treat policy has the potential to reduce the incidence of HIV infection and related morbidity and mortality yet reports from previous studies are inconsistent due to context-related issues [15,16]. Few studies have reported the incidence of IO under the UTT policy. In Ethiopia, a reduction of TB incidence by 75% in the UTT programme compared to the deferred programme was observed [17]. The WCA are once more trailing the rest of SSA in documenting their experiences in implementing UTT. Though substantial amounts and increasingly high quality routinely collected data (RCD) are stored by the HIV programmes in WCA owing to efforts from international partners, they have not been analysed rigorously to assess the effect of UTT on programme outcomes.

We aim to evaluate the level of uptake of UTT and the effect of this novel approach on CD4 testing, late presentation, and the detection of opportunistic infections among PLHIV by comparing a cohort of PLHIV who started ART under the UTT approach with a cohort who were initiated under the previous deferred treatment approach. We hope this evaluation would be an essential tool for determining how well the test and treat programme in real-life practice is performing to meet the needs of service users and whether improvements are required.

2. Methods

2.1. Setting

The study was conducted at the HIV Clinic of The Regional Hospital of Nkongsamba in the Mungo Division of the Littoral Region of Cameroon. The hospital is a second level of reference public health facility with a catchment area of over 321,295 inhabitants. Users of the HIV Clinic come from the city of Nkongsamba obviously but massively constitute of referrals from the rural municipalities of Melong, Bare-Bakem, Nlonako, Manjo, Loum, Njombe-Penja, Mbanga, Bonalea and Dibombari that make up the Mungo Division; equally from neighbouring rural areas of Bangem and Tombel in the South-West Region and the rural municipalities of Kekem and Santchou in the West Region of Cameroon. The clinic was established in 2005 and offers voluntary HIV counselling and testing (VCT), ART and limited community outreach services to over 2000 patients on ART. HIV services are provided by multidisciplinary teams composed of physicians, health officers, nurses, pharmacy attendants, laboratory technicians, psychosocial/adherence supporters, and data personnel. As of 2016, per the national ART guideline, PLHIV are immediately linked to an ART clinic for a confirmatory test, counselling, adherence preparation and rapid ART initiation - including same-day ART for persons who are ready to start ART at the first clinical visit in the absence of CD4 testing that would otherwise delay ART initiation.

Before 2016, The guideline recommended mandatory baseline laboratory tests such as CD4 cell count, and haematological, liver and kidney function tests, if available. ART initiation was deferred (several times) until eligibility criteria (CD4 threshold, WHO clinical stage) were met.

2.2. Participants

The study included two groups of PLHIV who were newly diagnosed and started on ART at the study site; those who were started on the same

day as HIV diagnosis and those who were started days after the initial diagnosis based on the deferred approach. Eligible PLHIV for OI surveillance were ≥15 years old and newly initiated on ART between 2010 and 2021. Records of ART clients who were initiated while pregnant and who were transferred in (TI) from another health facility were excluded.

The minimum sample size of 290 participants was determined using G*Power 3.1 (Universität Kiel, Germany) for cohort studies based on the difference in cumulative risk (proportions) of OI at the end of the follow-up period. Statistical assumptions of 95% confidence level, 80% power, risk of IO of 32.2% taken from a previous study [18], a risk reduction of 50% under UTT, and a 20% adjustment for the incompleteness of medical records were considered.

2.3. Study design

In the first phase, a chart review was conducted to describe the trend in uptake of UTT and the trend in CD4 testing using individual patient records enrolled into HIV care between 2002 and 2021, to extract their dates of HIV diagnosis, baseline characteristics including CD4 cell counts, and dates of ART initiation.

Then a facility-based retrospective cohort design using routine clinical service delivery data abstracted from facility-based medical records was undertaken. From the chart review, PLHIV enrolled up to the year 2016 were included in the pre-UTT (unexposed or control) group while those enrolled after the year 2006 were included in the UTT (exposed) group. Based on days from HIV+ diagnosis to ART initiation, PLHIV were further stratified into the same-day initiation (SDI) group, rapid initiation group (1 – 7 days) or the deferred initiation group (8+ days). The groups were then followed retrospectively up for a period of up to 100 months to compare the incidence of OI between the groups (Fig. 1). An OI was defined as any HIV-related infection occurring after the start of ART and recorded as a time to event outcome.

2.4. Data collection and study variables

Data were collected from HIV clinic pre-ART, ART registers, and individual patient medical records. The registers are designed by the National AIDS Control Committee (NACC) for the standardised collection and reporting of data. We extracted the following independent variables using a data extraction form: socio-demographic characteristics: date of birth, gender, place of residence, occupation, religion, alcohol and tobacco consumption, education, and matrimonial status; clinical features including date of HIV diagnosis, baseline weight and height, and clinical stage at presentation; treatment-related variables including date of ART initiation, ART regimen, drug side effects, cotrimoxazole preventive treatment (CPT), and isoniazid preventive treatment (IPT).

2.5. Data analysis

Data collected were exported to Stata® 15.1 (StataCorp LLC, Texas 77845, USA) for statistical analysis. The data set was explored for logical inconsistencies, illegal codes, omissions and improbabilities by tabulating, summarising, describing, and plotting variables. Missing observations were excluded where they constituted a small random proportion. Summary statistics were presented as proportions for categorical variables and as means (standard deviations) for normally distributed continuous variables or medians (IQR-Interquartile Range) for skewed distributed continuous variables.

Uptake of UTT was defined as the time from the date of an HIV-positive diagnosis to the date of ART initiation, categorised as follows: same-day initiation (SDI), 1– 7 days (rapid initiation) and 8+ days (deferred initiation).

To describe the relationship between the uptake of the UTT and baseline CD4 counts between 2016 and 2022, a scatter plot with the goodness of fit line is displayed. The coefficients of determination (R^2) and correlation (r) were recorded. The median time to ART initiation between the UTT and standard approaches was compared using Mood's test for equality of medians.

The incidence of OI was calculated by dividing all new OI events by the total person-time at follow-up. To evaluate the impact of UTT on the incidence of opportunistic infections, we plotted and compared Kaplan Meier curves of cumulative events of OI between the two groups using the log-rank test. The Cox regression model was used to screen for factors independently associated with the risk of acquisition of OI. Hazard ratios with their corresponding 95% confidence intervals and p-values were obtained from the final multivariable Cox model. The proportionality hazard assumption over time was assessed graphically using Aalen plots.

3. Results

3.1. Baseline characteristics of participants

From the chart review, a total of 1651 persons diagnosed HIV positive between 2002 and 2021 were identified. Of these, 756 (46.47%) were enrolled during the era of UTT with 545 (33.54%) initiated on ART on the same day of HIV diagnosis (Table 1). Same-day ART starters were mostly enrolled under the UTT era (93.03%), were likely to be women (71.38%),

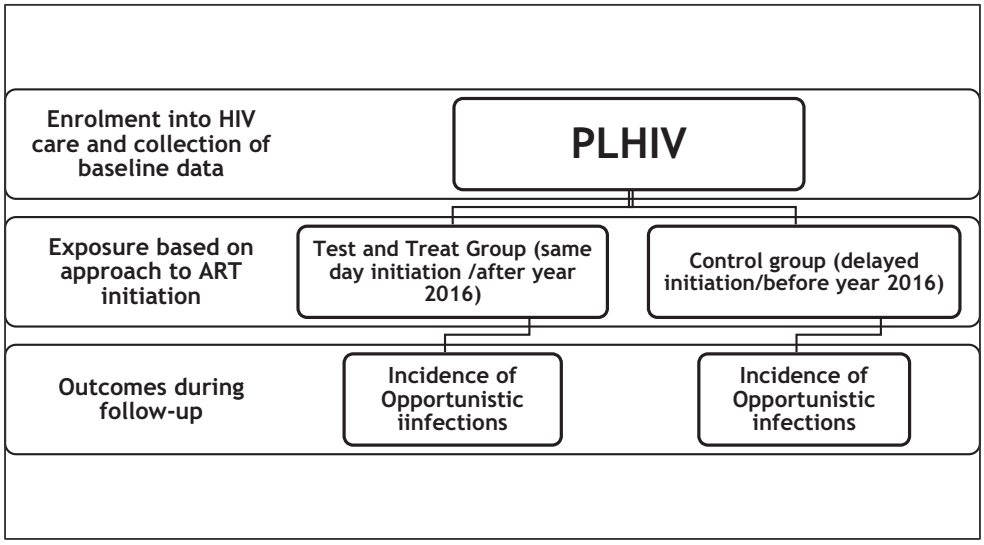

Fig. 1. The study flow chart.

Table 1
Baseline characteristics of the study population by ART initiation strategy.

Variables	Same day Initiation	Rapid Initiation	Deferred initiation	p-value
	n (%)	n (%)	n (%)	
Cohort				
Before UTT	38 (6.97)	135 (48.74)	698 (86.92)	<0.001
Under UTT	507 (93.03)	142 (51.26)	105 (13.08)	
Total	545 (100)	277 (100)	803 (100)	
Age group (years)				
<=40	262 (48.07)	112 (40.58)	395 (49.50)	0.036
>40	283 (51.93)	164 (59.42)	403 (50.50)	
Total	545 (100)	276 (100)	798 (100)	
Sex				
Female	384 (71.38)	208 (75.36)	507 (63.93)	<0.001
Male	154 (28.62)	68 (24.64)	286 (36.07)	
Total	538 (100)	276 (100)	793 (100)	
Marital status				
Single	247 (47.05)	118 (44.36)	366 (48.03)	0.195
Married	187 (35.62)	89 (33.46)	225 (29.53)	
Divorced	25 (4.76)	15 (5.64)	46 (6.04)	
Widowed	66 (12.57)	44 (16.54)	125 (16.40)	
Total	525 (100)	266 (100)	762 (100)	
Residence				
Local	256 (47.50)	122 (45.02)	300 (37.93)	<0.001
Regional	220 (40.82)	119 (43.91)	421 (53.22)	
Inter-regional	63 (11.69)	30 (11.07)	70 (8.85)	
Total	539 (100)	271 (100)	791 (100)	
Baseline CD4 testing				
No	507 (93.03)	144 (51.99)	142 (17.77)	<0.001
Yes	38 (6.97)	133 (48.01)	657 (82.23)	
Total	545 (100)	277 (100)	799 (100)	
Immune status (CD4 count per mm^3)				
<200	17 (45.95)	74 (55.64)	356 (54.27)	0.989
>=200	20 (54.05)	59 (44.36)	300 (45.73)	
Total	37 (100)	133 (100)	656 (100)	
WHO Clinical Stage				
Early (stages I & II)	426 (83.86)	152 (64.68)	338 (52.16)	<0.001
Advanced (stages III & IV)	82 (16.14)	83 (35.32)	310 (47.84)	
Total	508 (100)	235 (100)	648 (100)	
Smoking				
No	486 (89.17)	242 (87.36)	714 (88.92)	0.722
Yes	59 (10.83)	35 (12.64)	89 (11.08)	
Total	545 (100)	277 (100)	803 (100)	
Alcohol intake				
No	213 (39.08)	122 (44.04)	390 (48.57)	0.003
Yes	332 (60.92)	155 (55.96)	413 (51.43)	
Total	545 (100)	277 (100)	803 (100)	
Occupation				
None	151 (28.71)	96 (35.56)	286 (36.48)	0.053
Currently employed	369 (70.15)	171 (63.33)	492 (62.76)	
Retired	6 (1.14)	3 (1.11)	6 (0.77)	
Total	526 (100)	270 (100)	784 (100)	

of age >40 years (51.93%), and living close to the clinic (47.50%). Baseline CD4 testing was low among SDI and where available, almost half had a titre of fewer than 200 cells/mm^3 although late clinical presentation was uncommon among SDI (16.14%).

The trend in the uptake of the universal test and treat policy and its effect on baseline CD4 testing

A negligible proportion of patients varying from 3.91% to 8.77% has been documented to have been initiated on the same day of their HIV diagnosis before the adoption of UTT in 2016. A rapid scale-up of SDI was then observed from 39.09% in 2017 to 92.83% in 2020. Meanwhile, CD4 testing at baseline was common before the UTT era but declined drastically with the adoption and implementation of UTT, from 89.43% in 2015 to 0.38% in 2020 at an average rate of about 27% per year (Fig. 2). the steepest decline was observed during the first year of adopting the treat-all policy. Baseline CD4 testing dropped significantly by 1.2% for every 1% increase in the uptake of UTT (Fig. 3).

The trend in the late presentation and time to ART initiation before and under the universal test and treat policy

Overall, late presentation with advanced HIV infection (WHO stage 3 and 4) was recorded in 480 (34.16%). It was significantly higher in the pre-UTT era than in the UTT era (51.17% vs. 17.56%, $p < 0.001$). Late presentation remained stable above 50% between 2005 and 2015 but then fell sharply by over 30% between 2015 and 2020.

The overall median delay in ART initiation was 7 days (IQR: 0 – 35) declining significantly from 21 days (IQR: 9 – 113) in the pre-UTT era to the same day of diagnosis (IQR: 0 – 2) in the UTT era ($p < 0.001$). During the first 10 years of ART use when ART was highly dependent on CD4 below 200 – 350 cells/mm^3 the median time to ART start ranged from 315 to over 1000 days. It then fell remarkably between 11 to 21 days when the threshold to ART start was raised to 500 cells/mm^3 between 2013 and 2016. From 2017 when all restrictions based on CD4 count were removed, the median time ranges between 0 – 1 day since HIV diagnosis (Fig. 4).

Uptake of universal test and treat policy on the incidence of AIDS-defining infections

A total of 142 (22.72%) OI events were recorded among 625 patients included in the time-to-event analysis. The commonest OI reported were tuberculosis (58%), skin infections (23%), bacterial pneumonia (11%), oral thrush (4%) and central nervous system infections (4%).

After a total observation time of 39509 person-months (p-mo) on ART, the overall incidence of OI was 3.56 events per 1000 p-mo. The incidence during the UTT era was 7.23 cases p.1000 p-mo, higher than the rate of 1.96 cases p.1000 p-mo observed before the UTT era ($p < 0.0001$) (Fig. 5). The incidence was higher among ART same-day starters than late starters (4.41 vs. 1.70 cases p.1000 p-mo ($p < 0.0001$) (Fig. 6).

After controlling for demographic and clinical characteristics of patients, the incidence of IO reported was over five times higher during the UTT era than in the pre-UTT era [aHR = 5.55 (95% CI: 3.18 – 9.69), $p < 0.001$]. Similarly, the incidence of OI was about twice as high among SDI than among later initiators [aHR = 1.76 (95% CI: 1.06 – 2.94), $p = 0.030$]. Other strong predictors of OI occurrence were age above 40 years [aHR = 1.59 (95% CI: 1.12 – 2.26), $p = 0.010$] and zidovudine-based regimens [aHR = 1.88 (95% CI: 1.04 – 3.41), p =8 0.038] but switching to dolutegravir-based regimens was a weaker predictor of OI occurrence [aHR = 1.78 (95% CI: 0.96 – 3.28), $p = 0.066$] (Table 2).

4. Discussion

This is the first study that sought to assess the level of uptake of UTT and the effect of this novel approach on timely access to ART, CD4 testing, and the incidence of opportunistic infections in Central Africa. The study has indicated a successful rollout of the UTT policy with a remarkable reduction in delays to ART initiation and a significant decline in late presentation but paradoxically with a drastic decline in baseline CD4 testing and a higher incidence of reported cases of opportunistic infections.

Within the first five years of adopting the UTT policy in 2016, this study has observed that universal and immediate ART initiation was effectively implemented at this HIV clinic and has now become the standard approach. Nationally, the number of people receiving antiretroviral therapy in Cameroon increased steadily from 17156 in 2005 to 168249 in 2015 and then exponentially to 337342 in 2019 corresponding to a steady rise in ART coverage from 20% in 2010 to 40% in 2016 and then to a sharp increase to approximately 80% in 2021 [19]. This sharp increase from 2016 corresponded with the introduction of the test and treat-all strategy. Substantial uptake of the UTT policy has been reported across several sub-Saharan African countries [20–25]. This successful implementation of the UTT policy has been facilitated intuitively from the removal of the CD4 eligibility threshold for ART initiation, but also by experiences gained from the Option B+ approach that preceded UTT, the extraordinary financial support and pressures from different stakeholders (from governments,

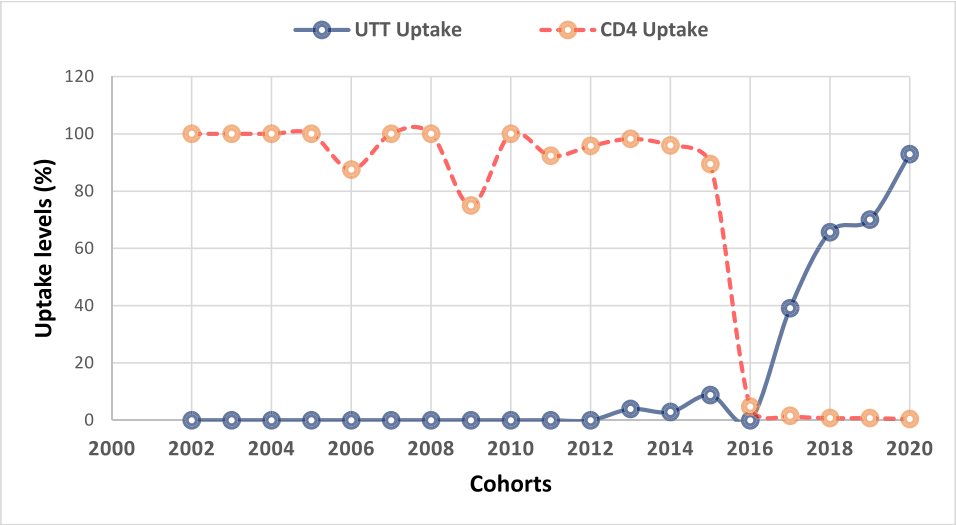

Fig. 2. Uptake levels of same-day initiation and CD4 testing across ART guideline periods.

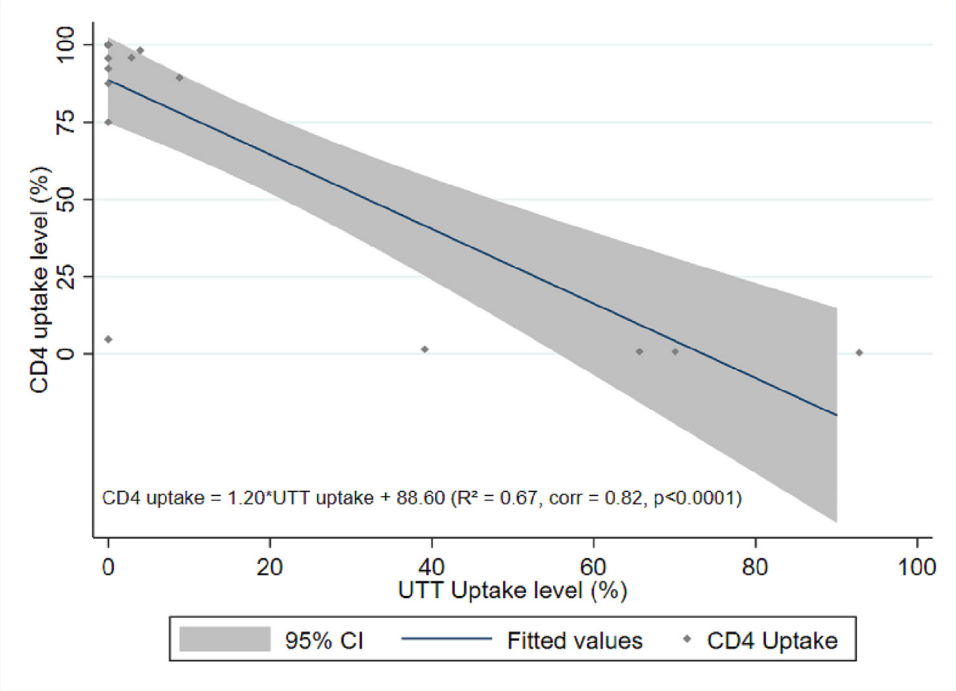

Fig. 3. The linear relationship between UTT uptake and baseline CD4 testing between 2016 and 2020.

civil society groups, researchers, and donors) to accelerate the implementation of UTT [26,27].

While removing the CD4 count as a criterium to decide when to start ART has been critical in scaling up the UTT policy uptake, a dramatic 89% decline in baseline CD4 testing between 2015 and 2020 was observed despite the WHO recommendation to perform baseline CD4 testing at enrolment into HIV care to determine whether a patient has advanced HIV disease (defined as CD4 cell count < 200 cells/mm^3 or WHO stage 3 or 4 events)[10]. A similar decline from 73% to 21% between 2013 and 2018 was reported in Uganda with the adoption of the treat-all policy [28], and a reduction from a peak of 78.1% in 2008 to a low of 38.0% in 2017 was recorded in six Southern African countries [29]. A regression discontinuity analysis found a 8.9% decrease in CD4 testing among low/lower-middle-income countries (L/LMICs) but a 1.6% increase in high/upper-middle-income countries (H/UMICs)[30]. People presenting with advanced HIV disease remain consistently high (30 – 50%) despite ART scale-up [31–33] and should be provided components of a package of interventions including screening, treatment and/or prophylaxis for major opportunistic infections, rapid ART initiation and intensified adherence support interventions to reduce the high morbidity and mortality in this group [10,11,34]. CD4 count testing remains crucial in identifying these persons with advanced HIV disease because the clinical definition has low sensitivity [35]. This rollback in CD4 testing meant rolling back the use of prophylactic medication and that a large proportion of patients with advanced HIV disease are missed and may then be at higher risk of morbidity and mortality. Sikombe et al. found that Zambian patients without baseline CD4 monitoring had 1.50 times the hazard of mortality in the first year compared with patients who had pretherapy CD4 testing (95% CI, 1.00–2.17, p = 0.046) [36].

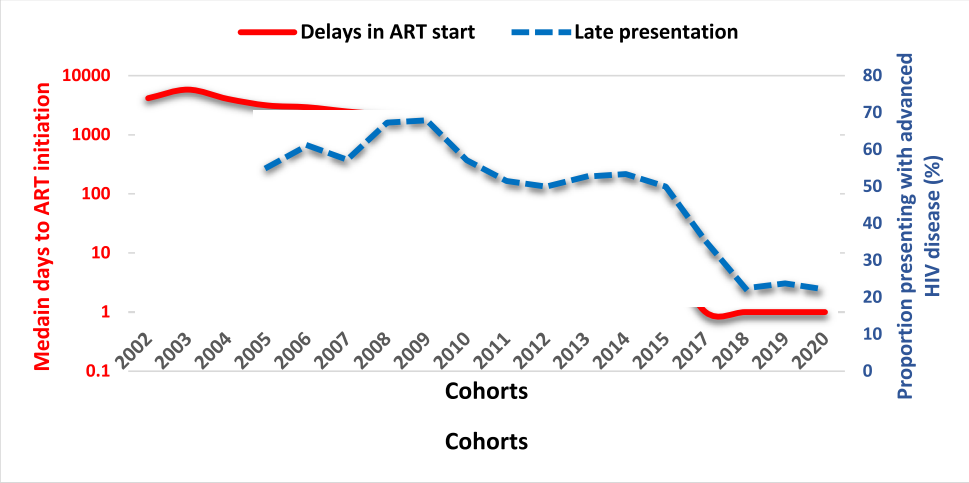

Fig. 4. Time to ART initiation and late clinical presentation across guideline periods.

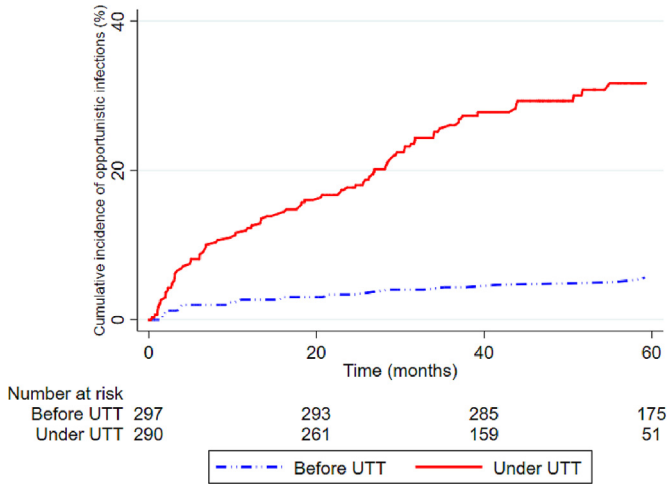

Fig. 5. Kaplan Meier curve of occurrence of opportunistic infections by ART policy periods

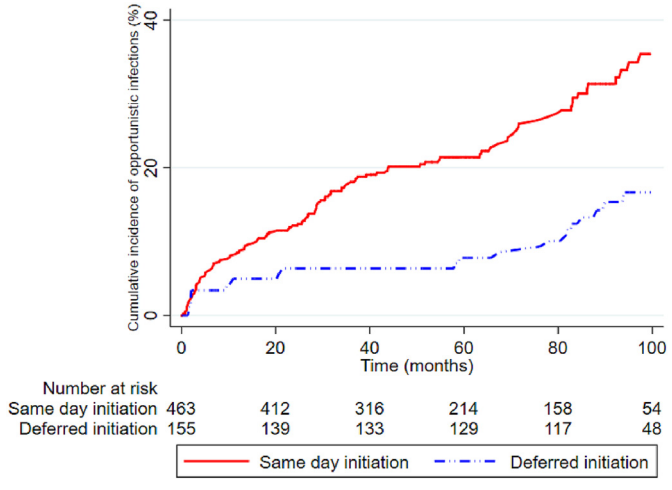

Fig. 6. Kaplan Meier curve of occurrence of opportunistic infections by ART initiation strategy.

The phasing out of CD4 testing could be understood as a misinterpretation of the UTT guidelines but also a result of the promotion of viral load testing over CD4 to monitor patients on ART and, the diminished donor support for CD4 testing [26,37]. Considering that a significant proportion of PLHIV still presented with low CD4 and thus at higher risk of mortality, it is urgent to return to mandatory CD4 testing that characterised the pre-UTT era to ensure optimal outcomes under the UTT policy.

This study has highlighted an increased incidence of OI under the UTT policy, a finding considered unexpected given prior knowledge of the impact of ART on HIV disease progression before UTT. Two systematic reviews and meta-analyses in LMIC conducted before the UTT era showed that the incidence of 15 OIs reduced by 57% to 91% during the first year of ART among children and adults [38,39]. The landmark TEMPRANO trial that contributed to the adoption of UTT demonstrated that early initiation of ART reduced the risk of severe HIV-related illness by 44% compared with the deferred initiation of ART [40]. A study from Ethiopia has found that the UTT programme reduced TB incidence by 75% among adults. We think our findings are contradictory for a couple of reasons. Firstly, the rapid initiation of ART without knowledge of the level of immune depression based on CD4 count, means a large proportion of PLHIV presenting with unrecognised advanced disease, go on to unmask their subclinical OIs shortly after starting ART because of the restoration of the functional immune responses. A high burden of unmasking TB has been reported in LMIC with an incidence of 5.6 to 22.1 cases per 100 patient years of observation [41,42]. Secondly, even during the UTT era, over 80% of PLHIV who were tested presented with CD4 counts of less than 350 cells/mm^3 and thus remained at a higher risk of HIV-related infections. Low CD4 has been unequivocally linked to a higher incidence of OIs: the lower the CD4 count before ART, the higher the risk of TB during ART [43]. Lawn et al. reported that the risk of clinical TB occurrence during the first months of ART, among patients with a low CD4, was 40% higher than among those with the same CD4 counts during long-term treatment and, that patients with a low CD4 had a 3 to 4 fold increase in the risk of unmasking TB than those with a higher CD4 count [44]. Thirdly, from the epidemiological surveillance standpoint, the increasing integration of TB services into HIV clinics, the expanding access to diagnostics technology and other surveillance tools to support clinical screening and diagnosis of OIs, and active case finding in the era of UTT have led to improved detection and reporting of OIs [45,46]. We observed a significant increase in active TB case finding from 44.19% to 76.80% between the pre-UTT and post-UTT periods. The cumulative incidence of TB in this study matches the pattern observed in the African Region characterised by an ascending trend in TB incidence between 2015 and 2019 [46,47]. So as UTT uptake will continue to expand the rapid and immediate ART initiation, programme managers should be aware of a potential rise in OIs directly attributable to the

Table 2
Demographic and clinical characteristics associated with the occurrence of opportunistic infections.

Factor	Incidence of opportunistic infection (per 1000 person-months)	HR (95% CI)	p-value	aHR (95% CI)	p-value
Strategy					
SDI	4.41	2.45 (1.53 – 3.93)	<0.001	1.76 (1.06 – 2.94)	0.030
Deferred	1.70	1		1	
Cohort					
Before UTT	1.96	1		1	
Under UTT	7.23	6.50 (3.85 – 10.99)	<0.001	5.55 (3.18 – 9.69)	<0.001
Age group (years)					
< = 40	2.53	1		1	
>40	4.70	1.83 (1.30 – 2.59)	0.001	1.59 (1.12 – 2.26)	0.010
Marital status					
Single	2.80	1		1	
Married	3.59	1.27 (0.82 – 1.97)	0.276	1.03 (0.64 – 1.66)	0.899
Divorced	3.24	1.14 (0.55 – 2.34)	0.725	0.64 (0.30 – 1.40)	0.267
Widowed	4.69	1.68 (1.02 – 2.76)	0.040	1.48 (0.82 – 2.67)	0.190
Immune status (CD4 count per mm^3)					
<350	3.87	1		1	
> = 350	2.97	0.80 (0.56 – 1.15)	0.228	0.83 (0.49 – 1.41)	0.496
WHO Clinical Stage					
Early (stages I & II)	3.45	1		1	
Advanced (stages III & IV)	6.79	1.88 (0.96 – 3.70)	0.067	1.54 (0.77 – 3.07)	0.222
TB Screening					
Yes	4.58	1.76 (1.24 – 2.52)	0.002	1.24 (0.84 – 1.82)	0.277
No	2.43	1		1	
ART regimen backbone					
TDF	3.23	1		1	
TLD	13.82	3.33 (1.82 – 6.07)	<0.001	1.78 (0.96 – 3.28)	0.066
PI	10.26	3.08 (0.97 – 9.73)	0.056	2.48 (0.77 – 7.98)	0.128
AZT	3.48	1.07 (0.62 – 1.84)	0.817	1.88 (1.04 – 3.41)	0.038
CPT					
Yes	4.24	1.43 (1.02 – 2.02)	0.039	1.08 (0.66 – 1.79)	0.746
No	2.81	1		1	
IPT					
No	3.17	1		1	
Yes	4.56	1.35 (0.95 – 1.93)	0.094	0.89 (0.61 – 1.29)	0.545

"unveiling" effect of ART-induced immune restoration. A multicentre study may be required to support this hypothesis.

The use of routine programmatic data in this study led to some limitations ranging from the incompleteness of data to errors in data collection and the inability to explore reasons behind uptake levels of UTT and CD4 to the inability to ensure comparability of data collected before and after the adoption of the UTT policy.

5. Conclusion

The study has indicated that five years after its adoption, the UTT approach has been effectively rolled out and has contributed to improved access to rapid and immediate ART initiation, but a higher incidence of opportunistic infections was observed with a rollback of baseline CD4 testing. We advocate for a U-turn to a routine baseline CD4 measurement to identify PLHIV who should benefit from interventions to prevent OIs and better finetune the UTT approach. Monitoring of unmasking OIs would be critical to achieving optimal outcomes under UTT.

Ethics approval and consent to participate

Ethical approval was obtained from The Regional Ethics Committee for Research in Humans. Permission to use data was duly obtained from the hospital management board. Consent from individual patients was not sought because we used routine data. However, all patient information was anonymised and de-identified before analysis. Access to the database was protected by a password.

Consent for publication

Not applicable

Availability of data and materials

Data can be obtained from the health facility upon request from the authors

Funding

The authors declare that they received no funding for this study

Authors' contributions

CEB: Conception, design, statistical analysis, write up
CPG, LLM, NM: data collection, extraction, and management
JA, PT, EM, NT, SDN, SPC: Conception, design, proof-reading, approval to publish

Declaration of Competing Interest

The authors declare that they have no competing interests

Acknowledgement

We are grateful to the staff and patients of The Nkongsamba Regional Hospital & The Centre Dream of St Vincent de Paul Hospital in Dschang, Cameroon.

References

[1] HIV/AIDS Key facts. https://www.who.int/news-room/fact-sheets/detail/hiv-aids.
[2] UNAIDS. UNAIDS Data 2021. Geneva: Joint United Nations Programme on HIV/AIDS; 2021.
[3] UNAIDS. Global AIDS report. Geneva: Joint United Nations Programme on HIV/AIDS; 2020; 2020.
[4] UNAIDS. Data 2018. Geneva: Joint United Nations Programme on HIV/AIDS; 2018.

[5] UNAIDS. Miles to go, closing gaps breaking barriers righting injustices. UNAIDS update 2018. In. Geneva: Joint United Nations Programme on HIV/AIDS; 2018.
[6] UNAIDS. The western and central africa catch-up plan putting hiv treatment on the fast-track by 2018. Geneva; 2016.
[7] WHO. Treat all: policy adoption and implementation status in countries. Geneva; 2017.
[8] Cameroun M. PLAN D'ACCELERATION DE LA THERAPIE ARV AU CAMEROUN 2016-2018. Yaounde; 2015.
[9] Cameroun M. Guide de Traitement pour tous. Yaounde; 2017.
[10] WHO Guidelines Approved by the Guidelines Review Committee. Guidelines for Managing Advanced HIV Disease and Rapid Initiation of Antiretroviral Therapy. 2017, Geneva: World Health Organization Copyright © World Health Organization; 2017.
[11] Ford N, Meintjes G, Vitoria M, Greene G, Chiller T. The evolving role of CD4 cell counts in HIV care. Curr Opin HIV AIDS. 2017;12(2):123–8.
[12] Lawn SD, Badri M, Wood R. Tuberculosis among HIV-infected patients receiving HAART: long term incidence and risk factors in a South African cohort. Aids. 2005;19 (18):2109–16.
[13] Lapadula G, Soria A, Bandera A, Squillace N, Sabbatini F, Franzetti F, et al. Unmasking tuberculosis in the era of antiretroviral treatment. European Respiratory Journal. 2012; 39(5):1064–75.
[14] Bonnet MM, Pinoges LL, Varaine FF, Oberhauser BB, O'Brien DD, Kebede YY, et al. Tuberculosis after HAART initiation in HIV-positive patients from five countries with a high tuberculosis burden. Aids. 2006;20(9):1275–9.
[15] Perriat D, Balzer L, Hayes R, Lockman S, Walsh F, Ayles H, et al. Comparative assessment of five trials of universal HIV testing and treatment in sub-Saharan Africa. J Int AIDS Soc. 2018;21(1).
[16] Ford N, Migone C, Calmy A, Kerschberger B, Kanters S, Nsanzimana S, et al. Benefits and risks of rapid initiation of antiretroviral therapy. Aids. 2018;32(1):17–23.
[17] Girum T, Yasin F, Dessu S, Zeleke B, Geremew M. "Universal test and treat" program reduced TB incidence by 75% among a cohort of adults taking antiretroviral therapy (ART) in Gurage zone, South Ethiopia. Trop Dis Travel Med Vaccines. 2020;6:12.
[18] Dagnaw Tegegne K, Cherie N, Tadesse F, Tilahun L, Kassaw MW, Biset G. Incidence and Predictors of Opportunistic Infections Among Adult HIV Infected Patients on Anti-Retroviral Therapy at Dessie Comprehensive Specialized Hospital, Ethiopia: A Retrospective Follow-Up Study. HIV AIDS (Auckl). 2022;14:195–206.
[19] NACC. Annual Report. Yaounde: National AIDS Control Committee; 2020; 2021.
[20] Tymejczyk O, Brazier E, Yiannoutsos CT, Vinikoor M, van Lettow M, Nalugoda F, et al. Changes in rapid HIV treatment initiation after national "treat all" policy adoption in 6 sub-Saharan African countries: Regression discontinuity analysis. PLOS Medicine. 2019; 16(6):e1002822.
[21] Kimanga DO, Oramisi VA, Hassan AS, Mugambi MK, Miruka FO, Muthoka KJ, et al. Uptake and effect of universal test-and-treat on twelve months retention and initial virologic suppression in routine HIV program in Kenya. PLOS ONE. 2022;17(11):e0277675.
[22] Mendez-Lopez A, McKee M, Stuckler D, Granich R, Gupta S, Noori T, et al. Population uptake and effectiveness of test-and-treat antiretroviral therapy guidelines for preventing the global spread of HIV: an ecological cross-national analysis. HIV Medicine. 2019;20(8):501–12.
[23] WHO. WHO HIV Policy adoption and implementaion status in countries. HIV Treatment and Care. Geneva; 2019.
[24] Mody A, Sikazwe I, Czaicki NL, Wa Mwanza M, Savory T, Sikombe K, et al. Estimating the real-world effects of expanding antiretroviral treatment eligibility: Evidence from a regression discontinuity analysis in Zambia. PLoS Med. 2018;15(6):e1002574.
[25] Mody A, Sikazwe I, Namwase AS, Wa Mwanza M, Savory T, Mwila A, et al. Effects of implementing universal and rapid HIV treatment on initiation of antiretroviral therapy and retention in care in Zambia: a natural experiment using regression discontinuity. The Lancet HIV. 2021;8(12):e755–65.
[26] Kumwenda M, Skovdal M, Wringe A, Kalua T, Kweka H, Songo J, et al. Exploring the evolution of policies for universal antiretroviral therapy and their implementation across three sub-Saharan African countries: Findings from the SHAPE study. Global Public Health. 2021;16(2):227–40.
[27] Nhassengo P, Cataldo F, Magaço A, Hoffman RM, Nerua L, Saide M, et al. Barriers and facilitators to the uptake of Test and Treat in Mozambique: A qualitative study on patient and provider perceptions. PloS one. 2018;13(12):e0205919.
[28] Nasuuna E, Tenforde MW, Muganzi A, Jarvis JN, Manabe YC, Kigozi J. Reduction in Baseline CD4 Count Testing Following Human Immunodeficiency Virus "Treat All" Adoption in Uganda. Clin Infect Dis. 2020;71(9):2497–9.
[29] Zaniewski E, Dao Ostinelli CH, Chammartin F, Maxwell N, Davies MA, Euvrard J, et al. Trends in CD4 and viral load testing 2005 to 2018: multi-cohort study of people living with HIV in Southern Africa. J Int AIDS Soc. 2020;23(7):e25546.
[30] Brazier E, Tymejczyk O, Zaniewski E, Egger M, Wools-Kaloustian K, Yiannoutsos CT, et al. Effects of National Adoption of Treat-All Guidelines on Pre-Antiretroviral Therapy (ART) CD4 Testing and Viral Load Monitoring After ART initiation: A Regression Discontinuity Analysis. Clinical Infectious Diseases. 2021;73(6):e1273–81.
[31] Avila D, Althoff KN, Mugglin C, Wools-Kaloustian K, Koller M, Dabis F, et al. Immunodeficiency at the start of combination antiretroviral therapy in low-, middle-, and high-income countries. J Acquir Immune Defic Syndr. 2014;65(1):e8–16.
[32] Carmona S, Bor J, Nattey C, Maughan-Brown B, Maskew M, Fox MP, et al. Persistent high burden of advanced hiv disease among patients seeking care in south africa's national HIV program: data from a nationwide laboratory cohort. Clin Infect Dis. 2018;66(suppl_2):S111–7.
[33] Leeme TB, Mine M, Lechiile K, Mulenga F, Mosepele M, Mphoyakgosi T, et al. Utility of CD4 count measurement in the era of universal antiretroviral therapy: an analysis of routine laboratory data in Botswana. HIV Med. 2021;22(1):1–10.
[34] Ford N, Meintjes G, Pozniak A, Bygrave H, Hill A, Peter T, et al. The future role of CD4 cell count for monitoring antiretroviral therapy. Lancet Infect Dis. 2015;15(2):241–7.
[35] Siika A, McCabe L, Bwakura-Dangarembizi M, Kityo C, Mallewa J, Berkley J, et al. Late Presentation With HIV in Africa: phenotypes, risk, and risk stratification in the reality trial. Clin Infect Dis. 2018;66(suppl_2) (S140-s146).
[36] Sikombe K, Eshun-Wilson IKA, Simbeza S, Mody A, Czaicki N, Beres LK, et al. Early mortality in HIV-infected patients initiating ART without a pre-therapy CD4. Conference on Retroviruses and Opportunistic Infections. Seattle, Washington; 2019.
[37] Rice B, Boulle A, Schwarcz S, Shroufi A, Rutherford G, Hargreaves J. The Continuing Value of CD4 Cell Count Monitoring for Differential HIV Care and Surveillance. JMIR Public Health Surveill. 2019;5(1):e11136.
[38] Drouin O, Bartlett G, Nguyen Q, Low A, Gavriilidis G, Easterbrook P, et al. Incidence and prevalence of opportunistic and other infections and the impact of antiretroviral therapy among HIV-infected children in low- and middle-income countries: A systematic review and meta-analysis. Clin Infect Dis. 2016;62(12):1586–94.
[39] Low A, Gavriilidis G, Larke N, Lajoie M-R, Drouin O, Stover J, et al. Incidence of opportunistic infections and the impact of antiretroviral therapy among HIV-infected adults in low- and middle-income countries: A systematic review and meta-analysis. Clinical Infectious Diseases. 2016;62(12):1595–603.
[40] Danel C, Moh R, Gabillard D, Badje A, Le Carrou J, Ouassa T, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. N Engl J Med. 2015;373 (9):808–22.
[41] Lawn SD, Myer L, Bekker LG, Wood R. Burden of tuberculosis in an antiretroviral treatment programme in sub-Saharan Africa: impact on treatment outcomes and implications for tuberculosis control. Aids. 2006;20(12):1605–12.
[42] Seyler C, Toure S, Messou E, Bonard D, Gabillard D, Anglaret X. Risk factors for active tuberculosis after antiretroviral treatment initiation in Abidjan. Am J Respir Crit Care Med. 2005;172(1):123–7.
[43] Kufa T, Mabuto T, Muchiri E, Charalambous S, Rosillon D, Churchyard G, et al. Incidence of HIV-associated tuberculosis among individuals taking combination antiretroviral therapy: a systematic review and meta-analysis. PLoS One. 2014;9(11):e111209.
[44] Lawn SD, Myer L, Edwards D, Bekker LG, Wood R. Short-term and long-term risk of tuberculosis associated with CD4 cell recovery during antiretroviral therapy in South Africa. Aids. 2009;23(13):1717–25.
[45] Abeid R, Mergenthaler C, Muzuka V, Goodluck A, Nkwabi T, Bigio J, et al. Increasing TB/HIV case notification through an active case-finding approach among rural and mining communities in Northwest Tanzania. Journal of Tropical Medicine. 2022;2022: 4716151.
[46] Chakaya J, Petersen E, Nantanda R, Mungai BN, Migliori GB, Amanullah F, et al. The WHO Global Tuberculosis 2021 Report - not so good news and turning the tide back to End TB. Int J Infect Dis. 2022;124(Suppl. 1):S26–9.
[47] WHO. Global tuberculosis report 2022. Geneva: World Health Organization; 2022.