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Early Treatment of All Persons with HIV Infection: From Immune Activation and Inflammation Studies to Randomized Clinical Trials

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Abstract

Treatment of people living with Human Immunodeficiency Virus (HIV) infection with antiretroviral therapy has dramatically reduced disease progression and death. There are strong supporting data and a public health argument that treatment prevents transmission of the disease. The optimal timing for starting antiretroviral therapy in asymptomatic people living with HIV infection was the subject of debate until 2015, when two large randomized studies (TEMPRANO and START) indisputably showed benefit of treating all people living with HIV regardless of CD4+ cell count. In this paper, we review the evidence from immune activation and inflammation studies to randomized clinical trials that supports early treatment of all asymptomatic people living with HIV regardless of CD4+ cell count, and we describe challenges and perspectives behind this strategy.

Keywords: Early treatment; Asymptomatic HIV; CD4+ cell count; Antiretroviral therapy; Human immunodeficiency virus; People living with HIV

Introduction

Antiretroviral therapy (ART) in the treatment of people living with human immunodeficiency virus (PLWHIV) infection has dramatically reduced disease progression and death rates [1,2]. Between 2000 and 2011, data supported the benefits of early ART, including a better response to therapy and preservation of immune function and reduced transmission [3-9], results which suggested improvement in the long-term outcomes. Several cohort studies [10-17] have examined the strategy of initiating ART at higher CD4+ cell counts. Some of these studies [11-13] (Table 1) have indicated that relatively modest immunosuppression (CD4+ cell counts between 350-500 cells/mm^3) is associated with an increased risk of major clinical events and death. Other studies have reported increased life expectancy when ART is started at higher CD4+ cell counts [16], or that life expectancy is like that of the general population in some PLWHIV [10,17]. Others, however, have shown little benefit of starting treatment earlier (CD4+ cell counts> 500) [11,14] (Table 1). Thus, the controversy over the optimal time of initiating ART was unresolved because of a lack of randomized clinical trials specifically designed to resolve the issue. This state was reflected by differences in guidelines, especially between U.S. guidelines [18-20] and European guidelines [21,22]. American colleagues were convinced by data from basic science and cohort studies [3,11-17] and by the efficacy of ART to prevent HIV transmission [3,23]. However, many European colleagues have remained skeptical and have wanted randomized controlled-trial evidence. One of the reasons for the latter opinion was that the Strategies for Management of Antiretroviral Therapy (SMART) study [24] had found that administering ART intermittently rather than continuously led to increased risk of AIDS-related events and serious non-AIDS-related renal, liver, or cardiovascular events or cancers. The mortality rate, which was primarily attributed to cancer and end-organ disease, not AIDS, was greater among participants who received intermittent ART than among those who received continuous ART. This result was unexpected and surprising, as before data from the SMART study were published, many experts considered

Table 1: Major cohort studies that have indirectly addressed the question of when to start antiretroviral therapy in HIV1-infected patient (references11-14)

Authors (date of publication)	Study design	Objective	Outcome	CD4 threshold (/mm³)	Duration (years)	Number of patients	Location	Sex (%)	Ethnicity	Age (median)	Duration of HIV (median)	Median CD4 (/mm³)	Median VL	Results	Comments
CASCADE (Funk et al. (2011, ref 14)	Observationnal cohort	- Estimate the clinical benefit of HAART initiation vs deferral in a given month in patients with CD4 cell counts less than 800/ µL.	- Time to AIDS or death	-CD4: 200-349 vs 350-499 vs 500-799	13	9455 patients (52 268 person-years)	Europe, Australia, and Canada	Men 73%	NA	30	1.3 years	NA	NA	-CD4: 200-349 vs 350-499 vs 500-799: for AIDS: HR (95% CIs) 0.59 vs 0.75 vs 1.10 -For all mortality, HR (95% CIs) 0.71 vs 0.51 vs 1.02	- Benefits of HAART initiation at CD4 less than 500/ mm³
KITAHATA et al. 2009 (NA-ACCORD, ref 11)	Observationnal cohort sudy	-Timing of initiation of therapy comparing group that initiated ART early or late	- Rates of death from any cause	First phase:- CD4<350 vs 350-500 Second phase: -CD4: <500 vs <500	9	17517 (50416 personn-years of follow-up)	United States and Canada	Men: 78.5%	Black: 40.5%	Median age: 39 years	NA	Median: 550 (429 in the first group and 671 in the second)	Median: 3.88 log10 copies/ ml (4.15 in the first group and 3.6 in the second group.)	-first part: 69% increase risk of death (if ART initiated <350) Second part: 94% increase in the risk of death (If ART initiated <500)	Older age, history of injected drugs users and hepatitis C were independant risk factors for death.
HIV-Causal Collaboration (cain et al., 2011 ref 13)	Prospective observationnal cohort	identify the optimal CD4 cell count at which cART should be initiated	- all-cause mortality and a combined end point of AIDS-defining illness or death	-CD4: <200 vs ><500	13	20971	Europe and US (Veteran health Administration)	Men: 76,3%	NA	NA	NA	660	NA	-HR: of mortality was 1.01 for the 350 threshold and 1.20 for the 200. threshold. The corresponding hazard ratios were 1.38 and 1.90 respectively, for the combined end point	- initiation of cART at a threshold CD4 count of 500 cells/mm³ increases AIDS-free survival. Not mortality between 300 and 500 cells/mm³.
START Consortium (Sterne et al., ref 12)	Prospective observationnel Cohort study	-Analysis of data from cohort studies to estimate the effect of initiation of combination antiretroviral therapy in different CD4 cell count ranges.	- Rates of AIDS or death	251-350 versus 351-450 versus 451-550	6	45691 (21247 in the era before cART and 24444 after era of cART	Europe and North America	Men: 74%	NA	35	NA	cART era: 230/ mm³ versus 354/ mm³ era before cART	4.9 log10 copies/ml	-Deferring combination therapy until a CD4 cell count of 251–350 cells per µL was associated with higher rates of AIDS and death than starting therapy in the range 351–450 cells per µL (hazard ratio [HR] 1,28, 95% CI 1,04–1,57). Although effects on mortality were less marked than effects on AIDS and death	-350 cells per µL should be the minimum threshold for initiation of antiretroviral therapy.

HAART: Highly Active Antiretroviral Therapy; cART: combination Antiretroviral therapy; ART: antiretroviral therapy; NA: Not applicable

intermittent ART a safe option. These opinions were based also on data from observational, uncontrolled studies of ART interruption or small and short-term randomized trials [25]. The unanswered key question remains whether initiation of ART early in HIV infection – when the risk of AIDS is low to negligible, and morbidity and mortality are almost driven by serious non-AIDS-related events – would provide clinical benefits that outweighed the risks of treatment [25]. Cohort studies published after the SMART study did not answer this question; thus, randomized clinical trials were designed.

In 2015, two large randomized clinical trials (Trial of Early Antiretrovirals and Isoniazide Preventive Therapy [TEMPRANO] [26] and the Initiation of Antiretroviral Therapy in asymptomatic HIV infection (START), describing the benefits of initiating ART in all PLWHIV regardless of CD4+ cell count, were published [26,27]. The results of these studies closed the debate about the optimal time to start therapy, and all international guidelines recommended treatment of all PLWHIV early and regardless of their CD4+ cell count [28-34]. However, many barriers and challenges to implementing this strategy remain in real-life settings, especially in low-resource countries.

In this paper, we review the evidence from immune activation and inflammation studies to randomized clinical trials that support treating all asymptomatic PLWHIV early in their illness regardless of CD4+ cell count. We also describe challenges and perspectives underlying this strategy.

Immune Activation, Inflammation and Reservoir Studies

Acute HIV infection covers a period of 4–5 weeks in which the virus disseminates from the initial site of infection to tissues and organs [35]. The virus quickly establishes a proviral reservoir within days of acquisition [36], and viremia rapidly increases to a peak of 107–108 HIV RNA copies/ml [37,38]. In the weeks following acquisition, the viral load decreases, ultimately reaching a stable level, termed 'set point,' that persists and predicts disease progression if ART is not started [39]. Pathways that predict the course of HIV diseases are complex and multifactorial. The use of ART has reduced viremia to undetectable levels and significantly prolonged life expectancy. Despite these encouraging results, ART is most often initiated during chronic infection, and immune function is not fully restored; HIV-1 persists in latently infected blood cells, and markers of residual immune activation remain elevated [40-42].

One approach for control of HIV replication is that of initiating ART in the earliest days after acquisition of the virus, with the aims of mitigating the long-term effects of immune activation, preventing immune dysfunction, and reducing the viral reservoir. Although studies have described persistence of high levels of immune activation despite viral suppression, until recently, most of these studies have described results in PLWHIV whose ART was begun at relatively late stages of HIV disease. Timing of the start of ART is important because low nadir CD4+ cell counts have been consistently associated with higher immune activation during viral suppression induced by ART.

In the earliest days after HIV acquisition, CD4+Th17 cells are depleted from the gut-associated lymphoid tissue, leading to structural and functional changes in the mucosa [43]. The selective loss of CD4+Th17 cells compromises the integrity of the gut barrier, and microbes enter the circulation by a process termed translocation [44]. Studies have shown recently that the initiation of ART in Fiebig I/II (antibody negative) acute infection stage prior to the development of HIV IgM antibodies prevents the quantitative and functional loss of CD4+CCR5+Th17 cells and preserves their poly functionality [45,46]. Also, ART started in Fiebig I/II reversed the systemic and mucosal immune activation. However, later initiation of ART in Fiebig III (HIV IgM+, HIV IgG-) only partially restored the population of CD4+CCR5+Th17 cells and the poly functionality of CD4+Th17 cells, and failed to normalize the activation of CD8+ T cells in the gut [46]. These findings support the concept that initial damage to the mucosal CD4+ T-cell compartment cannot be fully restored, even after long ART administration, if ART is not initiated in the very early stages of acute infection. Deleage et al. [47] reported that the magnitude of gastrointestinal tract damage, immune activation, and inflammation was significantly increased, with accompanying depletion of CD4+ cells in the lamina propria, in people acutely infected prior to receiving ART. While most persons treated during acute infection resolved gastrointestinal inflammation and immune activation after 24 weeks of ART, CD4+ T cells in the lamina propria were not restored in most acutely infected people after 96 weeks of ART [47]. Sereti et al. [48] characterized longitudinal changes in immune activation among HIV-infected Thai persons who had ART started at very early-stage disease (within the first 2–3 weeks of infection) and found that markers of immune activation and inflammation, such as C-reactive protein, interleukin-6, soluble interleukin-6 receptor, soluble glycoprotein 130, tumor necrosis factor, intestinal fatty acid binding protein, soluble CD14, D-dimer, and hyaluronic acid in the blood were already higher in these acutely infected persons than in a cohort of at-risk but HIV-uninfected controls. Furthermore, most of these markers declined during suppressive ART to levels that were significantly lower than those in a cohort of the same Thai persons who had ART initiated during chronic infection and at much lower CD4+ T cells in the blood. On the other hand, markers of immune activation and inflammation in the blood remained increased in those who started ART early, even after 2 years of ART viral suppression, compared with those markers in at-risk but HIV-uninfected controls. Abnormal immune activation persisted even in the subgroup of persons whose ART was begun before HIV-specific antibodies were detectable (typically <14 days of infection) [48]. The clinical relevance of the persistently elevated inflammatory biomarkers in the blood remains to be established.

Early initiation of ART limits viral reservoir sending and transmission and mitigates immune activation [49]. Kok et al. [50] reported that CD4+ and CD8+ T cells and CD3- CD8+ T cells producing IL-17 or IL-22 are significantly decreased in the gut mucosa of PLWHIV. Early ART initiation may favor restoration of a T cell regulatory (Treg)/Th17 ratio close to that of non-infected controls independent of the gut reservoir and peripheral CD4 +T cell count [50]. The loss of Treg/Th17 balance during acute infection is related to and predictive of progression of Simian immunodeficiency virus disease, and a normal Treg/Th17 ratio is associated with limited immune activation and thus no disease progression [50]. A study showed recently that the Treg/Th17 ratio in the blood of acutely infected persons is correlated with the viral set point [51]. Weiss et al. [52] found that T cell-associated HIV DNA levels before interruption of treatment predicted the level of CD38+CD8+ T cells and CD38+CD4+ T cells after 12 months of ART interruption. Hocqueloux et al. [53] emphasized the major viro-immunological benefit of initiating treatment at the primary HIV infection (PHI) phase in a study of 307 persons of whom 35 started their ART during PHI (<4 months post-infection) and 272 during the chronic HIV infection; 54% of persons who started their treatment during PHI achieved both a low blood viral reservoir (HIV DNA level 2.3log10copies/10^6 peripheral blood mononuclear cells) and normal values of three immunological parameters (CD4+ count and percentage and CD4+/CD8+ ratio). In contrast, only 3% of persons achieved these results when their ART was started later, during the chronic phase, and these persons had a high CD4+ cell nadir (>500 cells/mm). Lalani et al. [54] have argued in favor of initiating ART at the earliest possible stage after HIV infection, based on a study of 327 persons with 1305 cell-associated HIV-DNA (CA-HIV-DNA) quantifications. The timing of ART initiation had significant impact on the first slope of decrease: The earlier ART was initiated after HIV infection, the faster the CA-HIV-DNA level decreased during the first 8 months of ART. The predicted mean CA-HIV-DNA level achieved after 5 years of successful ART was 1.62 and 2.24 log10copies/10^6 PBMCs when ART was initiated 15 days and 3 months after infection, respectively (P=.0006) [55,56]. Recently, Cheret et al. [57] showed the impact of early ART on HIV blood and semen compartments at the time of PHI. Participants received two years of early ART. Nineteen participants of the trial were analyzed, of which 8 had acute PHI. HIV-RNA was undetectable in blood and semen after two years of suppressive ART. Semen HIV-DNA load declined similarly, except in one patient who used recreational drugs. These data showed that early ART purges both the virus and infected cells, reducing the risk of transmission during PHI [55].

ART initiated during acute HIV infection has also been found to protect central memory CD4+ T cells [56], thereby reducing the size and altering the distribution of the CD4+T-cell HIV reservoir [56]. T-cell activation normalized and viral diversity remained stable after two years when ART was initiated in early HIV-infection [56]. However, even though HIV DNA levels and viral diversity were decreased when ART was initiated during PHI, proviral DNA was still detectable, and no differences were found in T-cell activation between primary and chronic HIV infection; however, each group had only 8 members [57]. Remarkably, the VISCONTI study demonstrated that initiation of ART during the infection in a subset (15%) of patients with primary HIV infection and small viral reservoirs, infection was controlled after treatment interruption [58]. Globally, these studies [45-58] have tended to show a benefit of early initiation of ART on immune activation, inflammation and reduction of reservoir. However, none of these studies addressed the key question of whether the use of an intervention (e.g. ART, anti-inflammatory drugs, or statins) that may reduce or prevent inflammation and coagulation reduces the risk of clinical disease progression [25,59].

Randomized Clinical Trials

Randomized clinical trials not designed to directly answer the question

The HIV Prevention Trials Network 052 trial (HPTN052) [3], although not designed to answer directly the question of timing of initiation of ART, has been published, bringing insights to the question of when to start therapy.

HPTN 052

The HPTN 052 trial, published in 2011, is an international (Africa, Asia, South America), multicentre, randomized controlled trial. In this study, early ART initiation was associated with a 93% lower risk of linked-partner infection compared with that of delayed ART [23]. A sub-analysis of HPTN 052 [3], published by Grinsztejn et al. [3], was designed to compare early versus delayed ART for adult PLWHIV who had CD4+ cell counts of 350-550/mm^3 and was focused on morbidity and mortality related to HIV infection. Primary outcomes were death, tuberculosis, new-onset World Health Organization (WHO) stage 4 disease, severe bacterial infections, serious cardiovascular events, end-stage renal disease, new-onset diabetes mellitus, serious liver disease, and non-AIDS defining malignant diseases. Secondary outcomes were WHO stages 2 and 3 HIV-1 events and other medical disorders, such as malaria, liver enzyme elevation, lipodystrophy, chronic renal insufficiency, dyslipidaemia, peripheral neuropathy, hypertension, lactic acidosis, and thrombocytopenia. A total of 1763 people (4007 person-years of follow up) with HIV-1 infection and a serodiscordant partner were enrolled in the study; an equal number was assigned to early ART and to delayed treatment (886 versus 877) until CD4+ cell count reached <250/mm^3. Primary outcome was reported in 57 persons assigned to early ART and 77 people assigned to delayed ART (p=0.074). New-onset AIDS events were recorded in 40 participants assigned to early ART and 61 assigned to delayed ART (p=0.031). Tuberculosis developed in 17 patients who received early ART and in 34 patients who

received delayed ART (p=0.018). Primary non-AIDS events were rare (12 in the early-ART group and 9 in the delayed-ART group). Four hundred and ninety-eight primary and secondary outcomes occurred in the early ART group compared with 585 in the delayed ART group (p=0.025). Primary and secondary endpoints were reached not only among participants with low CD4+ cell count; most outcome events occurred when the most recent CD4+ cell count was higher than 350 cells/mm^3. The median CD4+ cell count for primary clinical events was 353 cells/mm^3 in persons assigned to delayed ART compared with 502 cells/mm^3 in persons assigned to early ART. Twenty-six people died, eleven of whom were allocated to early ART and 15 to delayed ART. Five deaths were associated with primary outcomes, and the remainder was attributable to causes that either did not meet the predefined primary outcome criteria or were suicides, accidental deaths, or death of indeterminate cause. The authors concluded that early ART initiation delayed the time to AIDS events and decreased the incidence of primary and secondary outcomes. The clinical benefit, combined with the important reduction in HIV-1 transmission risk [76], is evidence in favor of early initiation of ART.

RCT designed to directly answer the question

In 2015, two large randomized clinical trials, the TEMPRANO [26] and START [27], clearly demonstrated the benefit of treating all PLWHIV regardless of CD4+ cell count (Table 2).

The TEMPRANO ANRS 12136 trial [26] was an unblinded, multicenter (nine centers), randomized controlled superiority trial conducted in Abidjan, Ivory Coast (2008-2015). The study included participants who had HIV-1 infection and a CD4+ cell count <800/mm^3 and who did not meet the WHO guidelines for initiation of ART (Table 2). Participants were randomized and assigned to one of four treatment groups: deferred ART; deferred ART plus isoniazid preventive therapy (IPT); early ART (immediate initiation of ART); or early ART plus IPT. The primary endpoint was a composite of the diseases included in the case definition of AIDS: non-AIDS-defining cancer, non-AIDS-defining invasive bacterial disease, or death from any cause at thirty months. Two thousand and fifty-six persons (41%) with a baseline CD4+ cell count of ≥ 500/mm^3) were followed for 4757 person-years. Two hundred and four primary endpoint events were recorded (3.8 events per 100 person-years; 95% CI, 3.3-4.4), including 68 persons with a baseline CD4+ cell count of at least 500/mm^3 (3.2 events per 100 person-years; 95% CI, 2.4-4.0). Tuberculosis and invasive bacterial diseases accounted for 42% and 27% of primary endpoint events, respectively. The risk of death or severe HIV-related illness was lower with early ART than with deferred ART. The adjusted hazard ratio among patients with a baseline CD4+ cell count of ≥ 500/mm^3 was lower with IPT than without IPT. The overall rate of the primary endpoint was 3.8 events per 100 person-years, and the CD4+ specific rates of the primary endpoint for the time when CD4+ cell counts were at least 500/mm^3, between 350 and 499/mm^3, or less than 350/mm^3 were 2.8 events per 100 person-years, 4.1 events per 100 person-years, and 6.8 events per 100 person-years, respectively. The 30-month probability of grade 3 or 4 adverse events occurring did not differ significantly among the therapeutic strategies. The authors concluded that immediate ART and six months of IPT in an African setting independently reduced rates of severe illness more than did deferred ART or no IPT, both overall and among PLWHIV with CD4+ cell counts of at least 500/mm^3. The study showed later that in settings with high incidence of tuberculosis, 6 months of IPT has a durable protective effect in reducing mortality in HIV-infected people, even in people with high CD4 cell counts and who have started ART. It is important to note that in this trial, the ART-start threshold was adjusted upward over time according to WHO guidelines updates (from 200/mm^3 in 2008–2009 to 350/mm^3 in 2009–2013 and 500/mm^3 in 2013–2015).

The START study in asymptomatic HIV infection study was a large randomized clinical trial [27], published in 2015, that evaluated two strategies for initiating ART: immediate or deferred initiation (until the CD4+ cell count had declined to 350/mm^3, or an AIDS-related event or another condition that dictated the use of ART had developed (Table 2). The primary endpoint (composite) was any serious AIDS-related and serious non-AIDS-related events or death from any cause. From 2009 through 2013, the study randomly assigned 2326 persons to receive immediate ART and 2359 patients to receive deferred ART at 215 sites around the world (Africa, Europe and Israel, North America, South America and Mexico, Australia, and Asia). The primary endpoint was reached in 42 patients in the immediate ART group (1.8%; 0.60 events per 100 person-years) and in 96 patients in the deferred ART group (4.1%; 1.38 events per 100 person-years), for a hazard ratio of 0.43. Hazard ratios for serious AIDS-related and serious non–AIDS-related events were 0.28 and 0.61, respectively. Among the individual events, the three most common events in the immediate-initiation group and the deferred-initiation group were cardiovascular disease (29% and 15%, respectively), non–AIDS-defining cancer (21% and 19%, respectively), and tuberculosis (14% and 20%, respectively). Most of the tuberculosis events (16 of 26) occurred in patients living in Africa, and most of the cancers (22 of 27) and cardiovascular events (19 of 26) occurred in patients from Western countries. Of the 42 primary endpoints, only four (10%) in the immediate ART group were reached before the initiation of ART, whereas 68 of 96 (71%) in the deferred ART group were reached before this point. Of the 33 deaths, 20 (61%) were attributable to causes other than AIDS: cardiovascular disease, renal disease, liver disease, or cancer. Interestingly, in both groups, most primary events occurred when the CD4+ count was >500 cells/mm^3: 37 of 42 (88%) (0.6 per 100 person-years) in the immediate ART group, and 57 of 96 (59%) (1.1 per 100 person-years) in the deferred ART group. The authors concluded that starting ART in PLWHIV with a CD4+ count of >500 cells /mm^3 was beneficial compared with starting ART in persons with the CD4+ count <350 cells

Table 2: Randomized studies designed to answer directly the question of when to start Antiretroviral therapy in HIV-1 infected patients (References 26,27)

Study	Design	Objective	End Points	N° of patients	CD4 threshold (/ mm³)	Median Viral load	Median CD4 (/ mm³)	Age (years)	Sex	Ethnicity (%)	Location	Duration of Study	Results	Comments
TEMPRANO (Anglaret et al., 2015, Abidjan, Ivory Coast, ref 26)	- Unblinded, multicenter, individual-randomized, trial 2008-2015	- Assessing the efficacy of early ART in reducing the rate of severe illness among HIV-infected adults - the benefit of combining isoniazid preventive therapy (IPT) with early ART	- The primary end point was a composite of diseases included in the case definition of the acquired immunodeficiency syndrome (AIDS), non–AIDS-defining cancer, non–AIDS-defining invasive bacterial disease, or death from any cause at 30 months	2076 (4757 patient-years.)	>500 versus WHO* criteria of initiation (<200, <350, <500)	4.65 log10 copies/ml	463	35	78% of Women	-100% blacks	Abidjan (Ivory Coast)	7 Years	- A total of 204 primary end-point events were observed (3.8 events per 100 person-years; 95% [CI], 3.3 to 4.4), including 68 in patients with a baseline CD4+ count of at least 500 cells/ mm³ (3.2 events per 100 person-years; 95% CI, 2.4 to 4.0).	- In this African country, immediate ART and 6 months of IPT independently led to lower rates of severe illness than did deferred ART and no IPT, both overall and among patients with CD4+ counts of at least 500 cells/mm³
START (INSIGHT, 2015, Africa, Europe and Israel, North America, South America and Mexico, Australia, and Asia, ref 27**)**	Randomized 2009-2013	- two strategies for initiating antiretroviral therapy: immediate initiation and deferred initiation until the CD4+ count declined to 350 cells/ mm³ or the development of an AIDS-related event or another condition*	- The primary composite end point was any serious AIDS-related event, serious non–AIDS-related event, or death from any cause	4685 (2326 in early versus 2359 in deferred arm)	<350 vs >500	12759 copies/ml (13000 in de early versus 12550 in de deffered arm)	651	36	27% women	-30, 2% Blacks -43,6% White	-35 countries worldwide	4	- The primary end point: 42 patients in the immediate-initiation group (1.8%; 0.60 events per 100 person-years), vs 96 patients in the deferred-initiation group (4.1%; 1.38 events per 100 person-years), for a hazard ratio of 0.43 (95% [CI], 0.30 to 0.62; P<0.001). Hazard ratios for serious AIDS-related and serious non–AIDS-related events were 0.28 (95% CI, 0.15 to 0.50; P<0.001) and 0.61 (95% CI, 0.38 to 0.97; P = 0.04), respectively.	- The initiation of antiretroviral therapy in HIV-positive adults with a CD4+ count of more than 500 cells/mm³ provided net benefits over starting such therapy in patients after the CD4+ count had declined to 350 cells per cubic millimeter

*serious cardiovascular or vascular disease, serious liver disease, end-stage renal disease, and non-AIDS malignant disease.

/mm^3. In that study, most of the benefit of immediate (versus delayed) initiation of ART was due to a reduction in infections and cancers, especially those with an infectious cause. There was little evidence for a reduction in cardiovascular events or surrogate markers of vascular disease in immediate versus delayed initiation of ART. Similarly, immediate ART did not appear to decrease the incidence of other noninfectious, inflammation-associated morbidities, such as neurocognitive dysfunction, obstructive pulmonary disease, or osteoporosis [60-64]. It will be interesting to see if this little effect on cardiovascular, neurocognitive dysfunction continues over time.

Conclusion: Challenges and Perspectives

We now have solid evidence that all PLWHIV should be treated regardless of the CD4 + cell count [38,39]. Initiation of ART should not be triggered by clinical or immunological considerations, and the objective of ART is suppression of viral replication and prevention of inflammation and immune deficiency rather than cure. All international guidelines have been updated according to these principles [28-34].

To follow new guidelines [28-34] in practice---switching from treating PLWHIV at 500/mm^3 CD4+ cell count to treating all PLWHIV regardless of CD4+ cell count---several barriers and practical challenges will be encountered, especially in low-resource countries, but not only in them. The first challenge will be that of achieving early diagnosis in all HIV-infected people. Recently, Anderegg et al. [65] showed that even in high-income countries, although the median CD4+ cell count at initiation of ART had increased, it generally remained <350/mm^3. Even in high-income countries, 30-50% of patients present late, when the CD4+ cell count is <350/mm^3 [66-68], and in some regions of Asia and Africa, 70-80% of people living with HIV present late [69,70]. The Joint United Nations Programme on HIV and AIDS (UNAIDS) estimated that of the 35 million PLWHIV, about 19 million do not know they are HIV-positive, and most who know they are positive still present late, when CD4 cell counts are low [71]. A robust testing programme, including innovative approaches and technologies, such as community-based testing and self-testing to promote early testing, is needed. If stronger policies are made to diagnose core transmitters who are unaware of their diagnosis, and start ART early, we may dramatically reduce HIV transmission [23].

Another challenge will be that of providing ART to all PLWHIV worldwide and retaining them in care. Although high-resource countries are close to achieving the UNAIDS objective of 90% ART coverage, the coverage rate in low- and middle-resource countries, such as African countries, likely will be much less, despite the remarkable progress made in the last 10 years, with an 84% increase in patients on ART [72]. If all PLWHIV were diagnosed early and put under ART (test and treat), one of the barriers would be the difficulty of achieving long-term care. Shah et al. [73] showed that testing of couples and linkage to care could reduce HIV incidence by 54% and mortality rate by 64%, at a cost-effectiveness ratio of $45,300 per quality-adjusted life year gained ($27, 800-$72,300). The authors' results suggested that the most important factor to reduce HIV incidence and mortality is retention in care, which is essential for virological suppression [73]. Administering ART regardless of CD4+ cell count in countries with high HIV burden requires adequate resources (HIV testing, drugs, infrastructure, and trained staff) to support patients. Most of the health care systems in Western countries [74,75] have this capability, but many countries worldwide do not [71,76]. In low-resource countries, a stratified plan with phased approach to implementation may be needed. Nevertheless, some African countries with low resources made remarkable progress toward reaching the 90-90-90 UNAIDS target goal, as shown by the Sustainable East Africa Research in Community Health study. In that multisite study, 70% of people with HIV at baseline had been diagnosed previously; 80% had at sometime taken ART; and 86% of those treated with ART had viral suppression. Overall, 45% of all people with HIV had a viral load below 500 copies/ml. By the end of the first year, 96% of people with HIV had been diagnosed; 91% had taken ART; and 89% had viral suppression. By the end of year 2, the intervention had exceeded UNAIDS 90-90-90 targets. By that time, 97% of people with HIV were diagnosed; 94% had received ART; and 90% were virally suppressed. In addition, 82% of all people with HIV had a viral load below 500 copies/ml [77].

Long-term ART will require patients' adherence to achieve efficacy and mitigate the impact of resistance. Resistance to ART is steadily increasing and has reached 29% according to the recent WHO report about HIV resistance [78]. Even now, adherence is far from perfect, and some patients discontinue treatment for several reasons, including behavioral, psychosocial and structural barriers [79]. Bijker et al. [80] reported that in 3934 persons (13,001 adherence assessments) during the first 24 months of ART in Africa and Asia, 6.4% (837) had received suboptimal treatment (619/8484 [7.4%] in the African cohort and 218/4517 [4.8%] in the Asian cohort, a significant difference between the continents ($p<0.001$). In Africa, the factors for this suboptimal adherence were male sex, younger age, use of concomitant medication and attending a public facility. In Asia, adherence was lower in injecting-drug users than in others. The risk of suboptimal adherence decreased with longer ART duration in both regions. Participants in low- and lower-middle-resource countries had a higher risk of suboptimal adherence than did those in upper-middle or high-resource countries [80]. Suboptimal adherence was strongly associated with virological failure in Africa and Asia [80]. Adherence depends also on the health care structure and support of the provider-patient relationship and on reducing drug adverse effects [79]. Accordingly, the development of easy-to-take antiretroviral drugs (long-acting agents and implantables) and drugs with fewer adverse effects are needed. Although current single-tablet regimens with integrase inhibitors have improved the outcome of ART [81], we still need treatments that do not require biological monitoring and do not cause cardiovascular,

renal, and metabolic side effects, especially among ageing patients (>50 years), with their numerous comorbidities [67,68]. These comorbidities drive the remaining gap in life expectancy between PLWHIV and the general population, even if ART is started at CD4>500 cells/mm^3, especially in patients who are co-infected with hepatitis virus B or C or are intravenous drug users, smokers or consumers of excessive alcohol [17].

A final challenge to be faced in practice is that some asymptomatic patients with high CD4+ cell count may not wish to be treated [82]. In the HPTN 052 study, even though ART was offered to all PLWHIV and the incidence of HIV had reduced by 96%, at one year, 17% of participants declined treatment. Those persons argued that their CD4 counts were too high or they felt too healthy to start treatment, or they feared side effects [23]. In a study of 1958 PLWHIV partners in Kenya and Uganda, 50.1% of those eligible for ART had not started therapy after six months of documented eligibility, and even at 24 months, 12.4% of those eligible had not started therapy. The factors associated with delay were age below 25, higher CD4 cell count, higher education level and poor income [83]. For these kinds of patients, it is important to give priority to persons age over 50 years and those with high viremia (>50,000 copies/ml), a ratio CD4+/CD8+<0.5, as suggested by a subgroup analysis of the START study [81]. New efforts are needed to increase testing, with the aim of achieving earlier diagnosis, linkage, and ART initiation globally [75-85]. It is also important to continue developing and combining several preventive measures. Veermeersch et al. [86], in a model based on Belgian epidemiology and literature data, estimated that unless explicit new efforts are introduced, the number of new HIV diagnoses in Belgium will increase by 33% in 2030 compared to the number in 2015. The authors demonstrate that combining treatment as prevention (TasP), outreach and Pre-exposure prophylaxis (PrEP), could reduce the incidence by 51% (compared with 65% of the number of new diagnoses in 2015). Furthermore, this approach would result in an expected budgetary savings of €33.7 million in 2030 alone. Grabowski et al. [87], in a study performed in Uganda, found that the proportion of study participants living with HIV who reported taking ART increased from zero in 2003 to 69 percent in 2016, and the proportion of male study participants who were voluntarily circumcised grew from 15 percent in 1999 to 59 percent in 2016. While levels of condom use with casual partners and the proportion of people reporting multiple sex partners remained largely unchanged, the proportion of adolescents' ages 15 to 19 years who reported never having sex rose from 30 percent in 1999 to 55 percent in 2016. As an apparent consequence of these increases, particularly in ART use and voluntary male circumcision, the annual number of new HIV infections fell from 1.17 per 100 person-years in 2009 to 0.66 per 100 person-years in 2016, a 42 percent decrease [87]. These data showed that it's important to do what we can call precision prevention targeting key population depending of the risk of HIV acquisition.

If giving ART irrespective of CD4+ cell count is proven to have strong benefits globally, the question will remain of whether these benefits outweigh the risks in subgroups of PLWHIV, such as HIV elite controllers [30]. It remains to be seen whether the inflammatory state, which persists even among those who initiate ART in the first few weeks of HIV infection, will continue to lead to morbidity or a narrower spectrum of infectious diseases and neoplastic conditions. Earlier administration of ART alone will not suffice; other strategies that can mitigate the consequences of immune activation, such as anti-inflammatory drugs or statins (alone or in combination), or strategies to cure HIV, such as broad-spectrum or neutralizing antibodies, immunotherapy, and vaccines, will be needed [59]. While awaiting a cure or a vaccine, progress needs to be made in understanding the clinical relevance of the persistent inflammatory pathways that lead to comorbidities and clinical outcomes, and ways to prevent them.

Conflict of Interest

None

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