NHS England

Evidence review: Immediate initiation of Anti-Retroviral-Therapy

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Acronyms and definitions

AIDS – Acquired Immunodeficiency Syndrome

ARV – antiretroviral

ART – antiretroviral therapy

BHIVA - British HIV Association

BMD - bone mineral density

CD4 count – is a measure of the strength of a person's immune system. A low CD4 count, which occurs in HIV infection, indicates that the patient is at risk of opportunistic infections and illness.

CKD - chronic kidney disease

EACS - European AIDS Clinical Society

GRADE - Grading of Recommendations Assessment, Development and Evaluation criteria.

HIV – Human Immunodeficiency Virus

HIV-VL – HIV viral load

HR – Hazard ratio

IPT – Isoniazid preventive therapy

MSM – (men who have sex with men) - refers to all men, including bisexual men, who engage in sexual and/or romantic relations with other men.

NNT – numbers needed to treat

PHE – Public Health England

PHI – Primary HIV infection

RCT – Randomised controlled trial

SIGN - Scottish Intercollegiate Guideline Network

SNA – serious non-AIDS diseases

START - Strategic Timing of AntiRetroviral Treatment

Transgender: Refers to people who have a different sex, gender identity, and/or gender expression than the one assigned to them at birth.

Transwoman – a person who is born as a male but identifies themselves as a woman.

Treatment as prevention (TasP) – describes the use of ART, in HIV positive individuals, with the aim of preventing HIV transmission to others rather than primarily for their own clinical benefit

Viral load – refers to the activity of HIV in a bodily fluid (e.g. blood, semen)

1. Introduction

1.1. Epidemiology

Human Immunodeficiency Virus (HIV) infection is a disease of major importance in the UK and the number of people living with HIV continues to increase. Public Health England (PHE) estimated that 103,700 people (95% credible interval, CrI, 97,500 – 112,700) were living with HIV in the UK in 2014, with an overall prevalence of 1.9 per 1,000 population aged 15 and over (1.9 per 1,000 women and 3.7 per 1,000 men) (Skingsley et al., 2015). Approximately 6,000 patients are newly diagnosed with HIV each year in the UK (Skingsley et al., 2015); in spite of this the number of undiagnosed people living with HIV in the UK remains high, it is estimated that 17% of those living with HIV in the UK in 2014 (18,100 people, CrI 12,100 - 26,900) were unaware of their infection (Skingsley et al., 2015) and consequently did not access care services and could unknowingly pass HIV infection to others.

Without treatment, HIV causes progressive damage to the immune system characterized by increasing depletion of CD4+ T lymphocyte (CD4) count leading to deterioration of the immune system and the development of opportunistic diseases (acquired immunodeficiency syndrome (AIDS)) ultimately resulting in serious ill health and death. Recent data suggest that HIV infection is also associated with an increased risk of serious non-AIDS (SNA) morbidity including cardiovascular, renal, and liver diseases and non-AIDS-defining cancers and that these are more frequent in HIV infected adults at early stages of immunosuppression than in the general population (El-Sadr et al., 2006).

Anti-retro-viral (ARV) drugs prevent and reverse damage to the immune system through suppression of the HIV virus; anti-retro-viral therapy (ART) has transformed the outlook for people living with HIV from that of a significantly shortened lifespan to a manageable long term chronic condition. The life expectancy for those who are diagnosed in time and who have access to lifelong ART is equivalent to that of people who are HIV free. The average cost of one person treated over their lifetime, in the UK, has been estimated at around £360,000 (based on median life expectancy of 71.5 years), this is largely down to the cost of ARVs (Nakagawa et al., 2015).

Although the current NHS England Service specification for HIV services in adult patients with HIV-1 in England recommends starting ART when the patient's CD4 count falls to 350 cells/mm^3 or below or is approaching this threshold or when the patient develops symptoms (NHS England, 2013); according to PHE, the number and proportion of people initiating ART at CD4 counts higher than 350 cells/mm^3 in the UK has increased since 2012. In 2014, approximately half of those initiating ARTs had a CD4 count>350 cells/mm^3 (Figure 1) and over a quarter started ART with a CD4 greater than 500 cells/mm^3.

Figure 1. Number[1] of patients starting ART by CD4 count at initiation[2]: UK, 2010-2014
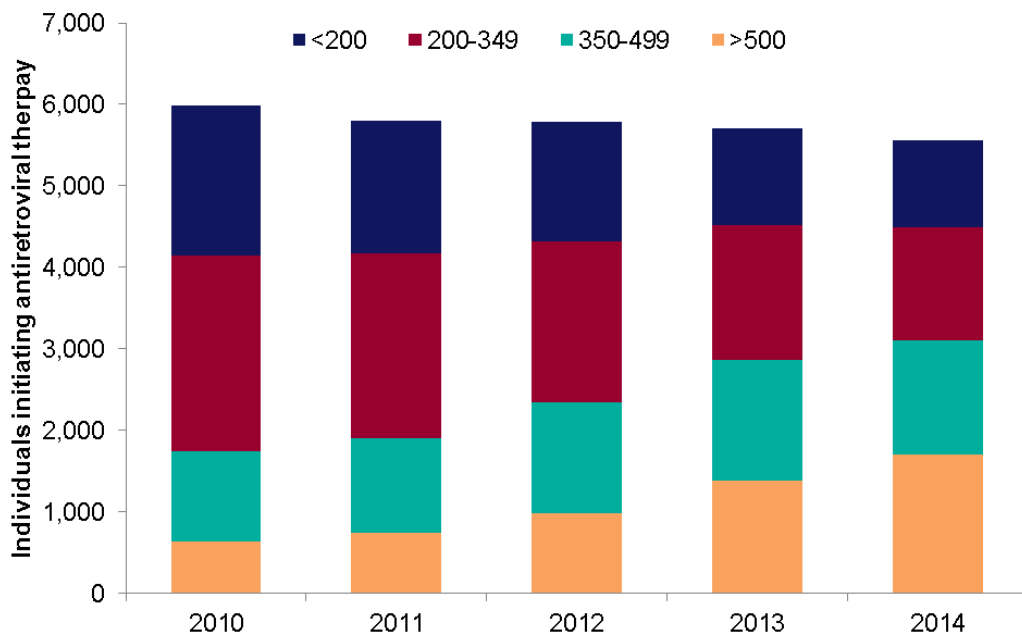
[1] Adjusted for CD4 count not reported.
[2] CD4 count available up to 9 months before ART intiation

Source: PHE (Skingsley et al., 2015)

Increasing evidence shows the positive impact of early ART used by people living with HIV both in terms of improvement of their own health as well as prevention of onward transmission to the wider population; effective ART lowers the amount and activity of the virus, making the person with HIV less infectious. Consequently, a significant proportion of the 6,000 newly diagnosed individuals each year would not meet the current criteria for starting ART immediately after diagnosis (see below).

Late diagnosis remains a significant problem in the UK, approximately a third of all new HIV diagnosis occur at a late stage of infection (when the CD4 cell count is approaching 350cells/mm^3); in 2015, there were 6,028 new HIV diagnosis in the UK, 39% of adults were diagnosed late (2,350/6,028) and the proportion of late diagnosis was higher among heterosexual men (55%, 490/890) and women (49%, 536/1,094); less than a third of HIV diagnosis among MSM were late (30%, 877/2,923) (Chau et al., 2016).

Population groups at increased risk of acquiring HIV in the UK include men who have sex with men (MSM), gay and bisexual men and transgender women (transwomen) (Skingsley et al., 2015). Despite high and increasing rates of HIV testing by MSM and high levels of effective ART coverage for those diagnosed positive, there remains evidence of ongoing HIV transmission in this population; annual numbers of new diagnoses amongst MSM have not declined for the past decade, and modelling estimates suggest that HIV incidence has actually increased (Phillips et al., 2013).

1.2. Immediate ART

The degree of damage to the immune system caused by untreated HIV infection is measured in blood as the CD4 T helper cell count. The CD4 T helper cell is the main target cell for HIV infection and it is integral to the normal function of the body's immune system; HIV associated morbidity and mortality increase with decreasing CD4 cell counts in blood. Up until now, based on observational studies or experts opinion, it has been common practice to defer ART initiation in asymptomatic individuals until they approach a certain CD4 threshold level and recommendations were inconsistent across different national and international guidelines. The current commissioning policy for initiating ART in patients with HIV-1 in England, as outlined in the NHS E HIV service specification (NHS England, 2013), reflects the 2012 British HIV Association (BHIVA) treatment guidelines that recommended patients start ART when their CD4 count falls to 350 cells/mm^3 or below or is approaching this threshold or when they develop symptoms (BHIVA, 2012).

Recent data from epidemiological studies indicate that the risk of AIDS is graded and persists at CD4 counts > 500 cells/mm^3. For a given CD4 count, the risk of AIDS appears to be lower in patients who have started ART than in those who are

ART-naïve. At the individual level, increased rates of SNA morbidity (e.g., renal, cardiovascular, and oncologic diseases) are more frequent in HIV infected adults at early stages of immunosuppression than in the general population (El-Sadr et al., 2006). Furthermore, observational studies report higher rates of co-morbidities such as cardiovascular disease, lung infections, bone disease and cognitive decline in HIV positive cohorts than in the general population, including HIV positive cohorts on ART and with a suppressed viral load (Deeks, 2011); thus starting ART earlier than it is currently recommended may prevent these early non-infectious co-morbidities (Kitahata et al., 2009; Sterne et al., 2009).

This is further supported by data from the SMART study, which tested structured interruptions of ART among 5,472 participants with a CD4+ count > 350 cells/mm^3; the SMART trial showed a higher rate of both AIDS and non-AIDS events in the interruption compared to the continuous ART arm (Siedner, 2016), with cardiac events as one of the drivers of the higher morbidity and mortality in this arm (Phillips et al., 2008). Several inflammatory markers are also increased in HIV infected individuals suggesting that some of the increased mortality in the interruption arm could be associated with inflammation and immune activation (Kuller et al., 2008).

The WHO 2016 consolidated guidelines on the use of ART recommend starting ART in all HIV positive adults regardless of WHO clinical stage and at any CD4 cell count; the "treat-all" recommendation acknowledges recent evidence from clinical trials confirming that using ART early results in better clinical outcomes for people living with HIV when compared with delayed ART initiation (WHO, 2016). Similarly, the US Department of Health and Human Services (CDC, 2014) and the International Antiviral Society – USA (Günthard et al., 2016) recommend starting ART in all HIV-1 positive individuals with detectable viremia regardless of CD4 cell count. In 2105, the European AIDS Clinical Society (EACS) guidelines version 8.0 (EACS, 2015 http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html) and the current British HIV Association guidelines (BHIVA, 2016) recommend starting ART in all HIV positive individuals irrespective of CD4 count, including individuals with primary HIV infection (PHI).

Data from two recently published studies, the START (Strategic Timing of Anti-Retroviral Treatment) (Lundgren et al., 2015) and TEMPRANO (Temprano ANRS

Study group, et al., 2015) studies have provided strong supporting evidence to the wider health benefits of early initiation of ART for reducing the risk of serious AIDS-related and non-AIDS-related morbidity and other infections in people with HIV. Immediate ART will apply to all newly diagnosed patients with CD4 cell counts above 350 cells/mm^3. In 2014, 85,489 people with HIV were seen for care in the UK, 91% of them were on ART of whom 95% responded well to treatment and were virally suppressed (Skingsley et al., 2015). During 2015, the proportion of patients on ART with a CD4 greater than 350 cell/mm^3 further increased as a consequence of the NHS England treatment as prevention (TasP) commissioning policy (NHS England, 2015). In 2015, 96% of people with HIV accessing care in the UK were receiving ART (Figure 2); and 94% of them were virally suppressed and therefore were extremely unlikely to pass on their infection (Chau et al., 2016).

Figure 2: Proportion of people who accessed HIV care in the UK who are on ART and virally suppressed, 2015
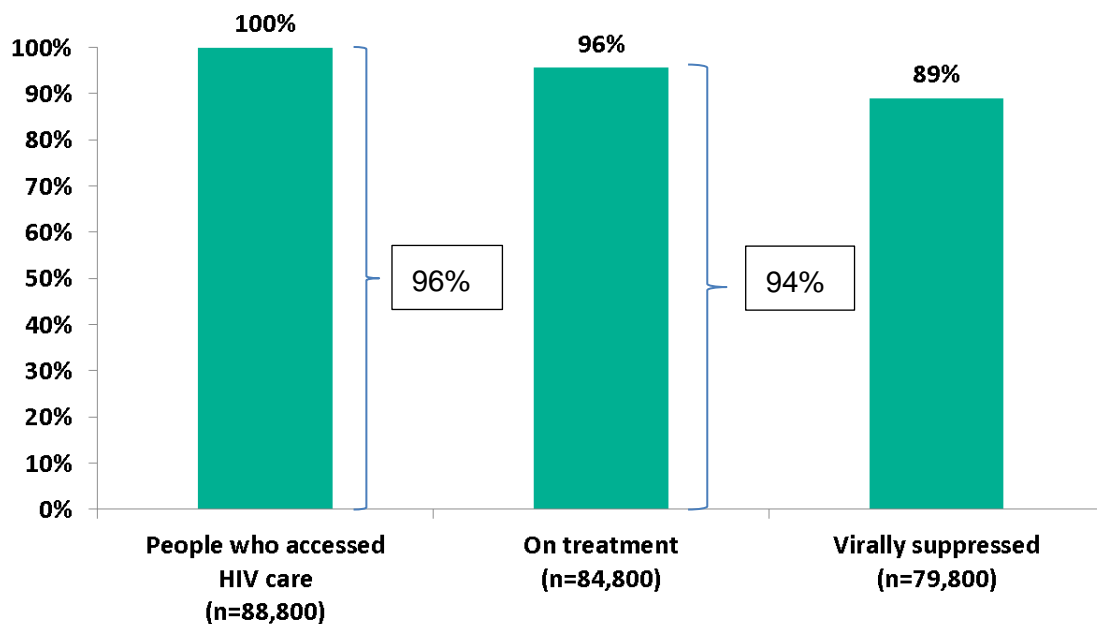
Source: PHE (Chau et al., 2016).

This policy would ensure that all patients attending a HIV treatment centre would be able to commence ART immediately after confirmation of their diagnosis. This means that there will be an increase in the numbers of patients taking ART.

1.3. Research Questions

Antiretroviral therapy has transformed the outlook for people living with HIV from a significantly shortened lifespan to a manageable long term chronic condition; however, there is still debate around the optimal point to start ART in asymptomatic patients to maximise clinical benefit. Early international recommendations based on experts opinion informed primarily by observational studies prioritised patients at high risk of AIDS (those with CD4 counts ≤ 200cells/mm^3 or with WHO clinical indications); this threshold has been increased as new RCT evidence on the beneficial effects of early ART have become available. The life expectancy for those who are diagnosed in time and who have access to ART is equivalent to that of people who are not infected by HIV. Recent data from two large RCTs has shown the positive impact of early ART in asymptomatic people living with HIV both to the individual and to the wider population, in terms of individual clinical benefits as well as preventing onward transmission.

This evidence review considers the following research questions with regard to ART initiation:

Is there evidence that initiating ART immediately after diagnosis (Immediate ART) and at any CD4 count results in improved outcomes (reduced morbidity and mortality) for patients living with HIV-1 infection when compared with deferred ART initiation when the CD4 count is approaching or below 350 cell/mm^3 or the patient developed AIDS or AIDS related condition?

Is immediate ART clinically effective and what factors affect cost-effectiveness?

The populations considered were:

- *Newly diagnosed HIV-1 ART naïve patients*

The evidence review compares the outcomes of immediate ART to CD4 related ART. Outcomes assessed were all cause morbidity and mortality; HIV related morbidity and mortality; treatment response as viral load; adverse events; sexual risk behaviours or risk compensation.

The objectives were:

To assess whether it is clinically and cost-effective for NHS England to fund

immediate ART for all newly diagnosed HIV-1 positive individuals.

2. Summary of results

Data from two large independent multicentre RCT (the START and the TEMPRANO RCTs) has shown that immediate initiation of ART in asymptomatic HIV-1 positive adults with a CD4 count > 500 cells/mm^3 provided net clinical benefits over delaying ART initiation until after the CD4 count had declined to 350 cells/mm^3 or after they had developed AIDS or AIDS related conditions.

The START trial, a large international multi-centre geographically diverse phase 2 RCT has assessed whether ART initiation at a CD4 count > 500 cells/mm^3 (immediate-ART initiation) provided greater clinical benefit than deferring ART until the CD4 count had declined to 350 cells/mm^3 or the patient had developed AIDS or an AIDS defining condition (deferred-ART initiation). This trial followed 4,685 HIV-1 positive, ART naïve, asymptomatic adults with two consecutive CD4 counts > 500 cells/mm^3 (2,326 randomised to immediate-ART initiation and 2,359 to deferred-ART initiation) at 215 sites in 35 countries across six continents for a mean follow-up period of 3.0 years. Although the rates of serious illness and death were low in both study groups, there was clear evidence of the net clinical benefit of early ART initiation. Immediate-ART reduced the risk of all cause morbidity and mortality by 57% as compared to deferred-ART initiation; furthermore, immediate-ART reduced the risk of AIDS related morbidity and mortality by 72% when compared to deferred-ART initiation. The risk of grade 4 drug-related adverse events was similar in both groups (Lundgren et al., 2015). The findings of this study were consistent across geographic regions and the beneficial effect of early-ART was consistent for individuals in high-income as well as low and middle-income countries. The START study had a follow up shorter than anticipated due to the early termination of the deferred-ART group, as all individuals in this group were offered ART early after the interim analysis demonstrated the beneficial effect of immediate-ART initiation. As a result, it is possible that in some instances the results reflected limited power to detect differences; however, this is likely to underestimate the benefits of immediate-ART initiation.

The TEMPRANO study, a multi-centre RCT in 9 HIV care centres in Ivory Coast,

explored the benefits of early ART alone or in combination with a six months course of isoniazid preventive therapy (IPT) started one month after enrolment, compared to deferred ART initiation (ART initiation following the concurrent WHO guidelines) or deferred ART in combination with IPT. The TEMPRANO trial included the use of IPT since tuberculosis (TB) is endemic in the Ivory Coast and IPT was not routinely used at the time of the study (Temprano ANRS Study Group et al., 2015). This study followed 2,056 HIV-1 positive ART-naïve asymptomatic adults for a total of 4,757 patient years. The early-ART group comprised 1,033 patients randomised to early-ART alone (515 individuals) or early-ART plus IPT (518 individuals) followed for 2,375 person-years; the deferred-ART group comprised 1,023 individuals assigned to deferred-ART alone (511 individuals) and deferred-ART plus IPT (512 individuals) followed for 2,382 person-years. The results of this RCT suggest that immediate ART initiation is the best strategy in low and middle income countries with high prevalence of TB and opportunistic infections; both immediate ART and IPT independently decreased the risk of severe morbidity and mortality. Early-ART significantly decreased overall morbidity; the risk of severe morbidity was 44% lower in individuals starting ART early when compared with deferred-ART and the beneficial effect remained when the analysis was restricted to individuals with a CD4 count > 500 cells/mm^3 (Danel et al., 2015). In addition, there were no statistically significant differences between the early and the deferred-ART groups in relation to the cumulative incidence of drug related severe adverse events recorded during the follow-up period. The cumulative probability of a grade 3 or 4 adverse event over a 30-month period was 7.7% among patients assigned to the deferred-ART *vs.* 7.1% for those in the early-ART groups (Temprano ANRS Study Group et al., 2015). This trial provides strong evidence of the clinical benefit of early ART for the individual patient; although the trial was conducted in the Ivory Coast, where TB and bacterial infections are endemic, its outcomes could be extrapolated with caution to the population in England.

3. Methodology

3.1. PICO

A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by the HIV Immediate ART Policy Working Group (see section 10 below).

3.1. Search strategy

We formulated a comprehensive and exhaustive search strategy in an attempt to identify all relevant published studies regardless of language. In August 2016, the following electronic databases were searched: MEDLINE, EMBASE (1996 to 2016 week 31), Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) and SCOPUS (1946 to Present). (see section 11 for search terms). National guidelines were examined and included where relevant.

3.2. Selection criteria

The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO. Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion. Papers which matched the PICO criteria were selected for inclusion in this review.

Randomized controlled trials that compared the effect of ART consisting of three drugs initiated early in the disease at high CD4 counts with deferred ART initiation were selected. Early initiation was considered at CD4 levels ≥ 500 cells/mm^3, with the comparison group initiating ART at CD4 counts below 350 cells/mm^3 or as defined by the trial.

The main evidence was extracted from the selected trials and recorded in the evidence summary tables (see section 7 below). Only outcomes specified in the PICO were extracted.

Data presented at conferences (published abstracts) where these have not, at the time of this review, been published in peer reviewed journals and where they provide important information have been included. However, the recommendations

of this review are based solely on peer reviewed published evidence.

3.3. Grading of the evidence

All papers included in this evaluation were assessed as to their quality using the National Service Framework for Long Term Conditions quality standards quality assessment (Department of Health, 2005) and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria.

The evidence to support individual outcomes was graded, and quality was recorded in grade of evidence tables (see section 8 below). Data extraction and methodological quality were checked by the HIV Early ART Policy Working Group.

4. Results

A total of 112 citations were identified in Embase; 110 in Medline and 51 in Scopus. After de-duplication, 143 potentially relevant citations were retrieved. All citation abstracts were reviewed and studies were classified according to the study type, the study population, the CD4 cut off point used to describe early-ART initiation and the key outcome measures.

All studies referred to 'early ART initiation' but the majority used CD4 counts lower than 500 cells/mm^3 to define 'early ART initiation', often the cut of CD4 was 350 cell/mm^3, the current CD4 count used in England to start ART. Papers also referred to early ART in different contexts or populations, 40 citations related to early ART specifically in people with comorbidities, namely infectious diseases (33) or other comorbidities (7); 17 studies related to early ART in specific groups such as infants and/or pregnant women; eight papers discussed acceptability of and adherence to early ART in low-income countries; seven papers, including two systematic reviews, related to early ART initiation in populations with CD4 cut off points significantly lower than 350 cells/mm^3 in low and middle income settings; 30 papers described early ART in the context of TAsP or public health benefit; a further 31 citations were comments, opinions or literature reviews (20) or comments/critique on national guidelines (11). Eleven papers referred to early-ART initiation at a CD4 > 500 cells/mm^3 and were retrieved in full. One paper was

a large observational study that used pooled data from several cohorts in Europe and the US (Lodi et al., 2015); nine papers fully matched the PICO criteria and were identified as eligible for inclusion in this review. Selected papers related to two large RCT studies; five citations related to the Strategic Timing of AntiRetroviral Treatment (START, Lundgren et al., 2015; Geffen et al., 2015; Acchra et al., 2015; Carr et al., 2015 and; Sharma et al., 2015) and four papers related to the TEMPRANO trial (Temprano ANRS Study Group et al., 2015; Danel et al. 2015; Jean et al., 2015a and Jean et al., 2015b). In addition, two further peer reviewed papers related to the START study were identified in October 2016 and were also included (Borges et al., 2016; Lodi et al, 2016). Furthermore, two abstracts relating to further analyses from the START trial recently presented at an international HIV conference were included in the discussion but their outcomes were excluded from the evidence tables as they have not undergone peer review process (Molina et al., 2016; Arenas-Pinto et al., 2016).

Several randomized studies have assessed the benefits and risks of 'early' ART but they have largely enrolled patients with CD4 counts significantly lower than 500 cells/mm^3. In such studies, deferred-ART has been defined as ART initiation at CD4 counts of 200 or 250 cells/mm^3. Two systematic reviews/meta-analysis were identified: a 2009 Cochrane systematic review of RCTs comparing the effect of 'early ART initiation' in treatment naïve HIV positive individuals to deferred ART initiation at CD4 > 200 cell/mm^3 or as defined by the trial (Siegfried et al., 2010). This review identified two trials involving 1,065 individuals; both studies defined "early ART" as ART initiated at CD4 of 350 cells/mm^3 compared to deferred ART at CD4 of 250 cells/mm^3. The authors found evidence of moderate quality that initiating ART at CD4 levels > 250 cells/mm^3 reduced mortality rates in asymptomatic ART naïve HIV positive people. Anglemeyer et al, conducted a systematic review of RCTs and cohort studies to support the revision of the 2013 WHO guidelines for ART initiation in low and middle-income countries (Anglemeyer et al., 2014), although the quality of the evidence was low, this systematic review identified 24 studies including 3 RCTs that reported reduced risks of mortality, reduced risk of progression to AIDS or death and diagnosis of non-AIDS defining illness in individuals starting ART at CD4 counts of at least 350 cells/mm^3; one good quality RCT included in this review reported no difference in

risk of severe adverse events between early and deferred ART. However, the CD4 count for early-ART initiation in these systematic reviews was too low for inclusion in the present evidence review since early-ART was defined as the current CD4 treatment cut off used in England.

A recent observational study (Lodi et al., 2015) used data from the HIV-CAUSAL consortium of prospective cohort studies in Europe and US to analyse the outcomes of 55,826 ART-naïve HIV positive adults diagnosed between 2000 and 2013 with CD4 and HIV-VL measurements and enrolled within six months of diagnosis. The median CD4 was 376 cells/mm^3, 77% were male and 71% started ART during the 7 years follow-up. This study stratified participants according to CD4 count at ART initiation in three groups: Immediate-ART, defined as initiation within 6 months of HIV diagnosis regardless of the CD4 count; ART initiation within 6 months of a CD4 count < 500 cells/mm^3 or an AIDS diagnosis, and ART initiation within 6 months of a CD4 cell count < 350 cells/mm^3 or an AIDS diagnosis and used the parametric g-formula to adjust for baseline and time-varying confounders such as CD4 count, HIV-VL and AIDS, to estimate the mean survival time, the proportion in need of ART, and the proportion with HIV RNA<50 copies/mm^3 as would have been observed under each ART initiation strategy after 7 years of HIV diagnosis. The primary end point was a composite of all-cause mortality and AIDS defining illness; relative risks of both death and of death or AIDS-defining illness. The estimated 7-year risk of AIDS defining illness or death was 7.1% (95%CI, 6.8 to 7.3) for the immediate-ART group; 7.5% (95%CI, 7.2 to 7.8) for those starting ART at CD4 < 500 and 8.5% (95%CI, 8.2 to 8.8) for those starting ART at a CD4 < 350 cells/mm^3. The findings in this study suggest that in high income countries, immediate ART initiation increases survival and AIDS-free survival compared with deferred ART initiation; conversely, for individuals with a CD4 count > 500 cells/mm^3 at diagnosis, deferring ART initiation increased the relative risk of death or AIDS diagnosis by more than 50% (Lodi et al., 2015)

No cost-effectiveness studies specific to the individual clinical benefit of early-ART were identified. The majority of publications refer to the cost-effectiveness of early-ART in the context of TasP or in the public health context of potentially reducing the community viral load and therefore having a likely positive impact in

reducing HV transmission.

4.1. Study design

The (START) trial (Lundgren et al., 2015.), a multicentre, multicontinental RCT, followed 4,685 HIV-1 positive treatment naïve adults randomised to either immediate-ART initiation -irrespective of CD4 cell count (2,326 participants) or to deferred-ART initiation - when the CD4 count approach 350 cells/mm^3 or the patient developed AIDS or AIDS related condition or any condition that dictated the use of ART, e.g. pregnancy (2,359 participants). Patients were enrolled from April 2009 to December 2013, and followed for a mean of 3.0 years (23% patients were followed for >4 years) with low lost to follow-up (defined as lack of contact for at least 10 months) rates of 4.0% in the immediate-ART and 5.0% in the deferred-ART groups. Although randomisation was not blind, participants and investigators were not blinded to the treatment group assignment, end points were reviewed blindly by an independent data and safety monitoring board.

In May 2015, an interim analysis identified that the primary research question of the study had already been answered; at that point in time 98% patients in the immediate-ART and 48% of those in deferred-ART initiation groups had started ART. The board, based on the beneficial effect of early ART, recommended that ART was offered to all those individuals not yet receiving ART in the deferred ART arm. As a result, 30% of participants in the deferred-ART group started ART earlier than per original protocol (i.e. with a CD4 count >350 cells/mm^3) and as a result, the ITT analysis may have underestimated the benefits of immediate-ART (Lodi et al., 2016). The most common drugs used for initial treatment in the immediate-ART and the deferred-ART groups were tenofovir (89% in both groups), emtricitabine (89% and 88%, respectively), and efavirenz (73% and 51%, respectively). Appropriate changes in regimens were mandated in cases of treatment-limiting adverse drug reactions or if the regimen did not fully suppress viral replication.

The TEMPRANO trial (Temprano ANRS Study Group et al., 2015), an unblinded, multicentre, individual-randomised controlled, 2-by-2 factorial, 1:1 superiority trial conducted at nine HIV care centres in Abidjan, Ivory Coast, between March 2008 and January 2015 explored the benefits of early ART alone or in combination with

a six months course of isoniazid preventive therapy (IPT, 300 mg isoniazid daily) started one month after enrolment, since tuberculosis (TB) is endemic in Ivory Coast and IPT was not routinely used at the time of the study, compared to deferred ART initiation (ART initiation following the concurrent WHO guidelines) or deferred ART plus IPT (deferred ART initiation until WHO criteria were met plus IPT started one month after enrolment). This study was designed to provide RCT evidence on the potential benefits of early ART initiation in low-income countries based on the evidence that the rates of TB and bacterial infections in these countries are high among people living with HIV, and there is a likely stepwise increase in prevalence at decreasing CD4 counts (Anglaret et al., 2012). Non–AIDS–defining non-infectious diseases were also included as an endpoint as there is increasing evidence that HIV infected people with uncontrolled viral replication exhibit raised inflammation markers and higher rates of death from non–AIDS–defining non-infectious diseases (Emery et al., 2008).

In the TEMPRANO study, 2,056 HIV-1 infected individuals were included in the analysis, 41% with a baseline CD4 count ≥ 500 cells/mm^3 were followed for 4,757 patient years; 1,033 patients were randomised to the early-ART strategy (groups 3 and 4, see table 7) and followed for 2,375 person-years; 1,023 individuals were assigned to the deferred ART strategy (groups 1 and 2, see table 7) and followed for 2,382 person-years. 57% of patients in group 1 and 59% of those in group 2 started ART during the 30 months study period; 100% of participants in groups 3 and 4 started ART. The first-line ART regimen used in TEMPRANO was tenofovir–emtricitabine plus efavirenz. Patients with contraindications to efavirenz received tenofovir–emtricitabine plus lopinavir–ritonavir, or tenofovir–emtricitabine plus zidovudine (this was stopped during the first year of the study due to high rates of upper digestive track side effects).

4.2. Outcomes

4.2.1. Clinical effectiveness

4.2.1.1 Overall morbidity and mortality

The START trial showed that immediate-ART initiation was superior to deferred-ART initiation. There were 42 composite primary end points reported in patients in

the immediate-ART and 96 in the deferred-ART initiation groups. The risk of severe morbidity was 57% lower in the immediate-ART group, estimated HR in the immediate-ART *vs.* the deferred-ART initiation group, was 0.43 (95% CI, 0.30 to 0.62; P<0.001) and did not vary significantly during the follow-up period (P = 0.77 by proportional-hazards testing). Four of 42 primary end points (10%) occurred before ART initiation in the immediate *vs.* 68/96 (71%) in the deferred-ART initiation group (Lundgren et al., 2015). The three most common events in both groups, the immediate and deferred-initiation groups were cardiovascular disease (29% and 15%), non–AIDS-defining cancer (21% and 19%), and tuberculosis (14% and 20%) respectively. There were 33 deaths during the study period, 20 (61%) were attributable to causes other than AIDS, including cardiovascular disease, renal disease, liver disease, or cancer. There was a 42% risk reduction for death from any cause in the immediate *vs.* the deferred-ART initiation groups; the estimated HR for death from any cause in the immediate *vs.* the deferred-initiation group was 0.58 (95% CI, 0.28 to 1.17; P = 0.13) (Lundgren et al., 2015). The event rates (absolute risk) for the primary end-point in the immediate and the deferred-ART groups were 0.6 and 1.38 per 100 person years (respectively) and the numbers needed to treat (NTT) to prevent one end point event was 128 (Molina et al., 2016). Furthermore, sensitivity analyses were performed by stratified analysis of the study population by demographic characteristics at study entry, including risk factors for serious AIDS-related and serious non–AIDS related disease; there were no statistically significant differences between the different subgroups (p≥0.25 for all interactions) and HRs consistently favoured the immediate-ART initiation group across all subgroups. However, the absolute risk reductions were higher among patients older than 50 years (NNT=50), those with a higher HIV-VL (HIV RNA≥50,000 copies/mm^3) at baseline (NNT=67) or a higher Framingham risk score (NNT=69); as well as a trend towards lower NNT with decreasing baseline CD4 counts (Molina et al., 2016).

The modification of the initial protocol of the START trial after the interim analysis resulted in approximately 30% of individuals in the deferred-ART group starting ART earlier than per original protocol; this could have resulted in an

underestimation of the beneficial impact of immediate-ART. To understand the level of underestimation of the beneficial effect of immediate-ART, Lodi et al., conducted a per-protocol analysis using the parametric g-formula to estimate the 3 and 5 year risk after randomisation of the primary outcome that would have been observed as per original protocol (Lodi et al., 2016). Using this methodology, the absolute risk reduction for individuals in the immediate ART group was 66% when compared to those in the deferred-ART group. Although these results are based on mathematical modelling they suggest that the change in the protocol of the START study could potentially have resulted in an underestimation of the net clinical benefit.

Both early-ART and IPT independently decreased the risk of severe morbidity and mortality in the TEMPRANO RCT; the risk of severe morbidity was 44% lower in those individuals randomised to the early-ART *vs*. the deferred-ART group, adjusted HR 0.56, (95%CI, 0.41 to 0.76). Early-ART significantly decreased overall morbidity and the beneficial effect remained when the analysis was restricted to individuals with a CD4 count > 500 cells/mm^3. Although there was no interaction between early-ART and IPT, the risk of severe morbidity in the IPT group was 35% lower than in the no-IPT group (Danel et al., 2015). The protective efficacy of early-ART in decreasing the relative risk of severe illness, as estimated by hazard ratios, was similar at CD4 counts above and below 500 cells/mm^3, and although the absolute risk of events across CD4 categories decreased with increasing CD4 counts, the risk of events remained clinically significant during the follow-up time when patients had CD4 counts of at least 500 cells/mm^3. These findings suggest that early-ART initiation before the CD4 count falls below 500 cells/mm^3 may be beneficial in patients living in countries with a high burden of TB and bacterial/opportunistic diseases.

4.2.1.2. AIDS related events

The START trial showed a 72% risk reduction of AIDS-related events in the immediate-ART *vs*. the deferred-ART initiation groups; the estimated HR for a serious AIDS-related event in the immediate *vs*. the deferred-initiation group was 0.28 (95% CI, 0.15 to 0.50; P<0.001). The relative risk reduction in serious AIDS-related events was mainly due to reductions in the rates of TB, Kaposi's sarcoma,

and malignant lymphomas; there was a 71% risk reduction for TB, estimated HR 0.29 (95% CI, 0.12 to 0.73; P=0.008); a 91% reduction in the risk of Kaposi's sarcoma, estimated HR was 0.09 (95% CI, 0.01 to 0.71; P=0.02), and a non-statistically significant 70% reduction in the risk for malignant lymphomas, estimated HR 0.3 (95% CI, 0.08 to 1.10; P=0.07). Observational studies have reported the association of HIV infection and/or ART with increased risk of cognitive decline, chronic kidney disease (CKD), low bone mineral density (BMD), cardiovascular disease and lung infections (Geffen et al., 2015). Several sub studies used descriptive statistics and logistic regression to report the baseline prevalence of these conditions in participants in the START trial as well as their association with traditional risk factors and HIV parameters. Achhra et al., 2016, described the prevalence of CKD and risk factors associated with CKD such as diabetes, hypertension and race/ethnicity (Achhra et al., 2016); Carr et al., 2015, using a subset of the START cohort, reported on the prevalence of low BMD and osteoporosis as well as traditional risk factors for osteoporosis and their association with HIV parameters (Carr et al., 2016), the outcomes of these sub-studies will provide further evidence on the effect of early ART in this population.

Early-ART also showed to be beneficial in reducing the risk of death or AIDS in the TEMPRANO trial with an overall risk reduction of 42% when compared with deferred-ART initiation, HR 0.58 (95% CI, 0.41 to 0.83); similarly there was a 50% risk reduction for AIDS diagnosis, HR 0.5 (95% CI, 0.33 to 0.76) and a 61% reduced risk of developing invasive bacterial disease, HR 0.39 (95% CI, 0.21 to 0.71). Tuberculosis accounted for 42% of primary endpoint events and invasive bacterial diseases for 27%. The overall risk reduction for TB observed in the early-ART group when compared to the deferred-ART group was 50%, adjusted HR for tuberculosis 0.50 (95% CI, 0.35 to 0.76); in this setting, early-ART initiation demonstrated a beneficial effect in reducing the risk of developing opportunistic infections (Temprano ANRS Study Group et al., 2015).

4.2.1.3. Serious non-AIDS related events

The START trial showed a beneficial effect of immediate-ART *vs.* deferred-ART initiation on the incidence of serious non-AIDS-related events with an overall 39% risk reduction; the estimated HR for a serious non-AIDS-related event in the

immediate *vs.* the deferred-initiation group was 0.61 (95% CI, 0.38 to 0.97; P = 0.04), and for death from any cause was 0.58 (95% CI, 0.28 to 1.17; P = 0.13). The 39% relative risk reduction in serious non–AIDS related events was mainly due to a reduction in the incidence of non–AIDS defining cancers in the early-ART group. Although TB was more common in Africa and cardiovascular disease and cancer were more common in high-income countries, the benefits of immediate ART were consistent across the different settings of the START trial even though specific outcomes differed by geographic regions.

Immediate-ART also significantly reduced the risk of cancer by 64% in the START study. Malignancies were classified as infection-related and infection-unrelated cancers; there were 14 malignancies in the immediate-ART group (6 infection-related and 8 infection-unrelated) *vs.* 39 malignancies in the deferred-ART group (23 infection-related and 16 infection-unrelated); immediate-ART significantly reduced the risk of infection-related cancer by 74% [HR 0.26 (95% CI; 0.11 to 0.64 P=0.003)]. The Kaplan-Meier curves for infection-related cancer overlapped during the first year of follow up but showed a lower risk of cancer afterwards that remained so during the study period. Immediate ART also reduced the risk of infection-unrelated cancer by 51% although this was not statistically significant [HR 0.49 (95%CI; 0.21 to 1.15 P=0.103)] (Borges et al., 2016). Cox models were used to assess factors associated with risk of developing both types of cancers; the reduction in the risk of infection-related cancers was mainly due to a reduction in the incidence of Kaposi sarcoma and non-Hodgkin lymphoma; this was surprising within this cohort with early HIV infection and the short follow up period. Adjustment for CD4 count had no impact on protective effect. This results should be interpreted with caution, this is a post hoc analysis of a trial whose sample size was not calculated to assess reductions in cancer risk; in addition, START had a follow up shorter than initially planned due to the change in the deferred-ART group. As a result, it is unclear whether the non-significant reduction in infection-unrelated cancer or for death from any cause, just reflected limited power to detect differences or was instead a true observation.

4.2.1.4. Virologic suppression

Patients enrolled in the immediate-ART initiation group in the START study

received ARVs for 94% of the study follow-up time compared to 28% in the deferred-ART group. The percentage of patients who had an HIV-VL suppression (HIV RNA level of 200 copies/mm^3 or less) mirrored the percentage of patients receiving ART (Lundgren et al., 2015). The median HIV-VL was lower in the immediate-ART than in the deferred-ART groups (13,462 and 41,525 copies/mm^3 respectively) but the proportion of patients achieving full viral suppression 12 months after initiating ART was similar in both groups (98% *vs.* 97%).

Virologic suppression was reported in the TEMPRANO study although not all the participants had viral load measurements. HIV-VL measurement at 12 months of ART initiation was undetectable in 84% of 911 patients in the early-ART strategy; HIV-VL at 24 months of ART initiation was undetectable in 83% of 872 patients in the early-ART strategy who had a HIV-VL measurement at 24 months. 331 of 391 patients who completed 12 months ART in the deferred ART strategy had a HIV-VL measurement and 80% were undetectable (Temprano ANRS Study Group et al., 2015).

4.2.1.5. CD4 count

The average CD4 count of participants enrolled in the immediate-ART group of the START trial increased markedly during the first year after treatment initiation and continued to increase gradually thereafter; in contrast, the average CD4 count of individuals in the deferred-ART group decreased during the first year and then stabilised and subsequently increased as more individuals in this group started ART. The average CD4 count during the follow-up period was 194 cells/mm^3 higher in the immediate *vs.* the deferred-ART groups (Lundgren et al., 2015).

Similarly, in the TEMPRANO study, the mean CD4 count of patients enrolled in the early-ART strategy group increased from 481 cells/mm^3 at baseline to 728 cells/mm^3 at 30 months whereas the mean CD4 for individuals in the deferred-ART groups decreased from 472 cells/mm^3 at baseline to 428 cells/mm^3 at 12 months and then gradually increased to 511 cells/mm^3 at 30 months as some patients in this group had also started ART (Temprano ANRS Study Group et al., 2015).

4.2.2. Safety

Safety events were reported in both RCTs. In the START study, the risk of grade 4 events, defined as potentially life-threatening symptomatic events not attributable to AIDS that required a medical intervention, was similar in the two groups [HR 1.01 (95%CI, 0.73 to 1.39; P=0.97)]. The most common grade 4 events were bacterial infections (14 in the immediate-ART and 36 in the deferred-ART arms, see section 7 table for HR); bone or joint injuries (17 and 11 respectively); mood disorder or depressed mood (12 and 9 respectively); unspecified infections (64 and 65 respectively); injuries (11 and 22 respectively); suicidal or self-injurious behaviour (27 and 24 events respectively) and; viral infections (12 and 15 respectively). Furthermore, the risks of unscheduled hospital admissions was similar in both treatment groups; there were 262 unscheduled admissions in the immediate-ART and 287 in the deferred-ART groups, HR 0.91(95%CI, 0.77 to 1.08; P=0.28). (Lundgren et al., 2015). A recent sub-analysis of drug related suicidal behaviour by Arenas-Pinto et al, using Cox proportional hazards model and ITT analysis (Arenas-Pinto et al., 2016) advised that patients in the immediate-ART group using efavirenz had an increased risk of suicidal behaviour when compared to individuals in the deferred-ART group or to those prescribed ART without efavirenz, and that this was even higher in patients with history of previous psychiatric diagnoses [HR=12.8, (95%CI 4.7 to 34.9; P<0.001)] or heavy alcohol use [HR=6.1, (95%CI 1.9 to 19.6; P=0.003)]. Although this observation was based on a very small number of events (only 3 completed suicides, all in the deferred-ART group), the authors recommend screening for pre-existing depression and other psychiatric conditions prior to initiating efavirenz. The early termination of the deferred-ART group, together with the lower incidence of end point events in both groups, could have resulted in a reduction in the power of this study to identify statistically significant differences. However, grade 4 events and unscheduled hospitalizations occurred more often than did the primary outcome, but rates of these events were similar in the two intervention and control groups. Future analysis in this cohort could strengthen the quality of this evidence.

The TEMPRANO RCT reported grade 3 or 4 clinical events defined as all severe adverse events including fatal or life threatening events, events leading to

hospitalisation, malignancies and overdoses as well as abnormal laboratory test results (Temprano ANRS Study Group et al., 2015). There were no statistically significant differences between the early-ART and the deferred-ART groups. Short-term adverse events were more common in the early-ART group and involved common side effects of ARV drugs, mainly digestive and neurologic symptoms; 165 serious adverse events in 144 patients were recorded during the follow-up period. The cumulative probability of a grade 3 or 4 adverse event over a 30-month period was 7.7% among patients assigned to the deferred-ART groups *vs.* 7.1% for those in the early-ART groups. Similarly, the cumulative probability of a grade 3 or 4 event among patients assigned to the no-IPT groups was 8.2% vs 6.6% among those in the IPT groups. The risk of grade 3 or 4 adverse events during the first 6 months of the study was 2.6 times as high among patients assigned to early-ART as for those in the deferred-ART group (Adjusted HR 2.57; 95% CI, 1.47 to 4.51) and 2.1 times as low among patients assigned to early-ART as among patients assigned to deferred-ART thereafter (Adjusted HR 0.48; 95% CI, 0.30 to 0.76). The 30-month probability of grade 3 or 4 adverse events did not significantly differ among groups. There is a risk of under estimation of clinical events including adverse events due to limited diagnostic capacity in Ivory Coast; furthermore, it is difficult to determine what proportion of adverse events were attributable to ART and what proportion may have been due to symptomatic disease; however, this form of bias would have been similar in both intervention and control groups. In summary, there were no statistical significant differences in the incidence of adverse events in the early *vs.* the deferred-ART initiation groups during the time of follow up.

4.2.3. Risk compensating behaviour

The possibility of risk compensation, i.e. increase in risky behaviours as a consequence of decreased perceived risks of HIV burden and/or transmission in those individuals receiving early-ART, may be of particular concern. A behavioural study nested in the TEMPRANO RCT assessed the potential impact of early-ART on risky sexual behaviours by comparing the proportion of risky behaviour, defined as self-reported unprotected sex with a partner of negative/unknown HIV status. The study population was heterosexual individuals recruited by the

TEMPRANO study between 1st January 2008 to 1 September 2011; 1,172 individuals were recruited but only 957 (81.7%) completed a face to face socio-behavioural questionnaire within 9 to 15 months after enrolment and were included in the 12 months analysis (Jean et al., 2014a). The majority of participants were female (80.4%), 467 were in the deferred-ART and 490 in the early-ART groups, the two groups were comparable on baseline characteristics. At the 12 month visit, only 15.0% of patients randomised to the deferred-ART group had started treatment (9.5 months median duration); the percentage of patients with an undetectable viral load was lower amongst those in the deferred than in the early-ART group. No significant differences were seen in the proportion of sexually active individuals in the past year (71.7% in the deferred and 69.8% in the early-ART groups, P=0.51), those reporting multiple partnerships (6.2% and 9.0% respectively, P=0.11) or those not cohabiting with their last sex partner (41.8% and 41.2% respectively, P=0.87). The last sex partner was reported to be uninfected by 26.6% of those in the deferred and 22.8% in the early-ART groups (P=0.47) or of unknown status by 43.9% and 47.7% respectively (P=0.47). There were no statistically significant differences between the two groups as regard to condom use and sexual activity in the past month. The proportion of subjects who reported risky sex in the previous month was 12.8% in the deferred-ART *vs.* 10.0% in the early-ART group (P=0.54). Sexual behaviours of patients in both groups were similar, however, participants in the TEMPRANO trial had a high frequency of contacts with health care professionals and this study only assessed behaviours in the first year of treatment which may explain the comparability of reported sexual activity and risky behaviour in the two groups. Furthermore, this study was nested on the TEMPRANO trial and over 80% of this subsample was female; the results rely on self-reported sexual behaviours which are potentially subject to social desirability bias and over-reporting of condom use could lead to an underestimation of HIV transmission risks. This subset included a relatively high proportion of individuals out of a stable partnership and therefore the lack of a detectable effect of early-ART on risky sexual behaviour could apply to other similar populations.

A second nested study in the TEMPRANO trial assessed the behavioural changes at entry into care (recruitment, month 0) and at ART-initiation (Treatment

Initiation, TI) as well as 12 and 24 months after ART initiation (TI$_{+12}$ and TI$_{+24}$ respectively) by describing changes in sexual behaviour at each stage (Jean et al., 2014b). This study involved 1,952 heterosexual individuals (977 in the deferred and 975 in the early-ART arms) recruited by TEMPRANO from March 2008 to July 2012 who completed at least one face to face questionnaire; 79% of participants were female, the median age was 35 years and the median baseline CD4 was 469 cells/mm^3; 57% of participants completed at least two face to face questionnaires. In this study, the frequency of sexual activity decreased from 79.9% at enrolment to 72.6% at M24 in the early-ART group and from 75.9% to 69.8% in the deferred-ART group; the frequency of multiple partners decreased from 14.4% to 8.7% in the early-ART and from 12.8% to 7.6% in the deferred-ART group. In relation to risky behaviours, there was a decreased in the frequency of unprotected sex from 40.7% at enrolment to 27.3% at M24 in the early-ART and from 38.1% to 23.9% in the deferred-ART group; furthermore, the frequency of risky sex decreased from 26.8% at M0 to 17.3% at M24 in the early-ART and from 28.4% at M0 to 15.5% at M24 in the deferred-ART group with the greater decrease in risk during the first year post ART initiation in both groups. There were 802 participants with at least one socio-behavioural questionnaire in the deferred-ART group, 492 of these initiated ART; the frequency of sexual activity did not changed significantly between M0 and TI; the frequencies of multiple partners, unprotected sex and risky sex significantly decreased between M0 and treatment initiation [multiple partners: Odds Ratio (OR)TI *vs.* M0 0.41, (95%CI 0.26 to 0.64); unprotected sex: OR TI *vs.* M0 0.65, (95%CI 0.49 to 0.85); risky sex: OR TI *vs.* M0 0.62, (95%CI 0.45 to 0.84)]. Subsequently, the frequencies of these three indicators did not significantly change over time within the 24 months following treatment initiation (each p=0.15). In this study, there were decreases in reported sexual behaviours within the 24 months following enrolment in all groups, suggesting that the decrease was likely to be related to contact with health care rather than ART initiation. The most significant change occurred in the first 12 months of access to health care. There was no evidence of risk compensation behaviours; early-ART initiation did not increase risky sexual behaviours, participants in all groups' decreased sexual behaviours including risky behaviours irrespective of ART initiation. However, the majority of participants in this study

were female and the study relies on self-reported sexual behaviours. Even though interviewers were trained to administer questionnaires in a non-judgmental way and interviews were conducted confidentially in private rooms, risky behaviours may have been under-reported due to social desirability. The effect of contact to health care on reduction of risky behaviours was maintained at all the nine HIV care centres participating in the study and could be explained by the additional health education and safe sex promotion provided by the trial over and above the local standard of prevention care. There was no evidence of compensating behaviours in those starting ART early.

4.3. Applicability

The START trial involved one of the largest international cohorts in HIV research; the cohort is diverse and well represented; 46% of participants were from high income countries, approximately 33% from Europe, 11% from the US and 2% from Australia, and over half were from low and middle-income countries. The START participants are comparable with the current cohort of globally untreated HIV-positive individuals, with the exception of injecting drug users (Sharma et al., 2015). Overall, 26.8% of START participants were female; this fraction was significantly lower in the European cohort were females represented 9.1% of the sample. Similarly, whereas the overall rate of MSM in START was 55% this sample was also overrepresented in Europe (76.6% participants were MSM). However, the broad inclusion criteria and the diversity in the participating sites in this trial enable its results to be broadly generalizable to the UK setting. Furthermore, in a sensitivity analysis carried out by Molina et al (Molina et al., 2016) the absolute risk reduction for primary end-point events was higher among patients in the immediate-ART initiation group from high income countries (NNT=116 *vs*. 144 for low and middle income countries) (Molina et al., 2016).

The TEMPRANO study provides strong evidence of the net clinical benefit of early-ART initiation in settings with a high prevalence of TB and opportunistic infections and as such it is not directly applicable to the UK setting; however, some of the evidence of effectiveness in relation to decreased HIV-VL and increase in the median CD4 after initiation of ART as well as the lack of

significant differences in the rates of cumulative adverse events could be applicable to similar populations in the UK setting with caution.

5. Discussion

We found evidence from two large independent multicentre randomised control trials on the net clinical benefit of early ART initiation (at a CD4 count > 500 cells/mm^3). In the START trial, the beneficial effects of immediate ART on serious illness and death (AIDS and non-AIDS related events) were seen even though a significant proportion of patients started ART in the deferred-ART group at a CD4 count > 350 cells/mm^3 after the independent data and safety monitoring board interim analysis recommended that all participants were offered ART. Early-ART treatment reduced the risk of developing serious illness or death by 57% compared with the control group and these finding were consistent across geographical regions and for high and low or middle-income countries.   Similarly, the TEMPRANO study demonstrated a net clinical benefit related to early-ART initiation, the 44% reduction in the risk of severe morbidity and mortality seen in the early-ART initiation group in this study was mainly related to a decreased incidence in the rates of TB and bacterial infections that are endemic in the Ivory Coast.

In both studies, the primary end point incorporated potentially serious positive and negative effects of antiretroviral therapy, and no safety concerns in the immediate-initiation groups were identified. In the START study, Grade 4 events and unscheduled hospitalizations occurred more often than did the primary outcome, but rates of these events were similar in the two intervention and control groups. In the TEMPRANO study, the cumulative probability of grade 3 or 4 adverse events was similar in both groups.

The early termination of the deferred-ART study group in the START study, combined with the lower incidence of primary events attributable to serious non–AIDS-related conditions (54% vs. anticipated 77%), resulted in low statistical power to precisely quantify benefit, thus limiting the evidence of the beneficial effects of immediate ART on the risk of individual serious non-AIDS conditions such as all-cause mortality, cardiovascular disease and non-infection related

cancers. This evidence could be strengthened by further follow up of this cohort. The follow up time of this trial, although based on statistical projections to evidence the differences between the two treatment groups, was actually brief for patients who will require life-long ART. It will be important to assess risks and benefits of long-term therapy in this and other cohorts.

6. Conclusion

Evidence from two large well designed independent multi-centre randomised control trials, the Strategic Timing of AntiRetroviral Treatment (START) and the TEMPRANO studies, suggest that the initiation of antiretroviral therapy in asymptomatic HIV-1 positive, treatment naïve adults with a CD4 count > 500 cells/mm^3 provides significant net clinical benefits over starting ART after the CD4 count had declined to 350 cells/mm^3 both in high- and low and middle-income countries.

Results from these two RCTs showed that early ART initiation can reduce the risk of serious AIDS-related and serious non-AIDS related events when compared with deferred ART initiation. Both studies reported no evidence of significant increase in adverse grade 3 or 4 events in individuals starting ART early when compared with those in the deferred-ART initiation groups. In addition, there was no evidence that the beneficial effect of immediate-ART initiation differed according to age, sex, and ethnicity, region of the world, CD4 count, viral load, or risk factors for serious non-AIDS diseases. These results align the clinical benefits for individual patients with the already demonstrated public health benefit of antiretroviral therapy in reducing the risk of viral transmission.

In conclusion, the findings of these two RCTs provide good quality evidence (Grade A) of the efficacy and effectiveness of initiating ART early, at CD4 counts > 500 cells/mm^3, compared to initiating ART when the CD4 count is approaching 350 cells/mm^3. Antiretroviral therapy should be started in all individuals with HIV infection with detectable viremia regardless of CD4 cell count.

7. Evidence Summary Table

						Immediate-ART *Vs.* Deferred-ART			
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
LUNDGREN et al., 2015.	**START** Multicentre, multicontinental RCT (Six geographic regions: Africa, Europe and Israel, North America, South America and Mexico, Australia, and Asia).	4,685 ART naïve HIV positive adults (18 years or older) with two consecutive CD4 counts >500 cell/mm^3 with no history of AIDS and in general good health, recruited from April 2009 to December 2013 in 215 sites at 35 countries. Median age in both groups was 36 years, 27% female, median CD4 count was 651 cell/mm^3 and median HIV-VL 12,759 copies/millilitre. Pregnant and breastfeeding women on enrolment were excluded; women who became pregnant after enrolment were included. At study entry, the	**Intervention:** Immediate-ART (2,326 patients) **Comparator:** Deferred-ART (ART started when CD4 count decreased to 350 cell/mm^3 or patient developed AIDS or AIDS related condition or any condition that dictated the use of ART, e.g. pregnancy) (2,359 patients) Groups compared using intention to treat analysis; time-to event methods, including Kaplan–Meier survival curves and Cox proportional-hazards models stratified by regions, for the primary end point analysis.	*Primary end-point*	Composite end point, time to any serious AIDS-related or serious Non-AIDS related event or death from any cause.	42 events in the immediate-ART group (1.8%; 0.60 events per 100 person-years), as compared with 96 in the deferred-ART group (4.1%; 1.38 events/100 person-years), <u>Hazard ratio</u> of 0.43 (95%CI, 0.30 to 0.62; P<0.001). 68% of primary end points occurred in patients with a CD4+ count <500 cells/mm^3.	10/10	Direct	A large multi-centre multi-country multi-continental study. Randomisation was stratified by clinical site in a 1:1 allocation ratio using permuted blocks. Due to the nature of the study both participants and investigators were not blinded to the treatment group assignment. However, end points were reviewed blinded to treatment group (see below). No significant differences between groups characteristics at baseline including age, gender, ethnicity, region, mode of infection, median time since HIV diagnosis, median CD4, median HIV-VL, smoking and median CHD risk at 10 years (Framingham Heart Study tool). An independent data and safety monitoring board review interim analysis and consider consistency of the findings in the two major components of the primary end point; study investigators were unaware of interim summary results or end point consistency. Design changed on 15th May 2015 after interim analysis, the data and safety monitoring board determined that the research question had been answered early and recommended that patients in the deferred-ART group be offered antiretroviral therapy. Analysis of data up to 26th May 2015. At 26th May 2015 98% patients in immediate-initiation and 48% of those in deferred-initiation group had started ART. An O'Brien–Fleming boundary and the Lan–DeMets spending function based on information time (fraction of primary events accrued) were
					Cardiovascular disease	<u>Hazard ratio</u> 0.84 (95%CI, 0.39 to 1.81; P 065).			
					Non-AIDS-defining cancer	<u>Hazard ratio</u> 0.50 (95%CI, 0.22 to 1.11; P 0.09).			
					Tuberculosis	<u>Hazard ratio</u> 0.29 (95%CI, 0.12 to 0.73; P 0.008).			
				Secondary end-points	Any serious AIDS-related events (including death from AIDS);	<u>Hazard ratio</u> 0.28 (95%CI, 0.15 to 0.50; P<0.001).			
					Any serious non–AIDS-related events, death from any cause	<u>Hazard ratio</u> 0.61 (95%CI, 0.38 to 0.97; P = 0.04).			
					Death from any cause	<u>Hazard ratio</u> 0.58 (95%CI, 0.28 to 1.17; P = 0.13).			
					Virologic suppression:	The percentage of patients who had an undetectable HIV-VL			

		median HIV viral load was 12,759 copies per millilitre, and the median CD4 count was 651 cells/mm^3.			assessed as percentage of patients with an undetectable HIV-VL at 12 months of starting ART;	mirrored the percentage of patients receiving ART. The median HIV-VL was lower in the immediate-ART than in the deferred-ART groups (13,462 and 41,525 copies/mm^3 respectively) but the proportion of patients achieving full viral suppression 12 months after initiating ART was similar in both groups (98% *vs.* 97%).			used to adjust for a type I error in the analysis of the primary end point. Several sub-studies have reported on the demographic characteristics, factors related to HIV history and baseline risk factors for common co-morbidities in the START cohort; Sharma et al., 2015 described the cohort as diverse and globally well represented with over half of the participants from low and middle income countries (Sharma et al., 2015). Approximately 33% of the participants were from Europe, 11% from USA and 2% from Australia. This increases the applicability of its results to the UK population. The change in the study design as recommended by the independent data and safety monitoring board resulted in a significant number of patients starting ART at a CD4 greater than 350 cell/mm^3; this could have reduced the power of the study. In addition, the observed percentage of primary end-points attributable to non-AIDS-related conditions was lower than anticipated. This in conjunction with the early termination of the deferred-ART arm resulted in low statistical power to adequately quantify benefit.
					Average CD4 count:	The average CD4 count of the immediate-ART group increased markedly during the first year after treatment initiation and continue to increase gradually thereafter; conversely, the average CD4 count of individuals in the deferred-ART group decreased during the first year and then stabilised and subsequently increased as more individuals in this group started ART. The average CD4 count during the follow-up period was 194 cell/mm^3 higher in the immediate *vs.* the deferred-ART groups			
				Safety	Any **grade 4 adverse events** [Cardiovascular disease, end-stage renal disease, liver disease, non-AIDS defining cancers]	There were 73 grade 4 events in each study arm; similar risk in both groups, Hazard ratio 1.01 (95%CI, 0.73 to 1.39; P=0.97)		
					Bacterial infections	Hazard ratio 0.38 (95%CI, 0.20 to 0.70; P=0.002)		
					Bone or joint injury	Hazard ratio 1.55 (95%CI, 0.73 to 3.31; P=0.26)		
					Depressed mood/mood disorder	Hazard ratio 1.34 (95%CI, 0.57 to 3.19; P=0.50)		
					Infection unspecified	Hazard ratio 0.99 (95%CI, 0.70 to 1.40; P=0.96)		
					Injury	Hazard ratio 0.50 (95%CI, 0.24 to 1.03; P=0.06)		
					Suicidal or self-	Hazard ratio 1.15 (95%CI, 0.66		

				injurious behaviour	to 1.99; P=0.63)				
				Viral infection	Hazard ratio 0.81 (95%CI, 0.38 to 1.72; P=0.58)				
				Unscheduled admissions	262 unscheduled admissions in the immediate-ART and 287 in the deferred-ART group. Hazard ratio 0.91 (95%CI, 0.77 to 1.08; P=0.28).				
				Serious adverse reactions	16 events in the immediate ART arm				
				Quality of life	Quality of life in the two groups was assessed using the self-administered SF-12, version 2 questionnaire and a visual analog scale for current health.				

Immediate-ART *Vs.* Deferred-ART									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Lodi et al., 2016	**START** Multicentre, multicontinental RCT (Six geographic regions: Africa, Europe and Israel, North America, South America and Mexico, Australia, and Asia).	**As for START** 4,685 ART naïve HIV positive adults (18 years or older) with two consecutive CD4 counts >500 cell/mm^3 with no history of AIDS and in general good health, recruited from April 2009 to December 2013 in 215 sites at 35 countries. Median age in both groups was 36 years, 27% female, median CD4 count was 651 cell/mm^3 and	**Intervention:** Immediate-ART (2,326 patients) **Comparator:** Deferred-ART (ART started when CD4≤350 cell/mm^3 or patient developed AIDS or AIDS related condition or any condition that dictated the use of ART, e.g. pregnancy) (2,359 patients) *As per-protocol analysis*	*Primary end-point*	Composite end point, time to any serious AIDS-related or serious Non-AIDS related event or death from any cause.	38* events in the immediate-ART group , estimated per-protocol 5 year risk 3.2% (95%CI 1.9 to 4.5%), as compared with 90* in the deferred-ART group, estimated as per-protocol 5 year risk 7.0% (95%CI, 5.3 to 9.4%), Per-protocol Hazard ratio of 0.34 (95%CI, 0.21 to 0.52). * Ten events reported in the original paper (Lundgren et al, 2015) were excluded.	8/10	Direct	To understand the potential underestimation of the beneficial effect of immediate-ART resulting from the early modification of the START protocol, the authors used the parametric g-formula to estimate and compare the cumulative 5 year risk of the composite primary end point in the immediate and the deferred-ART groups as per-protocol effect. This is the effect had all participants in the trial adhered to the treatment initiation strategy they were assigned to and, unless they had experienced the primary endpoint, remained under follow-up for the duration of the study. The authors used a simulated model that assumed all prognostic factors that predict protocol variations were identified and measured. Observations based on mathematical models informed by ITT START data. The number of primary events in both groups was lower than originally estimated and therefore observations and model are based on small numbers.

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
Immediate-ART _Vs_. Deferred-ART									

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
		median HIV-VL 12,759 copies/millilitre.							

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
Immediate-ART _Vs_. Deferred-ART									
Borges et al., 2016	**START** Multicentre, multicontinental RCT (Six geographic regions: Africa, Europe and Israel, North America, South America and Mexico, Australia, and Asia).	**As for START** 4,685 ART naïve HIV positive adults (18 years or older) with two consecutive CD4 counts >500 cell/mm^3 with no history of AIDS and in general good health, recruited from April 2009 to December 2013 in 215 sites at 35 countries. Median age in both groups was 36 years, 27% female, median CD4 count was 651 cell/mm^3 and median HIV-VL 12,759 copies/millilitre.	**Intervention:** Immediate-ART (2,326 patients) **Comparator:** Deferred-ART (ART started when CD4 count decreased to 350 cell/mm^3 or patient developed AIDS or AIDS related condition or any condition that dictated the use of ART, e.g. pregnancy) (2,359 patients)	_All malignancies_	All malignancies	Annual incidence remain stable in Immediate-ART arm (p for trend=0.79) and significantly increased in the deferred-ART group (p for trend =0.026) Hazard ratio 0.28 (95%CI, 0.13 to 0.58; P<0.001).	8/10	Direct	Comparison of the yearly incidence trends of infection-related and infection-unrelated cancers in both groups using Poisson regression models; Kaplan-Meier curves for cumulative percentage of events in each group were developed and HR for both arms were compared using a multivariate Cox regression model to identify factors independently associated with the risk of cancer. Immediate-ART initiation reduced risk of infection-related cancer by 74% and infection-unrelated cancer by 51%. Adjustment for potential mediators, such as HIV RNA, appeared to attenuate HRs of immediate/deferred ART for infection-unrelated cancer more than infection-related cancer. This is a post-hoc analysis of trial whose sample size was not calculated to assess differences in this outcome and the follow-up period was cut shortly by the early provision of ART to both study arms; as a result it is possible that the study did not have enough power to demonstrate a significant reduction in infection-unrelated cancer.
					Infection-related cancers	Immediate-ART significantly reduced the risk of infection-related cancer by 74% Hazard ratio 0.26 (95%CI, 0.11 to 0.64; P 0.003)			
					Infection-unrelated cancers	Immediate-ART reduced the risk of infection-unrelated cancer by 51% Hazard ratio 0.49 (95%CI; 0.21 to 1.15 P 0.103].			
TEMPRANO ANRS Study Group et al., 2015	**TEMPRANO** Unblinded, multicentr	2,076 ART naïve asymptomatic HIV-1 or dual HIV-1 and HIV-2 infected adults (18	**Intervention:** Early ART strategy: _Early ART_ (group 3, 515 individuals),	_Primary endpoint:_	Morbidity and mortality: a composite of AIDS-defining diseases, non-AIDS-defining	A total of 204 primary end-point events were observed in 175 patients (3.8 events/100 person-years; 95%CI, 3.3 to 4.4).	10/10	Indirect	Participants were randomised using computer-generated, sequentially numbered, block randomization lists, stratified according to study clinic, using a software tool that allowed access to the next available trial identification

Immediate-ART Vs. Deferred-ART									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
	e, individual-randomised controlled, 1:1 superiority trial at 9 HIV care centres in Ivory Coast. A 2-by-2 factorial design using Cox proportional models was used to compare outcomes between IPT and non-IPT groups. The study has 80% power to detect a 40% lower rate of primary end point events in the early ART or IPT groups assuming 10% rate of primary endpoints in the reference group.	years or older) in Ivory Coast with a CD4 count <800 cells/mm^3, with absence of active TB. 20 patients were excluded after randomisation due to having HIV-2 infection (15), being HIV negative (4) or non-ART naïve (1). Pregnant and breastfeeding women were excluded as well as HIV-2 infection alone, previous ART, known severe renal, cardiac or hepatic disease. 2,056 HIV -1 +ve individuals were included in the analysis, 41% with a baseline CD4≥500 cells/mm^3 were followed for 4,757 patient years.1,033 patients were randomised to the early ART strategy (groups 3 and 4) and followed for 2,375 person-years; 1,023 individuals were assigned to the deferred ART	in which ART was started immediately; and *early ART plus IPT* (group 4, 518 individuals) in which ART was started immediately and a 6-month course of IPT was started 1 month after enrolment. Comparator: Deferred ART strategy: *Deferred ART* (group 1, 511 individuals), ART initiation was deferred until concurrent WHO criteria were met; *deferred ART plus IPT* (group 2, 512 individuals), ART deferred until WHO criteria were met and a 6-month course of IPT started 1 month after enrolment. First-line ART consisted of tenofovir plus emtricitabine plus either efavirenz, zidovudine or lopinavir/ritonavir		cancers, non-AIDS-defining invasive bacterial diseases and all-cause deaths at 30 months.	Early ART significantly reduced the risk of primary end-point events by 44% <u>Adjusted Hazard ratio for primary end-point events</u> early ART as compared with deferred ART 0.56 (95% CI, 0.41 to 0.76) <u>Adjusted Hazard ratio for death</u> early ART as compared with deferred ART 0.80 (95% CI, 0.45 to 1.14)			number and treatment group. Baseline tests were performed after randomisation. No significant differences between groups' characteristics at baseline including median age, gender, educational level, WHO clinical stage of HIV infection, median CD4, median HIV-VL, dual HIV-1 1nd HIV-2 infection, creatinine clearance, haemoglobin, positive IGRA were observed. Patients in all groups were followed for 29.9 months and were seen monthly during the first three months and then quarterly. Study used intention to treat analysis for the primary endpoint; data were censored when participants were lost to follow-up before their 30 months visit. At the end of the study 47 patients had died (2%) and 58 (3%) were lost to follow up [no significant difference by strategy groups]. This was and unblinded open label study; an event-documentation committee review all clinical events and classified them as definite, probable, or possible according to standardized criteria; committee members were not blind to the randomization assignments. Kaplan-Meir method was used to estimate the cumulative probability of event occurrence in each group, and rates were estimated by dividing the number of first events by the cumulative time at risk. Multivariate Cox proportional-hazards models were used to compare strategies with respect to event rates for the primary endpoint and its components,
					AIDS related morbidity and mortality:	<u>Hazard ratio for death of AIDS</u> 0.58 (95% CI, 0.41 to 0.83)			
						<u>Hazard ratio for AIDS</u> 0.5 (95% CI, 0.33 to 0.76)			Several sensitivity analyses were performed. Analysis of end-points stratified by CD4 counts ≥ 350; ≥ 500 and < 500 cell/mm^3. The beneficial effect or early ART on the risk of morbidity was maintained in the stratified analyses.
						<u>Hazard ratio for invasive bacterial diseases</u> 0.39 (95% CI, 0.21 to 0.71)			
						<u>Hazard ratio for tuberculosis</u> 0.50 (95% CI, 0.35 to 0.76) Tuberculosis accounted for 42% of primary endpoint events (85 events, 57 in deferred-art and 28 in the early-ART group) and invasive bacterial diseases accounted for 27% of events (56 cases, 42 in the deferred-ART and 14 in the early-ART groups).			
				Secondary end-points:	Virologic suppression: assessed as percentage of patients with an undetectable HIV-VL at 12 and 24 months of starting ART;	84% of 911 patients in the early ART strategy who had a HIV-VL measurement at 12 months had undetectable HIV-VL and 83% of 872 had a HIV-VL undetectable at 24 months. 331 of 391 patients who completed 12 months ART in the deferred ART strategy had a HIV-VL			There is a risk of under estimation of clinical events including adverse events due to limited diagnostic capacity in this setting; however, this would have been similar in all intervention

									Immediate-ART *Vs*. Deferred-ART
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
	From March 2008 through January 2015.	strategy and followed for 2,382 person-years. 57% of patients in group 1 and 59% of those in group 2 started ART during the 30 months study period; 100% of participants in groups 3 and 4 started ART.				measurement and 80% were undetectable.			and control groups.
					Mean CD4 count:	Mean CD4 count increased from 481 cells/mm^3 at baseline to 728 cells/mm^3 at 30 months in the early-ART strategy groups and decreased in the deferred ART strategy groups from 472 cells/mm^3 at baseline to 428 cells/mm^3 at 12 months and then increased to 511 cells/mm^3 at 30 months as some patients in this group had started ART			
				Safety	Drug-related adverse events: all grade 3 or 4 clinical events;	165 grade 3 or 4 adverse events (90 in the deferred and 75 in the immediate-ART groups, Hazard ratio 0.82) were recorded during the follow-up period in 144 patients. The cumulative probability of a grade 3 or 4 adverse event over a 30-month period was 7.7% among patients assigned to deferred-ART *vs.* 7.1% for those in the early-ART group. The cumulative probability of a grade 3 or 4 event among patients assigned to no-IPT was 8.2% *vs.* 6.6% among those in the IPT group. The risk of grade 3 or 4 adverse events during the			

Immediate-ART *Vs.* Deferred-ART									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						first 6 months of the study was 2.6 times as high among patients assigned to early ART as for those in the deferred ART (Adjusted hazard ratio 2.57; 95% CI, 1.47 to 4.51) and 2.1 times as low among patients assigned to early ART as among patients assigned to deferred ART thereafter (Adjusted hazard ratio 0.48; 95% CI, 0.30 to 0.76). The 30-month probability of grade 3 or 4 adverse events did not significantly differ among the groups.			
					Hematologic	26 events in the immediate-ART *vs.* 45 in deferred-ART			
					Liver related	10 events in the immediate-ART *vs.* 15 in deferred-ART			
					Renal	1 event in the immediate-ART *vs.* 12 in deferred-ART			
					Digestive	17 events in the immediate-ART *vs.* 2 in deferred-ART			
					Neurologic	13 events in the immediate-ART *vs.5* in deferred-ART			
					Cardiovascular	3 events in the immediate-ART *vs.* 6 in deferred-ART			
					Cutaneous	3 events in the immediate-ART *vs.* 1 in deferred-ART			
					Other	2 events in the immediate-ART *vs.* 4 in deferred-ART			
					Adherence to treatment:	Assessed using the medication possession ratio; patients who were assigned to the deferred ART groups had their follow-up time extended to achieve 30 months of treatment follow-			

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<table>
<tr><td colspan="10" align="center">Immediate-ART Vs. Deferred-ART</td></tr>
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<th>Study reference</th>
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<tr>
<td>Jean et al., 2014a</td>
<td>Face to face socio-behavioural questionnaire nested on the TEMPRANO RCT</td>
<td>957 (81.7%) of 1172 Heterosexual individuals recruited by TEMPRANO from 1 January 2009 to 1 September 2011 who completed a face to face questionnaire. Median baseline CD4 478 cells/mm^3. 80.4% were female.</td>
<td>Early and deferred ART for TEMPRANO. Sexual behaviours face to face questionnaire within 9 to 15 months of enrolment to the TEMPRANO RCT</td>
<td>Risk compensating behaviour</td>
<td>Reported unprotected sexual intercourse with an HIV negative partner or a partner of unknown status during 12 months period</td>
<td>No significant differences were seen in the proportion of sexually active individuals in the past year (71.7% in the deferred-ART and 69.8% in the early-ART groups, P=0.51), those reporting multiple partnerships (6.2% and 9.0% respectively, P=0.11) or those not cohabiting with their last sex partner (41.8% and 41.2% respectively, P=0.87). The last sex partner was reported to be uninfected by 26.6% of those in the deferred-ART and 22.8% in the early-ART groups (P=0.47) or of unknown status by 43.9% and 47.7% respectively (P=0.47).
46% participants reported sexual activity in the past month; involving non-cohabiting partners in 41.5% of them. The proportion of subjects who reported risky sex in the previous month was 10.0% in the early-ART vs. 12.8% in the deferred-ART group (P=0.54)
(P =0.17).</td>
<td>8/10</td>
<td>Indirect</td>
<td>Study based on reported risky sexual activity during the past year and in particular during the past month collected on a face to face questionnaire. 81.7% of those recruited by the TEMPRANO study between January 2008 and September 2011 completed the questionnaire and over 80% were female (no differences in the two groups). More than half were not in a cohabiting relationship, and about two-thirds of those who were sexually active reported that their last partner was HIV negative or had an unknown HIV status.
The results should be interpreted with caution, participants in the TEMPRANO trial had a high frequency of contacts with health care professionals and this study only assessed behaviours in the first year of treatment which may explain the comparability of reported sexual activity and risky behaviour in the two groups. This study was nested on the TEMPRANO trial and over 80% of this subsample was female; the results rely on self-reported sexual behaviours which are potentially subject to social desirability bias and over-reporting of condom use could lead to an underestimation of HIV transmission risks.</td>
</tr>
<tr>
<td>Jean et al., 2014b</td>
<td>Face to face socio-behavioural study nested on the</td>
<td>1,952 heterosexual individuals recruited by TEMPRANO from March 2008 to July 2012 (977</td>
<td>Early and deferred ART for TEMPRANO. Sexual behaviours face to face</td>
<td>Risk compensating behaviour</td>
<td>Frequency of sexual activity, risky behaviours defined as unprotected sexual intercourse with</td>
<td>The frequency of sexual activity decreased from 79.9% at M0 to 72.6% at M24 in the early-ART group and from 75.9% to 69.8% in the deferred-ART group; the frequency of multiple</td>
<td>8/10</td>
<td>Indirect</td>
<td>The majority of participants in this study were female and the study relies on self-reported sexual behaviours. Even though interviewers were trained to administer questionnaires in a non-judgmental way and interviews were conducted confidentially in private rooms, risky behaviours may have been under-</td>
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	**Immediate-ART *Vs.* Deferred-ART**
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
	TEMPRANO RCT.	deferred-ART and 975 early-ART) followed during a mean time of 25.7 months who completed a face to face questionnaire 3,364 completed questionnaires (1,653 deferred-ART and 1,711 early-ART). Median age 35 years, 79% female, median baseline CD4 469 cells/mm^3.	questionnaire completed at recruitment (month 0, M0), at the start of ART (Treatment Initiation, TI) and at 12+3 and 24+6 months after TI (TI$_{+12}$ and TI$_{+24}$).			partners decreased from 14.4% to 8.7% in the early-ART and from 12.8% to 7.6% in the deferred-ART group. The frequency of unprotected sex decreased from 40.7% at M0 to 27.3% at M24 in the early-ART and from 38.1% to 23.9% in the deferred-ART group. The frequency of risky sex decreased from 26.8% at M0 to 17.3% at M24 in the early-ART and from 28.4% at M0 to 15.5% at M24 in the deferred-ART group. In patients in the deferred-ART group (802 participants with at least one socio-behavioural questionnaire), 492 initiated ART, the frequency of sexual activity did not changed significantly between M0 and TI; the frequencies of multiple partners, unprotected sex and risky sex significantly decreased between M0 and treatment initiation (multiple partners: Odds Ratio (OR)TI *vs.* M0 0.41, 95%CI 0.26 to 0.64; unprotected sex: OR TI *vs.* M0 0.65, 95%CI 0.49 to 0.85; risky sex: OR TI *vs.* M0 0.62, 95%CI 0.45 to 0.84). Subsequently, the frequencies of these three indicators did not significantly change over time within the 24 months following treatment initiation (each p=0.15).			reported due to social desirability.

8. Grade of evidence table

Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
Primary endpoint: composite end point, time to any serious AIDS-related or serious Non-AIDS related event or death from any cause.	Lundgren et al., 2015.	10/10	Direct	A	Data from the START trial found a significant reduction in the risk of experimenting a composite end point event of 57% in the ITT analysis (Lundgren et al, 2105) or of 66% when using the as per protocol analysis (Lodi et al, 2016). The event rates (absolute risk) for the primary end-point in the immediate and the deferred-ART groups were 0.6 and 1.38 per 100 person years (respectively) and the numbers needed to treat (NTT) to prevent one end point event was 128 (Molina et al., 2016). These studies involved one of the largest international cohorts in HIV research; the cohort is diverse and well represented; 46% of participants were from high income countries, approximately 33% from Europe, 11% from the US and 2% from Australia. Similar benefit was also identified in the Temprano trial with a 44% risk reduction (The TEMPRANO ANRS 12136 Study Group., 2015).
	Lodi et al., 2016	8/10	Direct		
	The temprano anrs 12136 study group., 2015	10/10	Indirect		
Cardiovascular disease	Lundgren et al., 2015.	10/10	Direct	B	In the START study participants randomised to the immediate-ART group showed a 26% risk reduction for cardiovascular disease, 50% risk reduction for non-AIDS defining cancers and a 71% risk reduction for TB. These results are based on a large randomised control multicentre study. The changes in the protocol after the interim analysis resulted in up to 30% of individuals in the deferred-ART group starting ART early and could have potentially underestimated the net benefit of early ART.
Malignancies: Non-AIDS-defining cancer	Lundgren et al., 2015.	10/10	Direct	A	In the START study, a large multicentre randomised control trial, immediate-ART initiation reduced the risk of all malignancies by 72% (Borges et al., 2016), participants randomised to the immediate-ART group showed a 50% risk reduction for non-AIDS defining cancers (LUNDGREN et al., 2015). Immediate ART initiation resulted in a risk reduction of infection-related cancer by 74% and infection-unrelated cancer by 51% (Borges et al., 2016). Adjustment for potential mediators, such as HIV RNA, appeared to attenuate HRs of immediate/deferred ART for infection-unrelated cancer more than infection-related cancer. These results are based on a large multicentre RCT. The changes in the protocol after the interim analysis resulted in up to 30% of individuals in the deferred-ART group starting ART early and could have potentially underestimated the net benefit of early ART.
All malignancies	Borges et al., 2016	8/10	Direct		
Infection-related cancers	Borges et al., 2016	8/10	Direct		
Infection-unrelated cancers	Borges et al., 2016	8/10	Direct		
Tuberculosis	Lundgren et al., 2015.	10/10	Direct	A	In the START study participants randomised to the immediate-ART group showed a 71% risk reduction for TB. These results are based on a large multicentre randomised control study.
	The temprano anrs 12136 Study Group., 2015	10/10	Indirect		

Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
Secondary endpoint: Any serious AIDS-related events (including death from AIDS);	LUNDGREN et al., 2015.	10/10	Direct	A	The START study showed a clear benefit of immediate-ART initiation in reducing the risk of serious AIDS-related events with a risk reduction of 72%. These results are based on a large multicentre randomised control study.
	The temprano anrs 12136 study group., 2015	10/10	Indirect		
Any serious non–AIDS-related events, death from any cause	Lundgren et al., 2015.	10/10	Direct	A	The START trial demonstrated a beneficial effect of immediate-ART initiation in reducing the risk of serious non-AIDS related events by 39% and of death from any cause by 42%. The number of observed events was lower than expected for both study arms; this in addition to the changes in the study protocol could have resulted in an underestimation of the beneficial effect of early ART initiation. These results are based on a large multicentre RCT.
	Lodi et al., 2016	8/10	Direct		
	The temprano anrs 12136 Study Group., 2015	10/10	Indirect		
Virologic suppression	Lundgren et al., 2015.	10/10	Direct	A	The percentage of patients who had an undetectable HIV-VL in the START study mirrored the percentage of patients receiving ART. The proportion of patients achieving full viral suppression 12 months after initiating ART was similar in both groups (98% *vs.* 97%).These results are based on a large multicentre randomised control study.
	The temprano anrs 12136 Study Group., 2015	10/10	Indirect		
CD4 count as average or mean	Lundgren et al., 2015.	10/10	Direct	A	Both the START and the TEMPRANO studies independently showed that early-ART initiation results in an increasing trend in the CD4 count that was more pronounced in the first year of ART treatment and continued to increase gradually thereafter. Similarly, the average CD4 count of individuals in the deferred-ART groups in both studies decreased during the first year of the study and then stabilised and subsequently increased as more individuals in these groups started ART. This is strong evidence of the effect of ARV treatment in restoring the CD4/CD8 balance and reconstituting the immune system. These results are based on two large multicentre randomised control studies.
	The temprano anrs 12136 Study Group., 2015	10/10	Indirect		
Safety: Adverse events grade 3 or 4	Lundgren et al., 2015.	10/10	Direct	A	The START trail showed non-significant differences in severe grade 4 events between the immediate-ART and the deferred-ART groups [HR 1.01 (95%CI, 0.73 to 1.39; P=0.97)]. The reduced follow-up time in the START study could have resulted in underestimation of the risk of side effects. Subsequent analysis of individuals receiving efavirenz in the START immediate initiation group showed an increased risk of suicidal ideation in individuals with previous psychiatric history [HR=12.8, (95%CI 4.7 to 34.9; P<0.001)] or heavy alcohol use [HR=6.1, (95%CI 1.9 to 19.6; P=0.003)] (Arenas-Pinto et al, 2016).
	The temprano anrs 12136 Study Group., 2015	10/10	Indirect		
Risk compensating behaviours	Jean et al., 2014b	8/10	Indirect	B	This study showed no evidence of risk compensation behaviours in the early-ART initiation group; both arms of the study showed a reduction in high risk sexual behaviours that was more pronounced during the first year of the study. This study is based on implementation of a sexual behaviours face to face questionnaire in a subsample form the TEMPRANO cohort; the majority of participants were female and risky behaviours may have been under-reported due to social desirability and the face to face nature of the data collection tool.

9. Literature Search Terms

9.1. Search terms

The following search terms were used in the evidence search: HIV; HIV Infections/drug therapy*; HIV Infection/mortality; HIV Infection/morbidity; HIV Infection/virology; CD4 count; CD4 Lymphocyte Count; Viral load; HIV-1 antibody positive

Antiretroviral treatment; ART; ARV treatment; ARV therapy; Highly Active* ; immediate clinical HIV management; Antiretroviral agents

Treatment outcome; mortality; AIDS-defining events; non-AIDS related events; survival analysis, effect modification

9.2. Search Strategy

P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Adult patients with confirmed HIV-1 infection; all persons living with HIV; HIV positive persons; Asymptomatic HIV positive persons; PLWHIV; HIV-1 antibody positive persons.
I – Intervention Which intervention, treatment or approach should be used?	Immediate initiation of ART at any CD4 count; immediate ART, Early ART
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	CD4 related ART initiation (initiation of ART when CD4 count approaching or below 350 cells/mm^3); observation; deferred ART
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission	*Critical to decision-making:* *AIDS related morbidity; Serious non-AIDS related morbidity; Death; Serious adverse events* *Important to decision-making:* *Viral load (HIV-VL); CD4 count; HIV drug resistance; ART related side effects; Adverse events; Cost-effectiveness*

9.3 Assumptions / limits applied to search

Inclusion Criteria	Articles published in peer reviewed journals; Language: English; Publication type: randomised control trial (RCTs); multicentre studies; systematic reviews; meta-analyses; Time frame: articles published from 2006 up until search date (August 2016)
Exclusion Criteria	Non-human studies; case series; case reports; conference abstracts*; publications older than 10 years.

* Several recent conferences abstracts were included in the discussion of the relevant section but were excluded from the evidence tables.

10. Literature search strategy

To be added

11. Evidence selection

- Total number of publications reviewed: 143 reviewed citations

- Total number of publications considered relevant: 18

- Total number of publications selected for inclusion in this briefing: 11

12. References

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