Clinical Commissioning Policy Proposition: Immediate Antiretroviral therapy for treatment of HIV-1 in adults and adolescents.

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Contents

1. Executive Summary

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain Language Summary

About immediate antiretroviral therapy

Treating HIV with anti-retroviral therapy (ART) has transformed the outlook for people living with HIV. ART allows most people with HIV to live their life - with a normal life expectancy. Untreated HIV infection leads to progressive damage to the body's immune system. Current HIV clinical commissioning policy allows ART to be started after a certain level of damage to the immune system has occurred (measured as CD4 count <350 cells/mm^3) or earlier when there is risk of onward HIV transmission. Immediate ART is about starting treatment soon after diagnosis of HIV, irrespective of how much damage to the body's immune system has occurred (at any CD4 count).

About current treatments

Under current HIV clinical commissioning policy, starting treatment in a HIV positive person is either determined by the degree of damage to the body's immune system (CD4 count <350 cells/mm^3), by the individual being symptomatic or having other complicating factors or by the risk of transmission of HIV to another individual.

About the new treatment

Immediate ART recommends all HIV positive people start treatment regardless of the degree of damage to the body's immune system or the risk of transmission of HIV to another individual.

What we have decided

NHS England has carefully reviewed the evidence to treat HIV-1 positive adults and adolescents with immediate antiretroviral therapy. We have concluded that there is enough evidence to recommend making the treatment available at the point of diagnosis.

2. Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission Immediate Antiretroviral Therapy.

This document also describes the proposed criteria for commissioning, proposed governance arrangements and proposed funding mechanisms.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether Immediate Antiretroviral Therapy will be routinely commissioned is planned to be made by NHS England following a recommendation from the Clinical Priorities Advisory Group.

3. Proposed Intervention and Clinical Indication

HIV treatment (antiretroviral therapy or ART) has transformed the outlook for people living with HIV from that of a significantly shortened lifespan to a manageable long term chronic condition. Without treatment, HIV causes progressive damage to the immune system that ultimately results in serious ill health and death. ART prevents damage to the immune system through suppression of the HIV virus and reduces the risk of a wide range of serious complications which are more frequent in untreated, HIV-infected individuals.

Damage to the immune system is measured by determining the CD4 count in blood.

The current commissioning policy for initiating antiretroviral therapy in patients with HIV-1, as outlined in the NHS England HIV service specification, reflects the 2012 BHIVA treatment guidelines (Williams et al., 2012) that recommend patients start ART when their CD4 count has fallen to 350 cells/mm^3 or below or when they develop symptoms.

In August 2015 the results of a large randomised control trial established the clinical benefit of starting ART immediately at higher CD4 counts above 500 cell/mm^3 compared to deferred initiation of ART until the CD4 count was 350 cell/mm^3 (Lundgren et al., 2015; The TEMPRANO ANRS12136 Study Group., 2015; Danel et

al., 2015). Immediate ART significantly 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.

As a consequence of these data the British HIV Association (BHIVA) together with other international guidelines including the World Health Organisation and European Clinical AIDS Society, recommended that all HIV -1 positive patients start ART irrespective of CD4 count (Waters et al., 2015).

Treatment outcomes for HIV positive patients in the UK are very good. As of December 2015, 96% of people with HIV accessing care in the UK were receiving ART and of those on ART, 94% were virally suppressed (Kirwan et al., 2016).

In July 2015 NHS England published a clinical commissioning policy for Treatment as Prevention (TasP) (NHS England, 2015) allowing patients at risk of transmitting HIV to start ART at any CD4 count irrespective of any potential for clinical benefit to the individual taking the therapy; TasP is designed to benefit the seronegative partner by reducing the risk of acquisition of HIV. Recent clinical studies have demonstrated significant benefit to individual patients from starting ART immediately, irrespective of the degree of damage to the immune system as measured by the CD4 cell count (Lundgren et al., 2015; The TEMPRANO ANRS12136 Study Group., 2015; Danel et al., 2015).

This policy proposes that all HIV-1 positive patients are recommended to start ART, irrespective of their CD4 cell count and risk of onward HIV-1 transmission.

4. Definitions

The key terms used in this policy and their definitions are:

Antiretroviral therapy (ART): This usually consists of a combination of 3 antiretroviral drugs. A backbone of 2 nucleoside reverse transcriptase inhibitors (NRTI) and a 3rd agent from one of the following classes of drugs: non-nucleoside reverse transcriptase inhibitors (NNRTI), ritonavir or cobicistat boosted protease inhibitors (PI/r) and integrase inhibitors (INI).

Viral load: HIV Ribonucleic acid (RNA) levels in plasma are used to monitor response to ART. Patients on effective therapy sustain viral load <50 copies/ml (undetectable).

CD4 count: A measure of the strength of a person's immune system which is impacted negatively by HIV infection. A low CD4 count indicates that the patient is at risk of opportunistic infections and illness.

Immediate Antiretroviral Therapy: Refers to starting antiretroviral therapy soon after diagnosis irrespective of CD4 count as compared to deferring till the CD4 count has fallen.

Treatment as Prevention (TasP): Describes the use of ART for people with diagnosed HIV with the aim of preventing onward HIV transmission to others rather than primarily for their own clinical benefit.

5. Aims and Objectives

This policy aims to reduce the risk of HIV clinical disease progression and other co-morbidities in HIV positive patients by the initiation of ART irrespective of CD4 count and at the same time to allow access to ART treatment to those not currently covered by the ART initiation criteria included in the existing NHS England HIV clinical commissioning policy.

The objective is to provide equitable access to antiretroviral therapy for all patients diagnosed with HIV infection which will result in improved clinical benefit and wellbeing for HIV positive people, at the same time as reducing the risk of transmission from infected to uninfected people as detailed in the Treatment as Prevention policy.

6. Epidemiology and Needs Assessment

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 in 2015, 101,200 people (95% credible interval (CrI) 97,500-105,700) were living with HIV in the UK; of those, 13,500 (95% CrI 10,200-17,800), or 13% (95% CrI 10-17%) were unaware of their infection and at

risk of passing on the virus to others. The majority, 69% (69,500; 95% CrI 66,300-73,700), were men and 31% (31,600; 95% CrI 30,600-32,800) were women (Kirwan et al., 2016). The HIV prevalence in the UK is estimated to be 1.6 per 1,000 population, or 0.16%. Approximately 6,000 patients are newly diagnosed with HIV each year in the UK. In 2015, 5,512 people were newly diagnosed with HIV in England (Kirwan et al., 2016).

Diagnosed population in care and on treatment

In 2015, 88,769 people were living with diagnosed HIV and accessed HIV care in the UK, of whom 81,062 accessed care in England (Kirwan et al., 2016). This represents a 73% increase on the number reported a decade ago (51,449 in 2006) and an increase of 4% over the preceding year. This rise is due to effective treatment, with few HIV-related deaths, as well as people newly diagnosed with HIV accessing care for the first time in 2015.

In 2015, 96% (83,931/87,813) of people with HIV accessing care in the UK were receiving ART. This is a rise from 90% in 2014 and is likely to reflect 2015 HIV treatment guidelines (Waters et al, 2016) and NHS England Treatment as Prevention clinical commissioning policy (NHS England, 2015) which recommend that all people living with HIV are offered treatment to prevent onward transmission. Treatment outcomes in the UK are very good. In 2015, 94% of all those receiving ART were virally suppressed (viral load, < 200 copies/ml) and compare favourably to the UNAIDS 90:90:90 Target (Kirwan et al., 2016).

Newly diagnosed with HIV per year

The number of people newly diagnosed with HIV in the UK has remained stable in recent years; in 2015, 6,095 people were newly diagnosed with HIV in the UK, of whom 5,512 were diagnosed in England (Kirwan et al., 2016). In 2015, 39% (2,350/6,028) of those diagnosed presented with a CD4 count <350 cell/mm^3 and would be eligible to start ART under the current clinical commissioning policy. Of the remaining 61% a high proportion would meet the criteria for starting ART as Treatment as Prevention.

Potential cohort for immediate ART

In 2015, 3,367 people accessing care for HIV in England were not receiving ART (4% of the total attending for care) of whom 398 had a CD4 count below <350 cell/mm^3 and would thus meet the current clinical commissioning policy criteria for starting ART for their own clinical benefit. Of the remaining 2,969, although a small proportion would meet other clinical criteria for starting ART, the majority are likely to be considered and be eligible under the TasP NHS England clinical commissioning policy. Of the almost 7,000 patients who started ART for the first time in 2015, 66% had a CD4 count above 350 cell/mm^3 and 41% above 500 cell/mm^3. However, patients who wish to start ART but do not fulfil the current ART initiation criteria included in the existing NHS England HIV service specification or the TasP requirements, currently suffer a health care inequity as they are unable to access ART which would be of proven benefit to them. Implementation of an immediate ART policy would simply bring forward the date for starting ART for these relatively small proportion of HIV-1 infected individuals, who would otherwise be eligible to start ART at a later stage in their illness under the current clinical commissioning policy. This policy will not result in a year on year increase in the number of people starting ART. After implementation of this policy, the number of people starting ART each year will be dependent on the number of newly diagnosed individuals per year, the underlying incidence of HIV transmission, which would be expected to decline with an immediate ART policy.

Clinical Impact of ART

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. HIV infection is also associated with an increased risk of serious non-AIDS related morbidity including cardiovascular, renal, and liver diseases and non-AIDS-defining cancers and these are more frequent in HIV infected adults at early stages of immunosuppression than in the general population (El-Sadr., 2006).

Antiretroviral (ARV) drugs prevent and reverse damage to the immune system through suppression of the HIV virus and reduce the risk of all-cause morbidity and

mortality substantially. The best health outcomes are achieved in those who start therapy early. 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 early and who have access to lifelong ART is equivalent to that of people who do not have HIV (Samji et al., 2013).

7. Evidence Base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of immediate ART initiation for the treatment of adults and adolescents with HIV-1 infection.

Randomised control Trials (RCT)

Data from two large independent multicentre RCT (Lundgren et al., 2015; The TEMPRANO ANRS12136 Study Group., 2015; Danel et al., 2015) 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 deferring ART initiation until after the CD4 count had declined to 350 cells/mm^3 or after they had developed AIDS or AIDS related conditions.

Strategic Timing of ART (START) Trial

The START trial (Lundgren et al., 2015), a large international multi-continental, 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 total follow up time of 14,060 person years and 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 (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. The reduction in the follow up time is likely to underestimate the benefits of immediate-ART initiation; for instance, a 42% risk reduction for death from any cause was reported in the immediate *vs*. the deferred-ART initiation groups, but this did not reached statistical significance. Lodi et al., conducted a per-protocol analysis using a mathematical model (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.

The risk of grade 4 drug-related adverse events was similar in both groups (Lundgren et al., 2015). The association between the use of efavirenz and increased risk of suicidal behaviour have already been documented; a sub-analysis of drug related suicidal behaviour 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 or heavy alcohol use. 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; this is already standard

practice in HIV services in England.

TEMPRANO Trial

The TEMPRANO study (The TEMPRANO ANRS12136 Study Group., 2015; Danel et al., 2015), 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, i.e. CD4 counts between 250-350 cells/mm^3 and WHO clinical stage 1, or CD4 counts of 351-500 cell/mm^3 and symptomatic - WHO clinical stages 1, 2 or 3) 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. 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 (The TEMPRANO ANRS 12136 Study group, 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.

Conclusion

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 or below 350 cells/mm^3. Antiretroviral therapy should be recommended to be started in all individuals with HIV infection regardless of CD4 cell count.

8. Proposed Criteria for Commissioning

Immediate ART will be routinely commissioned for the treatment of all HIV-1 infected adults and adolescents.

Initiation of ART in paediatric patients is linked to a number of factors including age, comorbidities and symptoms. Paediatric HIV services are commissioned to work to WHO Guidance and PENTA Guidelines, which state that ART should be initiated in all children living with HIV, regardless of clinical stage or CD4 count. As such, paediatric patients are excluded from this policy.

All adult or adolescent patients with known or newly diagnosed HIV infection attending for care should be recommended to start ART irrespective of CD4 count or risk of onward transmission of HIV.

The timing of ART initiation should also consider the willingness and ability of individual patients to start and continue ART.

9. Proposed Patient Pathway

Commissioned HIV care and treatment providers who meet the service specification initiate and monitor HIV drug treatment. Following approval of this policy, the recommendation to start ART would be available to all HIV-1 positive adults and adolescents regardless of CD4 counts.

10. Proposed Governance Arrangements

The initiation and management of ART is already routinely carried out in all clinical centres commissioned to provide HIV treatment services. Choice of ART regimen is informed by NHS England clinical commissioning policies, regional prescribing guidance and national best practice guidelines which are subject to regular review.

11. Proposed Mechanism for Funding

NHS England is responsible for the commissioning of all antiretroviral medicines for all indications. Funding to the provider will be in accordance with their agreed tariff arrangements.

12. Proposed Audit Requirements

The HIV and AIDS Reporting System (HARS) within Public Health England is the national surveillance system to monitor the HIV epidemic in the UK. Through collection of comprehensive data, PHE is able to monitor coverage of HIV treatment over time and by risk group, and describe changing HIV treatment patterns by CD4 count at ART initiation.

13. Documents that have informed this Policy Proposition

B06/S/a Specialised Human Immunodeficiency Virus (HIV) Services (Adult) – service specification.

B06/S/b Specialised Human Immunodeficiency Virus (HIV) Services (Children) – service specification.

British HIV Association Guidelines for the treatment of HIV-1 positive adults with Antiretroviral Therapy 2015 (updated 2016).

14. Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned.

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