CPAG Summary Report for Clinical Panel – Immediate Antiretroviral therapy for treatment of HIV 1 in adults and adolescents

The Benefits of the Proposition			
No	*Metric*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	There is a survival benefit [B]	There is evidence that anti-retroviral treatment (ART) increases survival in people with Human Immunodeficiency Virus (HIV). Most people with HIV receiving ART can live their lives with a normal life expectancy. The Strategic Timing of Anti-Retroviral Treatment (START) study (Lundgren et al., 2015) demonstrated that people with HIV receiving immediate-ART had a significant 57% reduction in the risk of all cause morbidity and mortality when compared to people with HIV deferring ART until their CD4 (cluster of differentiation 4; the CD4 count is a measure of the compromise of the immune system) count dropped to 350 cells/mm^3 or they became symptomatic (deferred-ART). The START study is one of the largest multi-centre, multi-continental randomised controlled trials in HIV research, involving over 4,600 patients with a total follow up of 14,060 person years. Patients involved in the study were diverse, 46% were from high income countries and nearly a third from Europe (Lundgren et al., 2015). The study was stopped early because the interim analysis demonstrated that

			immediate-ART was beneficial and the research board recommended offering ART to all patients enrolled in the study. The early termination of the study could have reduced the potential of the study to identify differences in the immediate-ART and the deferred-ART groups, for example the study showed a 42% reduction in the risk of death from all causes in the immediate-ART group, but was not statistically significant (change not supported by statistical methods, therefore the results could be attributable to chance). The reduced follow-up time of the START study could have underestimated the beneficial effect of immediate-ART.
2.	Progression free survival	There is a survival benefit [A]	ART also decreases the risk of progression to acquired immune deficiency syndrome (AIDS**)**. Immediate ART significantly reduced the risk of serious AIDS-related morbidity and mortality by 72% when compared with deferred-ART; this was also demonstrated by the START study (Lundgren et al., 2015).
3.	Mobility	Not measured	Not relevant for this intervention
4.	Self-care	Not measured	Not relevant for this intervention
5.	Usual activities	Not measured	Not relevant for this intervention
6.	Pain	Not measured	Not relevant for this intervention
7.	Anxiety / Depression	Not measured	
8.	Replacement of more toxic treatment	Not measured	Not applicable
9.	Dependency on care giver / supporting independence	Not measured	Not relevant for this intervention

10.	Safety	Advserse events identified [A]	Side effects were graded as grades 1, 2, 3, and 4 where they are defined as follows - grade 1 is mild, grade 2 is moderate, grade 3 is severe and grade 4 is potentially life threatening. The number of grade 4 adverse events recorded in both the immediate-ART and the deferred-ART groups in the START study was the same (73 adverse events in each group) and there was no evidence of increased risk in the immediate-ART group (Lundgren et al., 2015). The use of efavirenz in individuals with previous history of depression, psychiatric illness or alcohol use have been associated with an increased risk of suicide; subsequent analysis of data from the START study focussing on individuals receiving efavirenz showed a small but significant risk of suicidal ideation in individuals with previous psychiatric history or heavy alcohol use (Arenas-Pinto et al., 2016). This association is well documented and clinicians are recommended to screen for pre-existing depression (or other psychiatric conditions) before efavirenz initiation. This is already standard practice when prescribing ART regimens including efavirenz.
11.	Delivery of intervention	Not measured	

Other health metrics determined by the evidence review			
No	Metric	Grade of evidence	Summary from evidence review
1	Serious non-	A	The START trial demonstrated a

	AIDS related events		statistically significant (result supported when statistical methods were applied) beneficial effect of immediate-ART initiation in reducing the risk of serious non-AIDS related events by 39%; this was mainly due to a reduction in the number of non-AIDS defining cancers in the immediate-ART group. 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 immediate ART initiation (Lundgren et al, 2105).
2	Serious bacterial infections	A	The START study showed a statistically significant reduction in the risk of developing serious bacterial infections including bacterial pneumonia and tuberculosis in the immediate-ART group and that this is mediated by the beneficial effect of ART on increasing CD4 cell counts (O'Connor et al., 2017)
3	Virologic suppression	A	The START study demonstrated that the proportion of patients who had an undetectable viral load mirrored those patients receiving ART; 98% of patients in the immediate-ART group achieve full viral suppression 12 months after initiating ART (Lundgren et al, 2105). This has clinical relevance for individual patients but it is also important as it reduces onward transmission of HIV.
4	CD4 count	A	The CD4 count is a measure of the compromise of the immune system. The START study showed that immediate-ART initiation resulted in an increasing trend in CD4 count that was more pronounced during the first year of treatment (Lundgren et al, 2105).