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Abstract

Background: World Health Organization (WHO) antiretroviral therapy (ART) guidelines are regularly updated with the most current evidence on when to initiate ART.

Methods: We performed a systematic review and meta-analysis and identified published literature and conference abstracts for randomised controlled trials (RCT) and cohort studies that compared HIV-infected patients starting ART at \geq 500 CD4 cells/µL with those with <500 CD4 cells/µL.

Results: We identified 24 articles. Studies found a decreased hazard of HIV disease progression with initiation at >500 CD4 cells/ μ L (2 RCTs: relative risk [RR]=0.38, 95% CI 0.20-0.74; 1 cohort: hazard ratio [HR]=0.20, 95% CI 0.10-0.42). One RCT found a reduced risk of HIV transmission (RR=0.11, 95% CI 0.06-0.19), although this was not supported in two cohorts (RR=1.17, 95% CI 0.46-2.98). There was no increased risk of most Grade 3/4 adverse events identified in RCTs, but there was evidence of increased risk of laboratory adverse events for earlier initiation (RR=1.43; 95% CI 1.13-1.81) from one cohort study.

Conclusion: We found moderate quality evidence that the ART initiation at $CD4 \ge 500$ cells/ μ L leads to reduced risk of disease progression. The risk of adverse events for early initiators is not yet well understood and needs further investigation

Keywords: HIV, antiretroviral therapy, practice guidelines, World Health Organization

1. INTRODUCTION

As a result of antiretroviral therapy's (ART) clinical benefit in individuals infected with HIV-1 and its impact on the risk of HIV transmission, several HIV treatment guidelines committees have recommended initiating ART at earlier stages of HIV infection and at higher CD4 cell counts [1,2]. As early as 2014, the International Antiviral Society - USA [1] and the United States Department of Health and Human Services [3] recommend starting ART as close to diagnosis as possible without regard to clinical symptoms or degree of immune dysfunction. In contrast the World Health Organization's (WHO) guidelines did not recommend starting all patients on HIV regardless of clinical signs and symptoms or CD4 cell level prior to September 2015 and restricted starting therapy to patients with fewer than 500 CD4 cells/ μ L or those with concurrent tuberculosis, advanced HIV disease (stage 3 or 4), pregnancy, age <5 years, concurrent hepatitis B virus infection with severe liver disease or an HIV-infected person in a serodiscordant partnership [2,4,5]. The European AIDS Clinical Society and British HIV Association's guidelines did not broaden to recommend treating all patients until 2015 [6].

Previously, the available literature was reviewed to assess the impact of early versus delayed treatment and found evidence that early ART initiation (baseline CD4 count between 350 and 500 cells/ μ l) was associated with a reduction in the risk of HIV progression or death, a reduction in risk of a non-AIDS defining illness and increased likelihood of immunologic recovery [7], but an increased risk of grade 3 or 4 laboratory abnormalities [7]. This current

review updates this earlier review and reevaluates the clinical and public health impact of earlier initiation of ART in HIV-1-infected patients using a higher threshold for treatment initiation (CD4 \geq 500 cells/µl). These results were used to inform the 2016 WHO guidelines for use of antiretroviral drugs for the treatment and prevention of HIV infection.

2. MATERIALS AND METHODS

2.1. Search Strategy

We used Cochrane Collaboration methods to conduct a comprehensive and exhaustive search strategy [8]. We searched PubMed, CENTRAL, SCOPUS (including EMBASE 1996-present), Web of Science, and WHO's Global Index Medi cus using Medical Subject Heading (MeSH) terms and a range of relevant keywords. The search period ranged from 1 January 1996 to 1 October 2016. The search strategy was iterative, in that references of included studies were searc hed for additional references. All languages were included. Additionally, we searched for potentially relevant abstracts from key scientific conferences (the Conference on Retroviruses and Opportunistic Infections, the International AIDS Conference, and International AIDS Soci ety Conference on HIV Pathogenesis, Treatment and Prevention) within the search period.

2.2. Study Selection

2.2.1. Inclusion Criteria

We included randomised controlled trials (RCT) with randomisation at either the individual or cluster level, non-randomised trials with allocation at either the individual or cluster level and prospective cohort studies. Studies estima ting impact on clinical outcomes needed to have compared patients with HIV-infection and no other clinical indications for early ART plus CD4counts \geq 500 cells/µL at the time of initia tion with patients whose CD4 cell counts were <500 cells/µL at the time of initiation.

2.2.2. Exclusion criteria

We excluded single arm pre-post studies without distinct controls, case-control studies, cross-sectional studies and case series.

2.3. Data Extraction and Management

We imported search results into bibliographic citation management software (EndNote X4, Thomson Reuters, New York, New York USA) and excluded duplicate references. Reviewing only article titles, one author (HH) excluded all references that were clearly irrelevant. Two authors (GWR and AA), working independently, reviewed titles, abstracts and descriptor terms of the remaining citations to identify potentially eligible reports. We obtained full text articles for all references identified as potent ially meeting inclusion criteria. GWR and AA reviewed these full text articles and applied inclusion criteria to establish each study's eligibility or ineligibility. Where information was incomplete, we contacted authors for additional data. After identifying trials for inclusion, GWR and AA extracted data from each study independently and entered these data into standardised data extraction forms and then compared extract ed data. There were no disagreements.

2.4. Assessment of Methodological Quality

We used the Cochrane Collaboration tool for assessing risk of bias in the included RCTs [8]. The Cochrane tool assesses risk of bias in individual studies in six domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other potential biases. We used the Newcastle-Ottawa Scale to assess quality and risk of bias in the non-RCTs and observational studies [9]. This scale judges three general areas: selection of study groups, comparability of groups, and in the case of cohort studies ascertainment of outcomes.

2.5. Statistical Analysis and Data Synthesis

We used published relative risks (RR) if provided in study reports and, when necessary, calculated RRs for dichotomous outcomes and the 95% confidence interval (CI). We pooled data across studies and estimated summary effect sizes using Review Manager 5.2 (Cochrane Collaboration, London, UK). Due to anticipated heterogeneity between study designs and populations, we modeled meta-analyses using a DerSimonian-Laird random-effects model. We present estimates of heterogeneity as I^2 ; which is the percentage of variability in effect estimates due to heterogeneity rather than to chance.

2.6. Sensitivity Analysis

The observational literature for two major outcomes, mortality and mortality or clinical progression, included a number of studies that reported data from the same cohorts. To minimise the problem of duplication of patients, we conducted a sensitivity analysis of studies with no or minimal overlap between cohorts.

2.7. Assessment of Evidence Quality

We assessed the quality of evidence from the literature for each outcome using Grades of Recommendation Assessment, Development and Evaluation (GRADE) (Supplemental Table 1) [10]. GRADE ranks the quality of evidence on four levels: high, moderate, low and very low. Data from randomised trials are considered **3. RESULTS**

We identified 3366 unique reports and excluded 3087 (91.7%) based on titles and abstracts. Of the remaining 279 reports, 24 (8.6%) studies met inclusion criteria, 10 from our previous review and 14 new ones. Six reports were from three RCTs [11–16]: these included TEMPRANO [11-13], START [14-15] and ANRS 12249 TasP[16]. In two of these trials, START and ANRS 12249 TasP, patients randomised to not receive ART at CD4 counts >500 cells/µL did not initiate ART until their CD4 counts had fallen below 350 cells/µL, consistent with practice at the time the trials began. In TEMPRANO, the CD4 indication for to be of high quality but can be graded down for risk of bias, indirectness, inconsistency, imprecision or publication bias. Observational study data are considered to be of low quality, but can be graded up for large effect, if plausible confounding would increase confidence in an estimated effect or if there is a dose-response gradient.

beginning ART in the deferred treatment changed over time as WHO guidelines evolved from <200 cells/µL to <350 cells/µL to <500cells/µL in the absence of other clinical criteria [13]. Similarly participants in the early ART arm received ART when CD4 counts were >250 cells/ μ L, >350 cells/ μ L and >500 cells/ μ L as WHO guidelines changed [13]; unpublished analyses were made available to us for patients with>500 CD4 cells/µL at baseline. We also identified 18 observational studies (Figure 1) [17–34]. Studies were conducted in 40 countries across a range of high- and lowresource settings in Asia, the Americas, Europe and sub-Saharan Africa (Supplemental Table 2).



Figure 1. Articles Identified, Screened, Assessed and Included

3.1. Mortality

In two RCTs investigators reported no difference in the risk of mortality (pooled RR=0.73; 95% CI 0.39-1.36) [13,14]. Seven observational studies comprising 55 cohorts also reported on mortality [24,26–28,30,32,33]. Four studies found decreased risk of death in persons initiating ART at CD4 cell counts \geq 500

cells/ μ L [26–28,35]. In reporting the seven studies, there was substantial overlap among the 55 cohorts, with data from 34 cohorts reported in \geq 1 study. To obtain an appropriate pooled estimate we pooled data from one cohort [30] that had not had its results reported from large synthetic cohorts with those of two other large studies that had the least overlap. These two studies from North America and Europe

included 22 [28] and 23 [24] cohorts respectively and comprised 20 972 participants. In pooled data, overlap was minimal, with only 154 (0.6%) participants reported in both analyses. There was no difference in the risk of mortality (RR 0.68, 95% CI 0.39-1.21) [24,28,30]. The pooled point estimate across all seven observational studies was similar (RR 0.74, 95% CI 0.52-1.07). Evidence quality for mortality from RCTs was

very low; quality for mortality from KCTs was very low; quality was downgraded for very serious imprecision and serious inconsistency due to conflicting results. Evidence quality in the observational literature was also very low, with downgrading for indirectness. Across all seven observational studies, evidence quality was also downgraded for risk of bias.

3.2. HIV Disease Progression

Two RCTs found lower risk of progressing to AIDS among those initiating ART at ≥500 CD4 cells/µL compared to those deferring until their CD4 counts were <500 cells/µL [13,14]. The pooled RR of developing AIDS from the RCT literature was 0.38 (95% CI 0.20-0.74) (Figure 2). Similarly, one observational study, which compared patients initiating ART at ≥500 CD4 cells/µL to those deferring until their CD4 counts were <500 cells/uL, found a lower hazard of developing an AIDS-defining opportunistic infection among persons initiating ART early compared to those deferring treatment (HR=0.20; 95% CI 0.10-0.42) (Figure 2)[19]. The quality of the RCT literature was moderate and downgraded as a result of imprecision due to few events. The quality of the observational literature was very low due to a lack of adjustment in the estimates.



Figure 2. Forest plot of progression

CI confidence interval; RCT, randomised controlled trial

3.3. Severe HIV Disease Or Mortality

One RCT estimated the effect of early (\geq 500 CD4 cells/µL) compared to deferred ART initiation (<500 cells/µL) on the combined outcome of risk of death or severe HIV disease or incident malignancy [13]. Patients who initiated treatment earlier had a lower hazard of death, severe HIV disease or malignancy than patients who deferred treatment (HR=0.59; 95% CI 0.33-1.06). Another RCT estimated the effect of early compared to deferred ART initiation on the combined outcome of risk of death or serious AIDS or serious non-AIDS event [15]. Patients who initiated treatment early had a reduced hazard of death, severe AIDS or serious non-AIDS event than those who deferred treatment (HR=0.43; 95% CI 0.30-0.62). The quality of the RCT literature for these outcomes was moderate and downgraded for imprecision.

Six observational studies estimated the effect of early versus deferred ART initiation on mortality or disease progression [17,19, 22,26,27,33], and four found a decreased risk of progression to AIDS or mortality among early initiators; one study found a significant reduction [33].Early initiation of ART was not found to be associated with reduced risk of death or progression to AIDS in a pooled analysis of two studies with unique patients 95% CI 0.16-2.49) (RR=0.63;[24,34]. However, data from one observational study were fully contained in (ICONA) [29] CASCADE 2011 [24], and five of the 12 cohorts in a large HIV cohort collaboration (HIV-CAUSAL) were also contained in CASCADE 2011 [33]. An additional metaanalysis including the large HIV cohort collaboration in the pooled analysis and ignoring the non-independence of the data did not substantively change the results (RR=0.84; 95% CI 0.58-1.21). Among the observational studies, two of these five studies reported adjusted estimates [17, 26]. Additionally, four of the five studies were consistent in their finding of treatment effect. The quality of the observational literature for this outcome is very low due to its observational status, inconsistency and risk of bias resulting from a lack of confounder adjustment.

3.4. HIV Transmission

One RCT found a decreased risk of transmission of HIV to sexual partners of patients treated early versus those who delayed treatment (RR=0.11: 95% CI 0.06-0.19) [11]. Another RCT found no significant difference in risk between patients treated regardless of CD4 cells/µL and those who were treated according to the South African guidelines (aRR=0.95; 95% CI 0.79-1.14) [16]. Two observational studies also evaluated the risk of transmission: neither found a difference between patients treated early and those who received a delayed treatment (pooled RR=1.17; 0.46-2.98) [21,22]. The quality of the RCT literature was very low owing to very serious imprecision because of the very small number of events and indirectness. The quality of the observational literature was also very low largely due to the lack of confounder adjustment in estimates and very small number of events.

3.5. Severe Adverse Events and Laboratory Abnormalities

One RCT reported specific severe adverse events in early and deferred treatment groups [13], while another RCT reported unspecified, symptomatic grade 4 events [14]. Specifically, there was no noted increase in grade 3/4laboratory abnormalities (HR=0.58; 95% 0.30-1.11) or hepatic (RR=0.62; 95% CI 0.20-1.80), renal (RR=0.09; 95% CI 0.01-1.63) or cardiovascular severe adverse events (RR=0.50; 95% CI 0.05-5.45), although there was a increased risk of adverse neurological events associated with early initiation (RR=4.96; 95%) CI 1.09-22.53) [13]. Another RCT found no risk in symptomatic grade 4 severe adverse events between treatment arms (RR=1.01; 95% CI 0.73-1.40) [14]. The quality of the RCT literature for most outcomes, except grade 3/4 laboratory abnormalities and symptomatic grade 4 adverse events, was low due to low numbers of events and imprecise estimates. On the other hand, the quality of the RCT literature for the symptomatic grade 4 adverse event outcomes was high and moderate for grade 3/4 laboratory abnormalities.

One observational study compared reported severe adverse events between early and deferred treatment cohorts [17]. Investigators found an increased risk of any severe laboratory adverse event among those who were treated early when compared to those who initiated treatment with CD4 counts <350 cells/uL (RR=1.43; 95% CI 1.13-1.81). Additionally, they found an increased risk of severe hepatic adverse events in those patients who initiated treatment early (RR=1.45; 95% CI 1.03-2.04). However, no differences were noted between treatment arms for renal (RR=0.90; 95% CI 0.40-2.01), haematologic (RR=1.40; 95% CI 0.87-2.26) or other severe adverse events (RR=1.40; 95% CI 0.94-2.08). The quality of the observational studies literature for these outcomes was low with no observed study limitations aside from the studies' observational design.

3.6. Methodological Quality of Included Studies

All six RCT reports adequately discussed how the randomisation sequence was generated, and all allocation was adequately concealed prior to assignment. No studies suffered from attrition bias resulting from incomplete outcome data reporting (e.g., follow-up in all studies was adequate), and no studies suffered from reporting bias resulting from selective outcome reporting. However, the trials may have potentially been biased because of a lack of blinding of assigned treatment (treatment was pre-determined determined bv clinical characteristics and was open label) (Figure 3) [11–16].

No observational study suffered from obvious selection bias; all observational studies had study populations that were either truly or somewhat representative of average, HIVinfected persons, and all participants were drawn from the same community. Additionally, all treatment data were ascertained through health care records, and outcomes of interest were not present at the start of the study. Comparability between intervention and control arms was not strong as several studies did not adjust for confounding factors such as age or sex. Outcomes were adequately assessed in all studies either through independent blind

assessment or record linkage. Follow-up was long enough for outcomes to occur in all studies,

although six observational studies did not report follow-up rates of participants [17–20,22,31].



Figure 3. Risk of Bias in Randomised Controlled Trials

4. CONCLUSION

We found moderate quality evidence that early ART initiation in asymptomatic HIV-infected patients with baseline CD4 counts of ≥500 cells/µL is associated with a lower risk of disease progression. This was also found in the observational literature albeit with very low quality evidence. We found mixed evidence from two RCTs that early intervention was associated with lower risk of mortality or disease progression. Additionally, we found evidence of a reduced risk of HIV transmission, but this was of very low quality owing to very few events. Current WHO ART guidelines rate the quality of evidence for this outcome as high; those recommendations were, however, made based on the literature for serodiscordant couples in which the infected partners had \geq 350 CD4 cells/µL [36]. The literature is substantially less robust for infected partners with \geq 500 CD4 cell/µL, although the estimates of efficacy are quite similar. Finally we found high quality evidence from an RCT that early initiation of ART was not associated with an increased risk of symptomatic grade 4 adverse events. There is, however, low quality evidence from an observational study of an increased risk hepatic adverse events: the clinical of significance of this, especially in light of different findings in the RCT, is unclear.

The present review should be considered with its multiple limitations. As with all systematic reviews, the results are only as good as our identified literature-our ability to identify relevant studies. To reduce the possibility of missing key studies, we searched five targeted scientific databases and reviewed the bibliographies of included studies as well as abstracts from recent conferences. It should be noted, however, that the bulk of our identified literature comes from Europe, North America and Australia with only a few studies contributing data from Africa, Asia and Latin America, which may limit the generalisability of our results to the areas of the world with the greatest burden of disease. While publication bias is an ever-present risk in systematic reviews, the present review included large cohorts, synthesized (eg, NA-ACCORD, EUROSIDA, ICONA, CASCADE, HIV-CAUSAL), which may have reduced the likelihood of publication bias. Unfortunately, we identified too few studies to objectively test for publication bias.

Additionally, we calculated estimates of efficacy from RCTs and effectiveness from cohort studies. Three identified RCT reports [11-13] used data from the same study population (TEMPRANO), and the incidence of some of the major clinical outcomes was particularly low. As a result, the precision of the estimates of mortality from RCTs, for example, was low; using GRADE criteria, the overall quality of the RCT literature for mortality was downgraded because of this. Additionally, we did not include data from HPTN 052, a seminal study that compared risk of transmission in discordant couples as well as clinical outcomes [37,38]. This is because the study population was restricted to HIV-infected index patients with between 350 and 550 CD4 cells/µL and compared early treatment in patients with 350-550 CD4 cells/µL with those with <350 cells/µL. There has been no published analysis of patients who initiated with 500-550 cells, which would have been required for this systematic review.

Due to the lack of RCT data, and to be comprehensive in our data collection efforts, we also examined cohort studies. GRADE criteria dictate that cohort studies should provide a lower quality of evidence, and this is usually because of residual confounding. Our overall effectiveness estimates from the included cohort studies were likely biased as a result of a lack of independence between study populations, as we noted in our previous report [7]. Namely, all seven studies reporting mortality outcomes contained data from some of the same cohorts [15–21]. We attempted to minimise the lack of independence between studies by conducting sensitivity analyses, removing studies with the most overlap in populations. For example, for mortality we examined three studies--one from Italy [30], one large synthesized cohort from North America [28] and one large synthesized cohort mostly from Europe [24], which had minimal overlap with each other. The point estimate from this synthesis (RR=0.68) was approximately nine percent lower than the point estimate from the pooled estimate from the full sample (RR=0.74), suggesting that the lack of independence between study populations did not greatly affect the point estimates. Expectedly, however, the variability decreased considerably with the much larger sample size. Additionally, cohorts can suffer from a number of biases, including confounding and lead-time bias. As a result of evaluating a subgroup of patients whose CD4 at ART initiation was greater than 500 cells/µL, which until recently was not routinely studied, much of our analyses were performed post-hoc using unadjusted estimates. Lastly, though the GRADE system for rating the quality of the literature has its limitations and some have reservations about its use at WHO for guideline development [34], it is the current gold standard and has been adopted by WHO for its guideline development process [39].

In conclusion we found evidence from both RCTs and observational studies to support the WHO recommendation of initiating ART in everyone with HIV at diagnosis regardless of CD4 count or clinical stage. This strategy greatly simplifies ART prescribing and with sufficiently high coverage will impact HIV incidence as well. Additional data from studies still in the field, such as PopART [40] and SEARCH [41], as well as full publications from ANRS 12249 TasP, will provide additional evidence needed to answer the question of when

ACKNOWLEDGEMENTS

We thank Dr Xavier Anglaret of the Université Victor Segalen Bordeaux 2 for sharing the additional analyses of TEMPRANO.

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Supplemental Table 1

Author(s): Anglemyer, Andrew

Date: 25 September 2017

Question: Should ART in eligible patients with CD4 > 500 vs CD4 <500 be used for HIV treatment?

Settings: Africa, Asia, Australia, Europe, and North America

Bibliography: CASCADE 2003, CASCADE 2011, Danel (TEMPRANO) 2015, Donnell 2010, Garcia 2004, Gras 2007, He 2013, HIV CAUSAL 2010, HIV CAUSAL 2011, HIV CAUSAL 2015, INSIGHT START Study Group 2015, Iwuji (ANRS 12249) 2016, Jean 2013, Jean 2014, Jia 2012, Jose 2014, Kitahata 2009, Le 2013, Merito 2006, Molina (START) 2016, Okulicz 2015, Palella 2003, Schneider 2013, Sterne 2009, TEMPRANO ANRS 12136 Study Group 2015

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1										more		

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										to 29		
										fewer)		
	•		0		Morta	lity (over	lap)	r				
7	observat	very	serious ⁸	very	not	not	1,162/95	9165/38	RR	6		CRI
	ional	seriou		serious ⁹	serious	serious	,832	2,677	0.74	fewer	VERY	TIC
	studies	s′					(1.2)%	(2.4)%	(0.52	per	LOW	AL
									to	1000		
									1.07)	(from		
										2 more		
										to 11		
										fewer)		
]	HIV Dise	ease Progr	ession					
2	random	not	not	not	serious	not	28/3298	104/3/1	RR	17		CRI
	sed	seriou	serious	serious	10	serious	(0.8)%	8 (2.8)%	0.38	fewer	MODER	TIC
	trials	S							(0.2 to	per	ATE	AL
									0.74)	1000		
										(from		
										7		
										fewer		
										to 22		
										fewer)		
	•	1	1]	HIV Dise	ease Progr	ession	1	1	1		
1	observat	seriou	not	serious	not	not	98/257	295/398	HR	504		CRI
	ional	s 11	serious	12	serious	serious	(38.1)%	(74.1)%	0.2	fewer	VERY	TIC
	studies								(0.1 to	per	LOW	AL
									0.42)	1000		
										(from		
										308		
										fewer		
										to 615		
										fewer)		
		_		Death	, Severe 1	Infection,	Maligna	ncy	-	-		
1	randomi	not	not	not	serious ³	not	19/972	30/930	RR	13		CRI
	sed	seriou	serious	serious		serious	(2.0)%	(3.2)%	0.59	fewer	MODER	TIC
	trials	S							(0.33	per	ATE	AL
									to	1000		
									1.06)	(from		
										2 more		
										to 22		
										fewer)		
	1	1]	Death, Se	erious AI	DS or Ser	rious non	-AIDS	1	1		
1	randomi	not	not	not	serious ³	not	42/2,326	96/2,359	RR	23		CRI
	sed	seriou	serious	serious		serious	(1.8)%	(4.1)%	0.43	fewer	MODER	TIC
	trials	S							(0.30	per	ATE	AL
									to	1000		
									0.62)	(from		
										15		
										fewer		
										to 28		
										fewer)		
		1	· ·-	AIDS	or Death	ı (sensitiv	ity analy	sis)	1	1		
2	observat	seriou	serious ¹³	not	not	not	698/525	2058/12	RR	61		CRI
	ional	s		serious	serious	serious	2	491	0.63	fewer	VERY	TIC
	studies						(13.3)%	(16.5)%	(0.16	per	LOW	AL
									to	1000		
									2.49)	(from		
										138		
										fewer		
										to 245		
1									1	more)		

AIDS or Deeth (overlap)												
2	ahaamit		aami aa ¹³		AIDS OF	Deaul (0V	(eriap)	1762/50	מם	12		CDI
3	observat		serious	not	not	not	1,139/14	4,/03/39	KK	15		
	ional	S		serious	serious	serious	,252	,943	0.84	fewer	VERY	TIC
	studies						(8.0)%	(7.9)%	(0.58	per	LOW	AL
									to	1000		
									1.21)	(from		
										17		
										more		
										to 33		
										fewer)		
	•	•		•	HIV	Fransmiss	sion	•				
1	randomi	not	not	serious ²	verv	not	2/10000	20/1000	RR	0		CRI
	sed	seriou	serious		serious ³	serious	0 (0.0)%	00	0.11	fewer	VERY	TIC
	trials	S					- ()	(0.0)%	(0.06	per	LOW	AL
	uiuis	5						(0.0)/0	to	1000	2011	
									(0, 19)	(from		
									0.17)	0		
										fower		
										to		
										four for		
	TT	IV Tree		(Faules (4		ller abarra		ideline		
1			Institussion	i (Eariy	ireatmen	it versus a		ny-chang	ing gu		s) 	CDI
1	randomi	not	not	very 2	not	not	227/10,6	208/11,7	KK			
	sed	seriou	serious	serious	serious	serious	46	8/	0.95	fewer	LOW	TIC
	trials	S					(2.1)%	(2.3)%	(0.79	per		AL
									to	1000		
									1.14)	(from		
										3 more		
										to 5		
										fewer)		
					HIV	Fransmiss	sion					
2	observat	seriou	not	not	very	not	6/366	12/912	RR	2 more		CRI
	ional	s ¹¹	serious	serious	serious ³	serious	(1.6)%	(1.3)%	1.17	per	VERY	TIC
	studies							. ,	(0.46	1000	LOW	AL
									to	(from		
									2.98)	7		
										fewer		
										to 26		
										more)		
			Gra	de 3 or 4	Morhid	ity (other	than ner	itronenia		more)		
1	randomi	not	not	not	serious ³	not	15/212	25/201	, PP	52		CRI
1	sad	seriou	serious	serious	serious	serious	(7 1)%	$(12 \ 1)\%$	0.58	fower	MODER	
	triolo	scriou	scribus	scribus		scribus	(7.1)/0	(12.4)/0	(0.36)	nor	ATE	
	utais	8							$(0.5 \ 10$	1000	AIE	AL
									1.11)	1000		
										14		
										more		
										to 87		
						<u> </u>				fewer)		
<u> </u>	1	1	r	1	Liver	SAE (RC	TS)	0.15.1	-	-	Г <u> </u>	a= -
1	randomi	not	not	not	very	not	5/515	8/511	RR	6		CRI
	sed	seriou	serious	serious	serious	serious	(1.0)%	(1.6)%	0.62	fewer	LOW	TIC
	trials	s							(0.2 to	per		AL
									1.88)	1000		
										(from		
										13		
										fewer		
										to 14		
										more)		
			•	1	Renal	SAE (RC	Ts)	1		/	•	
1	randomi	not	not	not	verv	not	0/436	5/413	RR	11		CRI
1	sed	seriou	serious	serious	serious ³	serious	(0,0)%	(1 2)%	0.09	fewer	LOW	TIC

	trials	S							(0.01	per		AL
									to	1000		
									1.54)	(from		
										7 more		
										$t_0 12$		
										fower)		
				C	ndiovog	ulon SAE				ic wei)		
1	non domi	not	not	Ci not	II UIOVASC	not	$\frac{1}{515}$	2/511	DD	2		CDI
1	randonn	not	not	not	very	not	$\frac{1}{313}$	$\frac{2}{311}$		<u>ک</u>		
	sed	seriou	serious	serious	serious	serious	(0.2)%	(0.4)%	0.5	lewer	LOW	
	trials	S							(0.05	per		AL
									to	1000		
									5.45)	(from		
										4		
										fewer		
										to 17		
										more)		
					Neurolo	gy SAE (I	RCTs)					
1	randomi	not	not	not	very	not	10/515	2/511	RR	15		CRI
	sed	seriou	serious	serious	serious ³	serious	(1.9)%	(0.4)%	4.96	more	LOW	TIC
	trials	s					` '	~ /	(1.09	per		AL
									to	1000		
									22,53)	(from		
									,	0		
										fewer		
										to 8/		
										10 04 more)		
-				S	matomot	ia Crada	4 Evente			more)		
1	non domi	not	not	By.	nptoma	ne Graue	4 Events	72/2250	DD	0		CDI
1	randomi	not	not	not	not	not	13/2320	13/2339		0		
	sed	seriou	serious	serious	serious	serious	(3.1)%	(3.1)%	1.01	fewer	HIGH	TIC
	trials	s							(0.73)	per		AL
									to	1000		
									1.39)	(from		
										8		
										fewer		
										to 12		
										more)		
				-	A	ny SAE						-
1	observat	not	not	not	not	not	76/447	1207/78	HR	59		CRI
	ional	seriou	serious	serious	serious	serious	(17.0)%	60	1.43	more	LOW	TIC
	studies	S						(15.4)%	(1.13	per		AL
									to	1000		
									1.81)	(from		
										18		
										more		
										to 107		
										more)		
	Liver SAE											
1	observat	not	not	not	not	not	76/447	1207/78	HR	61		CRI
	ional	seriou	serious	serious	serious	serious	$(17.0)\%^{1}$	60	1 45	more	LOW	TIC
	studies	e	serious	5011005	5011043	5011043	4	(15.4)%	(1.73)	ner	L0 !!	AI
	staates	5						14	(1.03	1000		· · · ·
									2 04	(from		
									2.04)	4 more		
										+ more		
										10 155		
										more)		I
1	ah contra		/		K	enal SAE	761447	1007/70	IID	1.4		CDI
	observat	not	not	not	not	not	/6/447	1207/78	HR	14		CRI
	ional	seriou	serious	serious	serious	serious	$(17.0)\%^{1}$	60	0.9	tewer	LOW	TIC
	studies	S					+	$(15.4)\%^{1}$	(0.4 to	per		AL
								4	2.01)	1000		
										(from		

										89		
										fewer		
										to 131		
										more)		
Blood SAE												
1	observat	not	not	not	not	not	76/447	1207/78	RR	61		CRI
	ional	seriou	serious	serious	serious	serious	$(17.0)\%^{1}$	60	1.4	more	LOW	TIC
	studies	S					4	(15.4)%	(0.87	per		AL
								14	to	1000		
									2.26)	(from		
										20		
										fewer		
										to 193		
										more)		
		T			0	ther SAE	r	r			r	
1	observat	not	not	not	not	not	76/447	1207/78	RR	61		CRI
	ional	seriou	serious	serious	serious	serious	$(17.0)\%^{1}$	60	1.4	more	LOW	TIC
	studies	S					4	$(15.4)\%^{-1}$	(0.94	per		AL
								4	to	1000		
									2.08)	(from		
										9		
										fewer		
										to 166		
										more)		

Notes:

- 1. One study's point estimate is greater than 1
- 2. Comparison is <350
- 3. Less than 50 cases
- 4. One of three studies did not provided adjusted estimates
- 5. One study's point estimate was less than 1.0, while two were greater than 1.0.
- 6. One study compared 500 vs 350-499. Two studies compared 500 vs <500
- 7. There is large overlap of populations between the cohorts
- 8. Four point estimates were less than 1.0, while 3 were greater than 1.0.
- 9. Two studies did not make comparisons between 500 and <500 directly
- 10. Less than 200 cases
- 11. Unadjusted estimates
- 12. Study did not make direct comparisons between 500 and <500 (e.g., Early vs deferred)
- 13. One study's results suggested an increased risk
- 14. Counts of patients with SAE were not reported; counts of any SAE used as a proxy

Study and	Methods	Setting	Participants	Intervention	Outcomes
reference		C	1		Of Interest
ANRS 12249	Cluster-	South Africa	ART-naïve	Initiate ART	HIV transmission
2016[16]	Randomised		HIV-infected	regardless of	
	trial		patients	CD4 cell count	
			initiating	(vs <350 or	
			ART	<500 cells/µl)	
INSIGHT	Randomised	Africa, Asia,	ART-naïve	Initiate ART	Mortality, serious
START	controlled trial	Australia,	HIV-infected	with CD4 cell	AIDS event,
2015[14]		Europe and	patients	count >500	tuberculosis,
		Israel, North	initiating	cells/µl (vs <350	Kaposi's sarcoma,
		America, and	ART	cells/µl)	lymphoma,
		South America			symptomatic grade
					4 events
INSIGHT	Randomised	Africa, Asia,	ART-naïve	Initiate ART	Composite
START	controlled trial	Australia,	HIV-infected	with CD4 cell	outcome:
2016[15]		Europe and	patients	count >500	mortality, serious
		Israel, North	initiating	cells/µl (vs <350	AIDS event and

Jean Jean (from TEMPRANO) Randomised controlled rial (from TEMPRANO) Cells (I) vice (Cells (I) vice) ART naïve HIV infected patients initiating ART Initiate ART (vice) studies HIV transmission Jean 2014[12] (from TEMPRANO) Randomised controlled rial Cête d'Ivoire (Cells (I) (vs. 350 eells (I) (vs. 40 mortality eells (I) (vs. 40 m			Amorico and	ADT	aalla/ul)	antique non AIDS
Jean 2013[11] (from TEMPRANO) Randomised controlled trial Côte d'Ivoire and Côte d'Ivoire ART-naïve HIV-infected patients initiating arean 2014[12] (from TEMPRANO) Randomised controlled trial Côte d'Ivoire Controlled trial ART-naïve HIV-infected patients initiating colles(µ1) Initiate ART with CD4 cell count >500 None TEMPRANO 2015[13] Randomized controlled trial Côte d'Ivoire Controlled trial ART-naïve HIV-infected patients initiating colles(µ1) Mortality, Severe morbdity, TB (pulmonary and disseminated), ART Mortality, Severe morbdity, TB (pulmonary and disseminated), ART CASCADE 2003[23] Meta-analysis of 20 cohort studies Australia, Casca, Sudies ART-naïve HIV-infected patients initiating colles(µ1) Initiate ART with CD4 cell count >500 cells(µ1) Mortality, disease prelated events CASCADE 2003[23] Meta-analysis for 20 cohort studies Australia, Casca, Norway, Spain, Switzerland, Uganda, Uganda, Uganda, Uganda, Uganda, Uganda, Uganda, Uganda, Uganda, South Africa, South			South America	AKI	cens/µi)	event
2013[11] (from TEMPRANO) controlled trial (from TEMPRANO) mandomised controlled trial Côte d'Ivoire (from TEMPRANO) None with CD4 cell (sum > 500 (ells/µl (vs < 350 cells/µl (vs < 350 cells/µl (vs < 350 cells/µl (vs < 350 cells/µl) None TEMPRANO Randomized (from TEMPRANO) Côte d'Ivoire (antrolled trial Côte d'Ivoire (controlled trial ART-naïve (From Controlled trial Initiate ART (patients initiating controlled trial Mortality, Severe morbidity, TB (pulmonary and initiating controlled trial CASCADE 2003[23] Meta-analysis of 20 cohort studies Australia, Demmark, Spain, Switzerland, Uniced Kingdom ART-naïve HIV-infected NRT-naïve Gremany, Greece, Italy, Switzerland, Uniced Kingdom Initiate ART with CD4 cell count >500 cells/µl (vs 0- 500 cells/µl) Mortality, disease progression or mortality CASCADE 2011[24] Meta-analysis of 23 cohort studies Australia, Carada, Demark, Switzerland, Uniced Kingdom, Zambia, Zimbabwe ART-naïve HIV-infected Kingdom Initiate ART with CD4 cell count >500 cells/µl (vs 0- 309 cells/µl) Mortality, disease progression or mortality CASCADE 2011[24] Multicenter Cohort study Australia, Kwanda, South Africa, Spain, Switzerland, Uranda, Zimbabwe ART-naïve HIV-infected patients Initiate ART wit	Jean	Randomised	Côte d'Ivoire	ART-naïve	Initiate ART	HIV transmission
TEMPRANO) patients initiating count>500 cells/µl (vs.<350 cells/µl (vs.<350	2013[11]	controlled trial		HIV-infected	with CD4 cell	
Item Prevention Initiate and on isod controlled trial (or early in the control of the distribution of the distrebuticon of the distribution of the distribution of the distribu	(from			patients	count > 500	
Jean 2014[12] (from TEMPRANO Randomised controlled trial Côte d'Ivoire (arrolled trial ART-naïve (arrolled trial Initiate ART (actual triang) None 7EMPRANO Randomized controlled trial Côte d'Ivoire (arrolled trial Côte d'Ivoire (arrolled trial) ART-naïve (arrolled trial) Initiate ART (actual triang) Mortality, Severe morbidity, TB (pulmonary and disseminated) 7EMPRANO Randomized controlled trial Côte d'Ivoire (arrolled trial) ART-naïve (arrolled trial) Initiate ART (pulmonary and disseminated) Mortality, Severe morbidity, TB (pulmonary and disseminated) Mortality, Severe morbidity, TB (pulmonary and disseminated) CASCADE 2003[23] Meta-analysis of 20 cohort studies Australia, Carece, Italy, The Netherlands, Norway, Spain, Switzerland, United ART-naïve HIV-infected patients of 23 cohort Initiate ART with CD4 cell count >500 cells/µl) Mortality, discase progression or mortality CASCADE 2011[24] Meta-analysis of 23 cohort studies Australia, Carada, Denmark, Germany, Greece, Italy, Gerece, Italy, Gerece, Italy, Gerece, Italy, Gerece, Italy, Gerece, Italy, Greece, Italy,	TEMPRANO)			ART	cells/µl (vs <350 cells/µl)	
2014[12] (from TEMPRANO) controlled trial HIV-infected with CD4 cell count >500 TEMPRANO 2015[13] Randomized controlled trial Côte d'Ivoire ART naïve HIV-infected Initiate ART with CD4 cell count >500 Mortality, Severe montality, Severe montality, Severe count >500 2015[13] controlled trial Côte d'Ivoire ART naïve HIV-infected Initiate ART with CD4 cell count >500 Mortality, Severe montality, Severe montality, Severe montality, ART 2003[23] of 20 cohot polation studies Australia, Germany, Greece, Italy, The Netherlands, Norway, Spain, Switzerland, United Kingdom ART-naïve HIV-infected Initiate ART with CD4 cell count >500 None CASCADE Meta-analysis of 23 cohot studies Australia, Norway, Spain, Switzerland, United Kingdom ART-naïve ART Initiate ART with CD4 cell count >500 Mortality, disease progression or mortality CASCADE Meta-analysis of 23 cohot studies Australia, Norway, Spain, Switzerland, Ukraine, Ukraine, Ukraine, Ukraine, South Africa, Spain, Switzerland, Ukraine, Ukraine, Ukraine, Ukraine, South Africa, South A	Jean	Randomised	Côte d'Ivoire	ART-naïve	Initiate ART	None
TemPRANO) patients count->000 TEMPRANO Randomized Côte d'Ivoire ART Initiate ART 2015[13] Controlled trial Côte d'Ivoire ART Initiate ART 2015[13] Meta-analysis Australia, ART-naïve Initiate ART 2003[23] Meta-analysis Australia, ART-naïve Initiate ART 2003[23] Meta-analysis Australia, ART-naïve Initiate ART CASCADE Meta-analysis Australia, ART-naïve Initiate ART Vinted Kingdom ART S00 cells/µl Mortality, disease 2011[24] of 23 cohort Studies Australia, ART-naïve Initiate ART Vinted Kingdom ART ART apients count 500.79 CascADE Meta-analysis Australia, ART apients count 500.79 South Artica, South Artial, ART ART apients 12011[24] of 23 cohort	2014[12]	controlled trial		HIV-infected	with CD4 cell	
Instituting Colls (µ) (vs < >30 TEMPRANO Randomized Côte d'Ivoire ART -naïve Initiate ART Mortality, Severe 2015[13] controlled trial Côte d'Ivoire ART -naïve Initiate ART initiating 2015[13] controlled trial Côte d'Ivoire ART -naïve Initiate ART initiating 2015[13] controlled trial Côte d'Ivoire ART ART -naïve Initiate ART 2003[23] of 20 cohort Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Switzerland, United Kingdom ART -naïve Initiate ART None CASCADE Meta-analysis Australia, Switzerland, United Kingdom ART -naïve Initiate ART None CASCADE Meta-analysis Australia, Switzerland, United Kingdom ART -naïve Initiate ART Mortality, disease 2011[24] of 23 cohort Studies Australia, France, Germany, Greece, Italy, Kenya, The Netherlands, Norway, Poland, Portugal, Russia, Rwanda, South Africa, Spain, Switzerland, Uraited, Rwanda, South Africa, Spain, Switzerland, Uraited, Rwanda, South Africa, Spain, Zambia, Zimbawe Initiate ART HIV transmission	(from			patients	count > 500	
TEMPRANO 2015[13] Randomized controlled trial Côte d'Ivoire (controlled trial) ART-naïve Patients nitiating ART Initiate ART with CD4 cell count >500 cells/µl (v. <350 cells/µl) Mortality, Severe morbidity, TB (pulmonary and disseminated), ABS-related cancers, non-AIDS related events CASCADE 2003[23] Meta-analysis of 20 cohort studies Australia, Denmark, Germany, Greece, Italy, Norway, Spain, Switzerland, United ART-naïve HIV-infected patients Initiate ART with CD4 cell count >500 cells/µl) None CASCADE 2011[24] Meta-analysis of 20 cohort studies Australia, Denmark, Germany, Greece, Italy, Norway, Spain, Switzerland, United ART-naïve HIV-infected patients Initiate ART with CD4 cell count >500 cells/µl) Mortality, disease progression or mortality CASCADE 2011[24] Meta-analysis studies Australia, Canada, Norway, Prance, Germany, Greece, Italy, Kenya, The Netherlands, Norway, Poland, Portugal, Russia, Rwanda, South Africa, Spain, Switzerland, Ugranda, Ugranda, Ugranda, Ugranda, South Africa, Spain, Switzerland, Ugranda, South Africa, Spain, Switzerland, Ugranda, South Africa, Spain, Switzerland, Ugranda, South Africa, Spain, Switzerland, Ugranda, South Africa, Spain, Switzerland, Ugranda, Zimbabwe Initiate ART HIV infected patients HIV transmission	TEMPRANO)				$cells/\mu (vs < 350)$	
2015[13] controlled trial Core i hole HIV-infected patients initiating ont >500 morbidity, TB (controlled trial disseminated), ART 2015[13] controlled trial ART cells/µ(vs <330)	TEMPRANO	Randomized	Côte d'Ivoire	ART-naïve	Initiate ART	Mortality Severe
CASCADE Meta-analysis Australia, Demmark, studies ART-naïve ART Initiate ART with CD4 cell count >500 cells/µl) (pulmonary and fusceminated), AIDS-related cancers, orber non-AIDS related carcers, other non-AIDS related carcers, other non-AIDS CASCADE Meta-analysis studies Australia, Denmark, France, Germany, Greece, Italy, Norway, Spain, Switzerland, United Kingdom ART-naïve HIV-infected patients Initiate ART with CD4 cell count >500 cells/µl) None CASCADE Meta-analysis studies Australia, Canada, Denmark, France, Germany, Greece, Italy, Kenya, The Netherlands, Norway, Spain, Switzerland, United Kingdom ART-naïve ART Initiate ART with CD4 cell count >500 cells/µl) Mortality, disease progression or mortality CASCADE Meta-analysis of 23 cohort studies ART-naïve Germany, Greece, Italy, Kenya, The Netherlands, Norway, Poland, Portugal, Russia, Rwanda, South Africa, Spain, Switzerland, United Kingdom, Zambia, Zimbabwe ART-naïve HIV-infected patients Initiate ART with CD4 cell count >500 Mortality, disease progression or mortality Donnell Multicenter Botswana, Rwanda, South Africa, Spain, Zimbabwe ART-naïve HIV-infected patients Initiate ART with CD4 cell count >500 HIV transmission	2015[13]	controlled trial		HIV-infected	with CD4 cell	morbidity, TB
CASCADE Meta-analysis of 20 cohort studies Australia, Demmark, Gereacy, Sudies ART-naïve HIV-infected patients initiating Greece, Italy, Norway, Spain, Switzerland, United Kingdom Initiate ART with CD4 cell count >500 cells/µl) None CASCADE Meta-analysis of 20 cohort studies Australia, Denmark, Denmark, Gereacy, Italy, Norway, Spain, Switzerland, United Kingdom ART-naïve HIV-infected patients Initiate ART with CD4 cell count >500 cells/µl) None CASCADE Meta-analysis of 23 cohort studies Australia, Norway, Spain, Switzerland, United Kingdom ART-naïve HIV-infected patients ART Initiate ART with CD4 cell count >500. cells/µl) Mortality, disease progression or mortality CASCADE Meta-analysis of 23 cohort studies Australia, Pernace, Germany, Greece, Italy, Kenya, The Netherlands, Norway, Poland, Portugal, Russia, Rwanda, South Africa, Spain, Switzerland, United Kingdom, Zambia, Zimbabwe Initiate ART with CD4 cell count >500. 499 cells/µl) Mortality, disease progression or mortality Donnell Multicenter Botswana, Rwanda, South Africa, Spain, Switzerland, United Kingdom, Zambia, South Africa, South Afr				patients	count >500	(pulmonary and
CASCADE Meta-analysis Australia, of 20 cohort studies Australia, Prance, Germany, Greece, Italy, Norway, Spain, Switzerland, United Kingdom ART - naïve HIV-infected patients Initiate ART with CD4 cell count >500 cells/µl None CASCADE Meta-analysis of 20 cohort studies Australia, Demmark, France, Germany, Greece, Italy, Norway, Spain, Switzerland, United Kingdom ART - naïve HIV-infected patients Initiate ART with CD4 cell count >500 cells/µl None CASCADE Meta-analysis Orrece, Italy, Norway, Spain, Switzerland, United Kingdom ART - naïve HIV-infected patients Initiate ART with CD4 cell count >000 cells/µl Mortality, disease progression or mortality CASCADE Meta-analysis of 23 cohort Australia, Canada, Penmark, Studies ART - naïve patients Initiate ART with CD4 cell count >000 reglis/µl Mortality, disease progression or mortality Opland, Poland, Poland, Uganda, Ukraine, United Kingdom, Zambia, Zimbabwe ART - naïve HIV-infected patients Initiate ART with CD4 cell count >00 HIV transmission Donnell 2010[21] Multicenter cohort study Botswana, Kenya, Rwanda, South Africa, South				initiating	cells/µl (vs <350	disseminated),
CASCADE Meta-analysis Australia, Demmark, studies ART-naïve HIV-infected Germany, Greece, Italy, The Netherlands, Norway, Spain, Switzerland, United Kingdom, Zo11[24] Meta-analysis of 20 cohort studies Australia, Demmark, Germany, Greece, Italy, The Netherlands, Norway, Spain, Switzerland, United Kingdom, Zanda, Ukraine, United Kingdom, Zambia, Rwanda, South Africa, Spain, Switzerland, United Kingdom, Zambia, Rwanda, South Africa, Spain, Switzerland, United Kingdom, Zambia, Rwanda, Zambia, Rwanda, South Africa, Spain, Switzerland, United Kingdom, Zambia, Rwanda, South Africa, Spain, Switzerland, United Kingdom, Zambia, Rwanda, South Africa, Spain, Switzerland, United Kingdom, Zambia, Rwanda, South Africa, Spain, Switzerland, Ukraine, United Kingdom, Zambia, Rwanda, South Africa, Spain, Switzerland, Ukraine, United Kingdom, Zambia, Rwanda, South Africa, Spain, Switcerland, Ukraine, United Kingdom, Zambia, Rwanda, South Africa, Spain, Switcerland, Ukraine, United Kingdom, Zambia, Rwanda, South Africa, Spain, Switcerland, Ukraine, United Kingdom, Zambia, Rwanda, South Africa, Spain, Switcerland, Ukraine, United Kingdom, Zambia, Rwanda, South Africa, Spain, Swith CD4 cell Vin CD4 ce				ART	cells/µl)	AIDS-related
CASCADE 2003[23] Meta-analysis of 20 cohort studies Australia, Demmark, Gremay, Greece, Italy, The Netherlands, Norway, Spain, Switzerland, United 2011[24] ART-naïve MIV-infected of 23 cohort studies Initiate ART with CD4 cell count >500 cells/µl) None CASCADE 2011[24] Meta-analysis of 23 cohort studies Australia, Demmark, Greece, Italy, ART ART-naïve HIV-infected patients initiating Greece, Italy, Norway, Spain, Switzerland, United Kingdom Initiate ART with CD4 cell count >500 cells/µl) Mortality, disease progression or mortality CASCADE 2011[24] Meta-analysis of 23 cohort studies Australia, Canada, Demmark, France, Germany, Greece, Italy, Kenya, The Netherlands, Norway, Poland, Portugal, Russia, Rwanda, South Africa, Spain, Switzerland, Uganda, Ukraine, United Kingdom, Zambia, Zimbabwe Initiate ART with CD4 cell count 500.799 cells/µl Mortality, disease with CD4 cell count 500.799 cells/µl Donnell Multicenter cohort study South Africa, Spain, Switzerland, Uganda, Zimbabwe ART-naïve HIV-infected patients count >500 HIV transmission with CD4 cell count >500						cancers, non-AIDS
CASCADE Meta-analysis Australia, Denmark, France, Germany, Grece, Italy, The Netherlands, Norway, Spain, Switzerland, United ART-naïve HIV-infected patients Initiate ART with CD4 cell count >500 None CASCADE Meta-analysis Germany, Grece, Italy, The Netherlands, Norway, Spain, Switzerland, United ART-naïve HIV-infected Initiate ART with CD4 cell count >500 None CASCADE Meta-analysis Australia, United ART-naïve HIV-infected Initiate ART with CD4 cell count >500 rells/µl) Mortality, disease progression or mortality CASCADE Meta-analysis Canada, Denmark, Estonia, France, Germany, Grecec, Italy, Kenya, The Netherlands, Norway, Poland, Portugal, Russia, Rwanda, South Africa, Spain, Sitingdom, Zambia, Zimbabwe ART-naïve HIV-infected Kingdom, Zambia, Zimbabwe Initiate ART HIV-infected Mortality, disease progression or mortality Donnell Multicenter Botswana, Kenya, Rwanda, South Africe, Subit Africe Initiate ART with CD4 cell count ≥500 HIV transmission						related cancers,
CASCADE Meta-analysis Australia, Denmark, studies ART-naïve Denmark, Germany, Greece, Italy, Norway, Spain, Switzerland, United Initiate ART with CD4 cell count >500 cells/µl (vs 0- 500 cells/µl) None CASCADE Meta-analysis Australia, Norway, Spain, Switzerland, United ART-naïve HIV-infected Initiate ART None CASCADE Meta-analysis Australia, Norway, Spain, Switzerland, United ART-naïve HIV-infected Initiate ART Mortality, disease 2011[24] Meta-analysis Australia, Germany, Greece, Italy, Kenya, The Netherlands, Norway, Studies ART-naïve HIV-infected Initiate ART Mortality, disease Procee, Italy, Kenya, The Netherlands, Norway, Greece, Italy, Kenya, The Netherlands, Norway, Poland, Portugal, Russia, Rwanda, South Africa, Spain, Switzerland, Uganda, Ukraine, United Kingdom, Zambia, Zimbabwe ART-naïve HIV-infected Initiate ART HIV transmission Donnell Multicenter cohort study Botswana, Kusnda, South Africa, Spain, Zimbabwe ART-naïve HIV-infected Initiate ART with CD4 cell count ≥500						other non-AIDS
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CASCADE Meta-analysis Australia, Switzerland, United ART 500 cells/µl) CASCADE Meta-analysis Australia, United ART-naïve HIV-infected Initiate ART with CD4 cell count 500-799 Mortality, disease progression or mortality 2011[24] of 23 cohort studies Canada, Denmark, Estonia, France, Germany, Greece, Italy, Kenya, The Netherlands, Norway, Poland, Portugal, Russia, Rwanda, South Africa, Spain, Zimbabwe Initiate ART with CD4 cell count 500-799 Mortality, disease progression or mortality Donnell Multicenter South Africa, Rwanda, South Africa, South Africa, Rwanda, South Africa, South Af			Germany,	initiating	cells/µl (vs 0-	
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CASCADE Meta-analysis Australia, Australia, studies ART-naïve Denmark, Estonia, Initiate ART HIV-infected Mortality, disease with CD4 cell count 500-799 0 23 cohort Canada, Bermany, Greece, Italy, Kenya, The Netherlands, Norway, Poland, Portugal, Russia, Rwanda, South Africa, Spain, Zimbabwe ART Initiate ART with CD4 cell Mortality, disease progression or mortality 0 2010[21] Mortality, disease Mortality, disease Mortality, disease 0 2010[21] Multicenter cohort study ART HIV-infected HIV-infected Mortality, disease 0 Mortality, disease Mortality, disease Mortality, disease Mortality, disease 0 Greece, Italy, Kenya, The Netherlands, Norway, Poland, Portugal, Russia, Rwanda, South Africa, Spain, Zimbabwe ART HIV 0 HIV Norway, Poland, Ukraine, Uhited HIV HIV 0 Multicenter cohort study Botswana, Kenya, Rwanda, South Africa ART-naïve HIV-infected HIV transmission			United			
CASCADE Meta-analysis Australia, Canada, studies ART-naïve Canada, Denmark, Estonia, France, Germany, Greece, Italy, Kenya, The Notway, Poland, Portugal, Russia, South Africa, Spain, Zambia, Zimbabwe Initiate ART with CD4 cell count 500-799 Mortality, disease progression or mortality Donnell Multicenter 2010[21] Multicenter cohort study Botswana, Kenya, South Africa, South Africa, South Africa, Zimbabwe ART-naïve HIV-infected Kenya, HIV-infected with CD4 cell count 500-799 Multicenter HIV transmission			Kingdom			
2011[24] of 23 conort studies Canada, Denmark, Estonia, France, Germany, Greece, Italy, Kenya, The Netherlands, Norway, Poland, Portugal, Russia, Rwanda, South Africa, Spain, Switzerland, Uganda, Ukraine, United Kingdom, Zambia, Zimbabwe HIV-infected patients count 500-799 cells/µl (vs 0- 499 cells/µl) progression or mortality Denmark, Estonia, France, Germany, Greece, Italy, Kenya, The Norway, Poland, Portugal, Russia, South Africa, Spain, Zambia, Zimbabwe ART 499 cells/µl) # HIV-infected with CD4 cell with CD4 cell Donnell Multicenter cohort study Botswana, Kenya, HIV-infected Rwanda, South Africa, Zimbabwe ART-naïve HIV-infected count ≥500 HIV transmission	CASCADE	Meta-analysis	Australia,	ART-naïve	Initiate ART	Mortality, disease
Definitial A, patients Count 300-733 Inordarity Estonia, initiating cells/µl (vs 0- France, ART 499 cells/µl) Germany, Greece, Italy, Kenya, The Netherlands, Norway, Poland, Portugal, Russia, Rwanda, South Africa, Spain, Switzerland, Uganda, Ukraine, United Kingdom, Zambia, Zimbabwe Donnell Multicenter Botswana, ART-naïve Initiate ART HIV transmission Studies Kenya, HIV-infected with CD4 cell Rwanda, count ≥500	2011[24]	of 23 conort	Canada, Donmork	HIV-Infected	count 500 700	progression or mortality
Donnell Multicenter Donnell Multicenter 2010[21] Multicenter Bonnell Multicenter Boswana, ART HIV-infected With CD4 cell Rwanda, Donnell Multicenter Botswana, Resa, Right HIV-infected With CD4 cell Rwanda, Donnell		studies	Estonia	initiating	cells/ul (vs 0-	mortanty
Germany, Germany, Greece, Italy, Kenya, The Netherlands, Norway, Poland, Poland, Portugal, Russia, Rwanda, South Africa, Spain, Switzerland, Uganda, Ukraine, United Kingdom, Zambia, Zimbabwe Donnell Multicenter Botswana, ART-naïve Initiate ART HIV transmission South Africa, initiating Cohort study Kenya, Botswana, ART-naïve South Africa, with CD4 cell South Africa, initiating Cohort study Kenya, Butter Count 2500			France.	ART	499 cells/ul	
$\begin{tabular}{ c c c c c c c } \hline Greece, Italy, & & & & & & & & & & & & & & & & & & &$			Germany,			
Image: Second state of the second			Greece, Italy,			
Netherlands, Norway, Poland, Portugal, Russia, Rwanda, South Africa, Spain, Switzerland, Uganda, Ukraine, United Kingdom, Zambia, 2010[21] Netherlands, Norway, Poland, Russia, South Africa, Uganda, Ukraine, United Kingdom, Zambia, Zimbabwe Initiate ART Donnell 2010[21] Multicenter cohort study Botswana, Kenya, Kenya, South Africa, South Africa, South Africa, ART-naïve With CD4 cell coll (vs 0-			Kenya, The			
Norway, Poland, Portugal, Russia, Rwanda, South Africa, South Africa, Spain, Switzerland, Uganda, Ukraine, United Kingdom, Zambia, Zimbabwe Initiate ART Donnell Multicenter Botswana, ART-naïve Initiate Study Kenya, HIV-infected with CD4 cell Rwanda, patients count ≥500 South Africa, initiating			Netherlands,			
$\begin{array}{ c c c c c c c c c c c c c c c c c c c$			Norway, Doland			
Image: Portugal, Russia, Russia, Russia, Rwanda, South Africa, Spain, Switzerland, Uganda, Ukraine, United Kingdom, Zambia, Zimbabwe Image: Portugal, Russia, Russia, Russia, South Africa, Spain, Switzerland, Uganda, Ukraine, United Kingdom, Zambia, Zimbabwe Image: Donnell 2010[21] Multicenter cohort study Botswana, Kenya, HIV-infected With CD4 cell Rwanda, patients HIV transmission Image: Donnell 2010[21] Multicenter South Africa, Imitiating Color study South Africa, Imitiating Color study HIV-infected With CD4 cell Color study			Portugal			
Rwanda, Rwanda, South Africa, Spain, Switzerland, Uganda, Uganda, Ukraine, United Kingdom, Zambia, Zimbabwe Donnell Multicenter 2010[21] Cohort study Kenya, HIV-infected with CD4 cell Rwanda, South Africa, initiating South Africa, initiating			Russia.			
$\begin{array}{ c c c c c c c c c c c c c c c c c c c$			Rwanda,			
$\begin{array}{ c c c c c c c c c c c c c c c c c c c$			South Africa,			
Switzerland, Uganda, Ukraine, United Uganda, Ukraine, United United Kingdom, Zambia, Zimbabwe Donnell Multicenter Botswana, ART-naïve Initiate ART HIV transmission 2010[21] cohort study Kenya, HIV-infected Rwanda, patients South Africa, initiating cells/ul (vs 0-			Spain,			
Uganda, Ukraine, United Kingdom, Zambia, Zimbabwe Ukraine, United Kingdom, Zambia, Zimbabwe HIV Donnell Multicenter cohort study Botswana, Kenya, Kenya, South Africa, South Africa, ART-naïve initiate ART with CD4 cell count ≥500 cells/ul (vs 0- HIV transmission			Switzerland,			
Image: Containe, United United United Kingdom, Zambia, Zambia, Zimbabwe Initiate ART Multicenter Botswana, 2010[21] cohort study Kenya, HIV-infected With CD4 cell Rwanda, patients South Africa, initiating cells/ul (vs 0-			Uganda,			
Donnell Multicenter Botswana, ART-naïve Initiate ART HIV transmission 2010[21] cohort study Kenya, HIV-infected with CD4 cell Rwanda, patients count ≥500 South Africa, initiating cells/ul (vs 0-			United			
Zambia, Zimbabwe Zambia, Zimbabwe Donnell Multicenter 2010[21] Cohort study Kenya, HIV-infected Rwanda, patients South Africa, initiating cells/ul (vs 0-			Kingdom.			
Zimbabwe Zimbabwe Donnell Multicenter Botswana, ART-naïve Initiate ART HIV transmission 2010[21] cohort study Kenya, HIV-infected with CD4 cell HIV transmission Rwanda, patients count ≥500 cells/ul (vs 0- Cells/ul (vs 0-			Zambia,			
Donnell 2010[21]Multicenter cohort studyBotswana, Kenya, Rwanda, South Africa,ART-naïve HIV-infectedInitiate ART with CD4 cell count ≥500 cells/ul (vs 0-HIV transmission			Zimbabwe			
$\begin{bmatrix} 2010[21] \\ cohort study \\ Rwanda, \\ South Africa, \\ initiating \\ cells/ul (vs 0-) \\ \end{bmatrix}$	Donnell	Multicenter	Botswana,	ART-naïve	Initiate ART	HIV transmission
Kwanda, patients count ≥500 South Africa, initiating cells/ul (vs 0-	2010[21]	cohort study	Kenya,	HIV-infected	with CD4 cell	
			South Africa.	initiating	cells/ul (vs 0-	

			4.075	400 11 (1)	
		Tanzania,	ART	499 cells/µl)	
		Uganda,			
		Zambia			
Garcia	Cohort study	Spain	ART-naïve	Initiate ART	Disease
2004[34]			HIV-infected	with CD4 cell	progression or
			patients	count ≥ 500	mortality
			initiating	cells/µl (vs 0-	
			ART	499 cells/ul)	
Gras	Multicenter	The	ART-naïve	Initiate ART	None
2007[25]	cohort study	Netherlands	HIV infected	with CD4 cell	rtone
2007[25]	conort study	i vetitei tanus	nationts	count > 500	
			initiating	$count \ge 500$	
			initiating	$\frac{1}{\sqrt{2}}$	
		at i	AKI	499 cells/µl)	
He	Cohort study	China	ART-naïve	Initiate ART	HIV transmission
2013[22]			HIV-infected	with CD4 cell	
			patients	count ≥ 500	
			initiating	cells/µl (vs 0-	
			ART	499 cells/µl)	
HIV-	Meta-analysis	France, The	ART-naïve	Initiate ART	Mortality
CAUSAL	of 12 cohort	Netherlands,	HIV-infected	with CD4 cell	
2010[26]	studies	Spain.	patients	count > 500	
2010[20]	studies	Switzerland	initiating	cells/ul (vs 0-	
		United		$\frac{100}{100}$ cells/ul)	
		Vingdom		499 cclis/μl)	
		Kinguoin,			
		United States			
		of America			
HIV-	Meta-analysis	France, The	ART-naïve	Initiate ART	Mortality, disease
CAUSAL	of 12 cohort	Netherlands,	HIV-infected	with CD4 cell	progression or
2011[27]	studies	Spain,	patients	count ≥500	mortality
		Switzerland,	initiating	cells/µl (vs 0-	
		United	ART	499 cells/µl)	
		Kingdom,		• *	
		United States			
		of America			
HIV-	Meta-analysis	France The	ART-naïve	Initiate ART	Mortality disease
CAUSAI	of 12 cohort	Netherlands	HIV-infected	with CD4 cell	progression or
2015[33]	studies	Spain	natients	count > 500	mortality
2015[55]	studies	Spain,	initiating	$could \leq 500$	mortanty
		Junited		$400 \text{ cells/}\mu (vs 0-$	
		Vinced	AKI	499 cells/µl)	
		Kingdom,			
		United States			
		of America			
Jia	Cohort study	China	ART-naïve	Initiate ART	HIV transmission
2012[31]			HIV-infected	with CD4 cell	
			patients	count >550	
			initiating	cells/µl (vs 0-	
			ART	550 cells/µl)	
Jose	Cohort study	United	ART-naïve	Initiate ART	Any AE, liver AE,
2014[17]		Kingdom	HIV-infected	with CD4 cell	renal AE, blood
		8	natients	count > 500	AE other AE
			initiating	cells/ul (vs ≤ 350	·, ouner ·
				cells/ul)	
Kitahata	Moto opolycic	Canada		Initiato ADT	Mortality
	ivicia-allalysis	Callaua,	AKI-haive	minuate AKI	wortanty
2009[28]		United States	riiv-infected	with CD4 cell	
	studies		patients	count >500	
			initiating	cells/µl (vs 351-	
			ART	500 cells/µl)	
Le	Cohort study	United States	ART-naïve	Initiate ART	None
2013[18]			HIV-infected	with CD4 cell	
			patients	count ≥500	
			initiating	cells/µl (vs 0-	

			ADT	400 as 11 s / 1 s	
		T. 1		499 cells/μl)	D'
Merito	Multicenter	Italy	ARI-naive	Initiate ARI	Disease
2006[29]	cohort study		HIV-infected	with CD4 cell	progression or
			patients	count >500	mortality
			initiating	cells/µl (vs 0-	
			ART	500 cells/µl)	
Okulicz	Cohort study	United States	ART-naïve	Initiate ART	Disease
2015[19]			HIV-infected	with CD4 cell	progression
			patients	count ≥ 500	
			initiating	cells/µl (vs 0-	
			ART	499 cells/µl)	
Palella	Cohort study	United States	ART-naïve	Initiate ART	Mortality
2003[30]	5		HIV-infected	with CD4 cell	5
[]			patients	count 501-750	
			initiating	cells/ul (vs 351-	
			ART	500 cells/ul)	
Schneider	Cohort study	United States	ART-naïve	Initiate ART	None
2013[20]	Conort study	United States	HIV infacted	with CD4 cell	None
2013[20]			notionts	with CD4 ten	
			initiating	count > 500	
			initiating	$\frac{1}{500} = \frac{1}{10} \frac{1}{10} \frac{1}{10}$	
			AKI	500 cells/µl)	
When to Start	Meta-analysis	Australia,	ARI-naive	Initiate ART	Mortality, disease
Consortium	of 18 cohort	Austria,	HIV-infected	with CD4 cell	progression or
2009[35]	studies	Belgium,	patients	count >450	mortality
		Czech	initiating	cells/µl (vs 0-	
		Republic,	ART	450 cells/μl)	
		Denmark,			
		Estonia,			
		France,			
		Germany,			
		Greece,			
		Hungary,			
		Ireland, Israel,			
		Italy, Latvia,			
		Lithuania,			
		Luxembourg.			
		The			
		Netherlands.			
		Norway			
		Poland			
		Portugal			
		Romania			
		Slovakia			
		Snoin			
		Sweden			
		Swettenland			
		Switzerland,			
		Vine 1			
		Kingdom,			
		United States			

Citation: Andrew Anglemyer, George Rutherford, Hacsi Horvath, Marco Vitoria, Margaret Doherty Antiretroviral Therapy for Asymptomatic Adults and Adolescents with HIV-1 Infection and CD4+ T-Cell Counts \geq 500 Cells/MI: A Systematic Review and Meta-Analysis. ARC Journal of AIDS: 38–53.

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