

The secular trend in CD4+ T cell count at initiation of antiretroviral therapy in China

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Abstract

Background: We aimed to look at the trends in CD4 cells counts (at initiation of ART) over calendar years and to investigate its influential factors in Chinese populations.

Methods: We searched PubMed, Wanfang, Chinese Biomedical Literature Database, and China National Knowledge Infrastructure to acquire relevant papers published from January 2002 to Twelve 2015. We abstracted the mean or median CD4+ T cell counts from the included studies. Random-effect meta-regressions were used to estimate the mean CD4+ T cell counts across studies and corresponding 95% CIs.

Results: A total of 220 eligible articles, which included 426283 HIV-positive individuals, were identified in this meta-analysis. The mean CD4+ T cell counts at ART initiation increased from 136.63 (95%CI=120.63–152.63) cells/ μ L in 2003 to 199 (95%CI=188.38–209.62) cells/ μ L in 2014. In the univariate meta-regression model, we found that the estimated change in CD4+ T cell counts at ART initiation was +8.73 cells/ μ L per year (95% CI= 4.57 to 12.90 cells/ μ L per year). The highest CD4+ T cell counts at ART initiation (441.00 cells/ μ L, 95% CI=438.96-186.33 cells/ μ L) was reported in serodiscordant couples, followed by pregnant women (385.82 cells/ μ L, 95% CI=327.19-444.44 cells/ μ L), MSM (293.78, 95% CI=126.59-460.96 cells/ μ L), and children 267.36 cells/ μ L, 95% CI=126.65-408.07 cells/ μ L.

Conclusions: In China, the CD4+ T cell counts at ART initiation have dramatically increased during the past decade. However, there remains a substantial gap between CD4+ T cell counts at ART initiation and the WHO updated HIV treatment guidelines in some groups, highlighting the need for strategies to improve earlier ART initiation.

Background

By the end of 2014, there were about 500 000 HIV/AIDS patients and 160 000 deaths had been reported in China, and the reported patients continued to increase[1]. Although the HIV/AIDS epidemic remains a low-prevalence trend as a whole, the people living with HIV/AIDS have concentrated in some high-risk groups in China. In 2010 an estimated 9.08% of injecting drug users and 5.98% of men who have sex with men(MSM) were infected with HIV[2].

Antiretroviral therapy (ART) has greatly reduced HIV-attributable mortality and morbidity and improved the quality of life of HIV-infected patients. Evidence also indicates that ART is the most effective prevention strategy, which can effectively reduce the likelihood of transmitting HIV to others[3], 'Treatment as prevention' has been proposed because recent evidence has demonstrated that expanded ART coverage among HIV-infected individuals was associated with lower transmission rates at a population level[4].

Early initiation of ART with a higher CD4 cell counts (> 500 cells/ μ L) is a good predictor of successful ART. In 2015, the Strategic Timing of AntiRetroviral Treatment (START) trial was stopped early because

the results showed that risk of developing serious illness or death was reduced by 53% due to the early initiation of ART [5]. Another randomized clinical trial had also reported a reduction in the hazard of death, AIDS, or a serious clinical condition of 40% if they start taking antiretroviral drugs earlier [6]. On the basis of these evidences, World Health Organization (WHO) has recently issued new ART guidance which recommends starting ART in HIV-positive adults with a CD4 + T cell counts ≤ 500 cells/ μL [7].

In 2014, the Chinese government also adjusted the criteria for initiation ART of adults and children living HIV/AIDS, so ART can now be initiated at CD4 cell counts of 500 cells per μL or less [1]. However, despite these changes in worldwide clinical guidance, CD4 + T cell counts at ART initiation in sub-Saharan Africa and developed countries have not appreciably increased during the past decade [8, 9]. Although ART has been rapidly scaled up in Asia, to our knowledge no systematic review has assessed temporal trends of the CD4 + T cell counts at ART initiation in Asian country. We aimed to look at the trends in CD4 cells counts (at initiation of ART) over calendar years in China.

Method

Search Strategy and Selection Criteria

We searched PubMed, Wanfang, Chinese Biomedical Literature Database, and China National Knowledge Infrastructure to acquire relevant papers published from January 2002 to December 2015. The following detail search strategy was used: (HIV, "human immune*", "acquired immunodeficiency syndrome", AIDS) and (China, Chinese) and (ART, HAART, "antiretroviral*", CD4, "CD4 cell count", "T cell"). In addition to database searches, we also screened the references of the selected paper to identify any additional articles. No language restrictions were the whole process of database searches. We chose 2002 as the beginning year for database searches because it was the first year of published WHO guidelines for ART.

The studies that (1) focused on Chinese people living with HIV/AIDS; (2) reported a summary measure of CD4+ T cell counts at ART initiation; and (3) published during 2002–2015, were eligible. We excluded reviews, meeting reports and news articles. We excluded studies that did not report original CD4+ T cell counts data, had fewer than 30 participants, or with a pre-specified CD4+ T cell counts range for inclusion. We also excluded the studies that only reported the number or proportion of patients with CD4 cell counts in particular ranges. When one study presented results of multiple years, we treated them as different computed yeas.

Study Selection and Data Extraction

The titles and abstracts of the retrieved papers were carefully screened by two of us (W.M., Z.H.). One author searched the database and deleted the unavailable papers, and then another author checked the accuracy. When disagreements occurred between these two authors, a third author (H.Z.H.) was invited and a seminar was hold to discuss and resolve the disagreements. All data were extracted and filled using a data abstraction form that developed by us. Characteristics of studies (authors, years, design,

regions, population), data type, number of intervals, average interval length (years), and CD4+ T cell counts at initiation (cells/ μ L) were extracted.

Data type was divided according to the sources of data, and the sources of data included the data from national free antiretroviral treatment program (NFATP), the data from prevention of mother-to-child transmission (PMTCT) program, the data from clinical trial, and the data from descriptive study.

The study region was categorized to eastern China, north China, northeast China, northwest China, southwestern China, and south-central China. The income level was divided into low income, low-middle income, high-middle income, and high income based on the gross domestic product per individual in 2013 in China[10, 11].

We abstracted the mean CD4 cell counts from every include paper. When the mean value was unavailable, we would reconstruct mean value or use median value. We abstracted the imputed study years using the method described previously by Siedner MJ et al.. We treated the first years of data collection as the imputed year if the last years was unavailable, and we treated 2 years before the publication year as the imputed year when the first and the last years both were unavailable[8].

Quality Assessment

Because of the majority of included study were descriptive epidemiologic studies, we used the Agency of Healthcare Research and Quality (AHRQ) assessment to assess the study quality. The total score of the AHRQ is 11, and the score from 0 to 3 was assessed as low quality, the score from 4 to 7 was assessed as moderate quality, and the score from 8 to 11 was assessed as high quality[12].

Statistical Analysis

Random-effect model was used to estimate the mean CD4+ T cell counts across studies and its 95% *CIs* because that it is more conservative and provide better estimates with wider confidence[13]. The I^2 (and its 95% *CIs*) and tau-square were used to assess the between-study heterogeneity, and the I^2 was used to assess the within-study heterogeneity [14, 15]. The following subgroup analyses were performed: economic level (high income, high-middle income, low-middle income, low income), study regions (eastern China, mid-southern China, northeast China, northern China, northwest China, southwestern China, and multi-regions), imputed year (from 2003 to 2014), years spanned by data collection (0-3 years, 4-5 years, ≥ 6 years), data type (Chinese NFATP, clinical data, descriptive study, national PMTCT program), populations (children, elderly patients, general population, injection drug users, MSM, pregnant women, and serodiscordant couples), and sample size (≤ 100 and ≥ 100).

Some sensitivity analyses were performed to assess the robustness of the outcome, for example re-performed all primary analyses using fixed effect model, and re-performed all primary analyses after excluding studies with fewer than 50 participants. We also re-performed all primary analyses including

studies reporting data that spanned ≤ 5 years only, because study with long-term data might easily produce bias. We performed all analyses using Stata software (version 13.0).

Results

Characteristics of included studies

We identified 8292 articles from database searches and 68 additional articles through screening the references of the retrieved articles. During the titles and abstracts screening, 5550 articles were excluded, leaving 382 full-text articles to be assessed for eligibility. Finally, we included 220 articles in this meta-analysis (Supplementary Appendix Table 1). Figure 1 notes the process of selecting articles.

Table 1 noted the characters of the included articles. The included articles spanned all of Chinese provinces, and the majority of articles were conducted in mid-southern china ($n=80$, 36.36%), followed by eastern China ($n=41$, 18.64%), northern China ($n=40$, 18.18%), and south-western China ($n=38$, 17.271%). Approximately half of the articles ($n=103$, 46.82%) included data spanning ≤ 3 years, whereas 41 (18.64%) articles spanned 4- 5 years, and 76 (34.55%) articles spanned ≥ 6 years.

The estimated CD4+ T cell counts at ART initiation

A total of 220 studies, which included 426283 HIV-positive individuals, reported CD4+ T cell counts at initiation of ART, and the mean CD4+ T cell counts at ART initiation was 177.82 (95%CI=169.28–186.35) cells/ μ L; however, high levels of heterogeneity were observed between studies ($I^2=99.85\%$, 95%CI=99.85%-99.86%)(Table 1). The mean CD4+ T cell counts at ART initiation was 136.63 (95%CI=120.63–152.63) cells/ μ L in 2003 and 199 (95%CI=188.38–209.62) cells/ μ L in 2014 (Table 2).

A total of 38 studies reported CD4+ T cell counts at ART initiation in south-western China, which reported the highest mean CD4+ T cell counts at ART initiation (224.99 cells/ μ L, 95%CI=213.25-236.73 cells/ μ L) (Table 1). The variation of mean CD4+ T cell counts between different Chinese provinces is noted in Figure 2.

There was significant difference on the mean CD4+ T cell counts at ART initiation between different groups, and serodiscordant couples, pregnant women, MSM, and children were detected higher CD4+ T cell counts at ART initiation. Only one study, which included 38 862 serodiscordant couples, reported the highest CD4+ T cell counts at ART initiation (441.00 cells/ μ L, 95% CI=438.96-186.33 cells/ μ L), followed by pregnant women (385.82 cells/ μ L, 95% CI=327.19-444.44 cells/ μ L), MSM (293.78, 95% CI=126.59-460.96 cells/ μ L), and children 267.36 cells/ μ L, 95% CI=126.65-408.07 cells/ μ L (Table 1).

Meta-regression analyses of temporal trend in CD4+ T cell counts at ART initiation

In the univariate meta-regression model, we found that the estimated change in CD4 cell counts at ART initiation was +8.73 cells/ μ L per year (95% CI= 4.57 to 12.90 cells/ μ L per year). Adjusting for study

regions, study populations, data type, and average interval length did not significantly modify the estimated annual change in CD4 cell counts (+7.46 cells/ μ L, 95% CI=3.64 to 11.29 cells/ μ L) (Table 2).

The subgroup analyses were noted in Table 2. In the subgroup of only Chinese NFATP data, we found the highest increase in CD4 cell counts at ART initiation per year (+10 cells/ μ L, 95% CI= 4.17-15.82 cells/ μ L). While, in the subgroup of only clinical data, we found the lowest increase in CD4 cell counts at ART initiation per year (+6.64 cells/ μ L, 95% CI= 0.38-12.90 cells/ μ L).

Sensitivity Analyses

Sensitivity analyses did not result in substantive changes to our findings (Table 2). Exclusion of studies that with fewer than 50 participants yielded a similar estimate of the trend (+8.47 cells/ μ L, 95% CI= 4.04-12.89 cells/ μ L). Exclusion of studies that reporting >5 years of data also yielded a similar estimate of the trend (+8.23 cells/ μ L, 95% CI= 3.24-13.21 cells/ μ L).

Evaluation of Publication Bias

We generated funnel plots and visually examined the asymmetry of these funnel plots. For total sample, the asymmetry observed in the funnel plots was minimal. We also assessed the asymmetry funnel plot using the Egger's linear regression test and Begg's test, and the results noted that there were no significant publication bias across all outcomes.

Discussion

Our analyses presented that the mean CD4+ T cell counts at ART initiation was increased from 136.63 cells/ μ L in 2003 to 199 cells/ μ L in 2014, and the estimated change in CD4+ T cell counts at ART initiation was +8.73 cells/ μ L per year. However, CD4+ T cell counts at ART initiation remained below present treatment guidelines in general population and elder patients. Moreover, remarkable variation between regions was found in our analyses. We therefore argue that greater resources should be focused on earlier ART initiation, especially in the groups that with low CD4+ T cell counts at ART initiation. The results of this meta-analysis were robust due to a large number of include papers and numerous sensitivity analyses.

Recent published meta-analysis in developed country and sub-Saharan Africa both reported that CD4+ T cell counts at ART initiation have not increased over the past decade[8, 9]. On the contrary, our study showed substantial improvements in the mean CD4+ T cell counts at ART initiation during the past decade in China. The temporal trend observed in our study could mainly be explained by the change of national guidelines on HIV treatment. According to the first guidelines for ART released by WHO, the Chinese government initiated National Free Antiretroviral Treatment Program (NFATP) in 2002, and recommended that all persons with CD4+ T cell counts \leq 200 cells/ μ L should initiate ART. In 2010, the new WHO guidelines recommended increasing eligibility to 350 cells/ μ L, therefore we observed remarkably increase in CD4+ T cell counts at ART initiation after 2010. The change of ART guidelines

dramatically altering the trajectory of temporal trends observed over the last decades in China[16]. However, any evidence for increasing CD4+ T cell counts at ART initiation during from 2011 to 2014 was not observed, when the most recent updated HIV treatment guidelines recommended increasing eligibility to 500 cells/ μ L[17].

These results reinforce a critical challenge to achieving the goal of eliminating HIV/AIDS, despite remarkable increases in CD4+ T cell counts at ART initiation in China in the past decade, because there remains a substantial gap between CD4+ T cell counts at ART initiation and the WHO most recent updated HIV treatment guidelines. Our study revealed the fact that many general patients are still initiating ART at low CD4 cell counts, and realizing the goal of eliminating HIV/AIDS would largely depend on identification and treatment of the remaining eligible people living with HIV/AIDS who are not receiving ART.

A very interesting finding in our study was that higher CD4 cell counts at ART initiation were reported in serodiscordant couples and pregnant women. According to the recent updated Chinese guidelines, ART should be initiated for all HIV-positive pregnant women and serodiscordant couples irrespective of CD4 cell count, which may be the main reason that CD4 cell counts at ART initiation were significant higher in serodiscordant couples and pregnant women than that in other groups[18]. In China, nationwide PMTCT of HIV program was incorporated into child health-care system or antenatal care (ANC) services, which could provide the effective test-and-treat strategies for all HIV-infected pregnant women and partially promote early ART initiation[19]. Recent meta-analyses observed an estimate of nearly 80% of Chinese pregnant women who had 100% ART adherence and HIV vertical transmission rate substantially decreased from 31.8% prior to the program to 2.3% in 2011 due to the Chinese government investing in integrated PMTCT[20, 21]. Despite earlier ART initiation can improve individual patient survival, decrease the risk of spread of HIV/AIDS, and lower the burden of the healthcare system, successful scale-up of the new updated treatment guideline remains a major constraint in China due to funding gaps, poor infrastructure, weak health systems and shortage of health manpower, among other challenges. Therefore, exploring additional resources and strategies to promote the implementation of the new updated ART guideline in China were needed [22, 23].

Our study had some limitations. First, all included articles in this meta-analysis were published articles. Published articles may be more likely to be based on data from centers partnering with academic or research institutions, which often provide additional financial resources and/or health infrastructure for study sites. Second, a high heterogeneity was observed between studies. Although we performed subgroup analyses by income, regions, years, years spanned by data collection, data type, populations, and sample size, and these factors may be the sources of between-study heterogeneity. However, other unmeasured factors likely affected the detected heterogeneity; unfortunately, we did not obtain sufficient information about these aspects for further analysis. The last, the number of studies in pregnant women and serodiscordant couples was too small, so the results would be interpreted with caution.

Conclusion

In summary, due to the new WHO guidelines recommendation that increasing eligibility to 350 cells/ μ L in 2010, the CD4+ T cell counts at ART initiation have appreciably increased in the past decade. However, there remained a substantial gap between CD4+ T cell counts at ART initiation and the WHO most recent updated HIV treatment guidelines in some groups.

Abbreviations

ART : Antiretroviral therapy; MSM Men who have sex with men; START: Strategic Timing of AntiRetroviral Treatment; WHO : World Health Organization; NFATP: national free antiretroviral treatment program; PMTCT : prevention of mother-to-child transmission; AHRQ: Agency of Healthcare Research and Quality; ANC: antenatal care.

Declarations

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Availability of data and materials

The dataset supporting the conclusion of this article is included within the article and its additional files.

Contributors

Z.-H. and X.-J. conceived and designed the study. X.-Y.Q., L.-B., and L.-L. searched the papers and extracted the data. P.-W., W.-S.Y., and Z.-M. analyzed the data. Z.-H. wrote the article. G.-H.Q. contributed to conceptualization and provided scientific advice of the study.

Competing interest

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

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Tables

Table 1 Summary of articles and population included in meta-analysis to estimate trends in CD4 count in china during 2003–2014

Characteristic	Articles, No. (%)	Sample Size, No. (%)	CD4 Count, Cells/ μ L, Mean (95%CI)
Total sample	220 (100%)	426283(100%)	177.82 (169.28 to 186.35)
GDP (in \$US per head)\$			
High income (>10915)	53(24.09%)	41157(9.65%)	177.34(162.20 to 192.47)
High-middle income (6892-9961)	58(26.36%)	20117(4.72%)	148.72(133.14 to 164.31)
Low-middle income (5635-6750)	18(8.18%)	215672(50.56%)	171.50(127.23 to 215.77)
Low income (<5520)	91(41.36%)	149337(35.03%)	177.81 (169.29 to 186.33)
Region			
Eastern China	41(18.64%)	35712 (8.38%)	164.34(144.17 to 184.50)
Mid-southern China	80(36.36%)	84835(19.90%)	165.26(153.26 to 177.26)
Northeast China	1(0.45%)	101(0.023%)	161.43(149.53 to 173.33)
Northern China	40(18.18%)	14167(3.32%)	163.93(150.98 to 176.87)
Northwest China	6(2.72%)	2600(0.61%)	177.42 (94.78 to 260.05)
Southwestern China	38(17.27%)	73488(17.24%)	224.99(213.25 to 236.73)
Multi-regions	14(6.36%)	215380(50.23%)	184.70(133.32 to 236.09)
Imputed year			
2003	10(4.27%)	11620(0.17%)	136.63(120.63 to 152.63)
2004	9(3.85%)	17110(0.25%)	132.23(84.65 to 179.82)
2005	17(7.26%)	115900(16.98%)	136.03(130.82 to 141.25)
2006	26(11.11%)	53810(0.79%)	137.20(121.70 to 152.71)
2007	39(16.67%)	202380(29.65%)	185.17(153.73 to 216.60)
2008	37(15.81%)	173815(25.46%)	169.23(158.83 to 179.62)
2009	40(17.09%)	146611(21.48%)	169.08(161.01 to 177.15)
2010	16(6.84%)	87830(1.29%)	209.71(196.17 to 223.25)
2011	20(8.55%)	14944(2.19%)	218.65(166.64 to 270.67)
2012	14(5.98%)	44310(0.65%)	190.99(158.42 to 223.55)
2013	5(2.14%)	70270(1.03%)	212.23(197.29 to 227.16)
2014	1(0.43%)	4600(0.07%)	199.00(188.38 to 209.62)
Years spanned by data collection (years)			
0-3	103(46.82%)	144740(33.95%)	185.23(176.14 to 194.33)
4-5	41(18.64%)	14275(3.35%)	173.50(143.70 to 203.30)
≥ 6	76(34.55%)	267268(62.70%)	177.81(169.29 to 186.33)
Data Type			
Chinese NFATP	96(43.64%)	391628(91.87%)	168.87(154.75 to 182.99)
Clinical data	104(47.27%)	30744(7.21%)	181.17(171.25 to 191.08)
Descriptive study	16(7.27%)	2483(0.58%)	154.92(123.70 to 186.14)
National PMTCT program	4(1.82%)	1428(0.33%)	370.05(333.63 to 406.47)
Populations			
Children	7(3.18%)	418(0.10%)	267.36(126.65 to 408.07)
Eldly patients	3(1.36%)	247(0.06%)	158.09(145.60 to 170.57)

General population	195(88.64%)	382495(89.73%)	166.91(160.96 to 172.85)
Injection drug users	6(2.73%)	776(0.18%)	173.41(139.34 to 207.48)
MSM	3(1.36%)	2007(0.47%)	293.78(126.59 to 460.96)
Pregnant women	5(2.27%)	1478(0.35%)	385.82(327.19 to 444.44)
Serodiscordant couples	1(0.45%)	38862(9.12%)	441.00(438.96 to 186.33)
Sample size			
≤100	78(35.45%)	4740(1.11%)	182.27(160.45 to 204.09)
≥100	142(64.55%)	421543(98.89%)	176.55(166.35 to 186.74)

Note: \$ Income level is divided to high income (>10915), high-middle income (6892-9961), low-middle income, low income (<5520) according to GDP (in \$US per head); PMTCT, prevention of mother-to-child transmission;NFATP,national free antiretroviral treatment program

Table 2. Random-effects meta-regression models estimating trends in CD4 count at time of antiretroviral therapy initiation—china, 2003–2014

Model	Studies	Initiation of Antiretroviral Therapy Change in CD4 Count (Cells/ μ L) per y	95% Confidence Interval	P Value
Primary analyses (unadjusted)	237	8.73	4.57 to 12.90	<0.001
Primary analyses (adjusted)#	237	7.46	3.64 to 11.29	<0.001
Subgroup analyses				
Multi-regions studies excluded	222	9.1	4.81 to 13.19	<0.001
Multi-regions studies only	14	15.16	-22.80 to 53.11	0.401
Pregant women excluded	231	7.67	3.74 to 11.60	<0.001
Serodiscordant couples and pregnant women excluded	230	7.87	4.08 to 11.67	<0.001
General population only	211	8.9	5.47 to 12.33	<0.001
National PMTCT program studies excluded	232	8.23	4.22 to 12.23	<0.001
Chinese NFATP only	107	10	4.17 to 15.82	<0.001
Clinical data only	109	6.64	0.38 to 12.90	0.038
Descriptive study only	16	9.8	-3.32 to 22.91	0.131
Sensitivity analyses				
Excluded studies >5 years	160	8.23	3.24 to 13.21	<0.001
Excluded studies with fewer than 50 participants	205	8.47	4.04 to 12.89	<0.001

Abbreviations: CI, confidence interval; PMTCT, prevention of mother-to-child transmission;NFATP,national free antiretroviral treatment program.

adjusted by regions,populations, data type, and average interval length

Figures

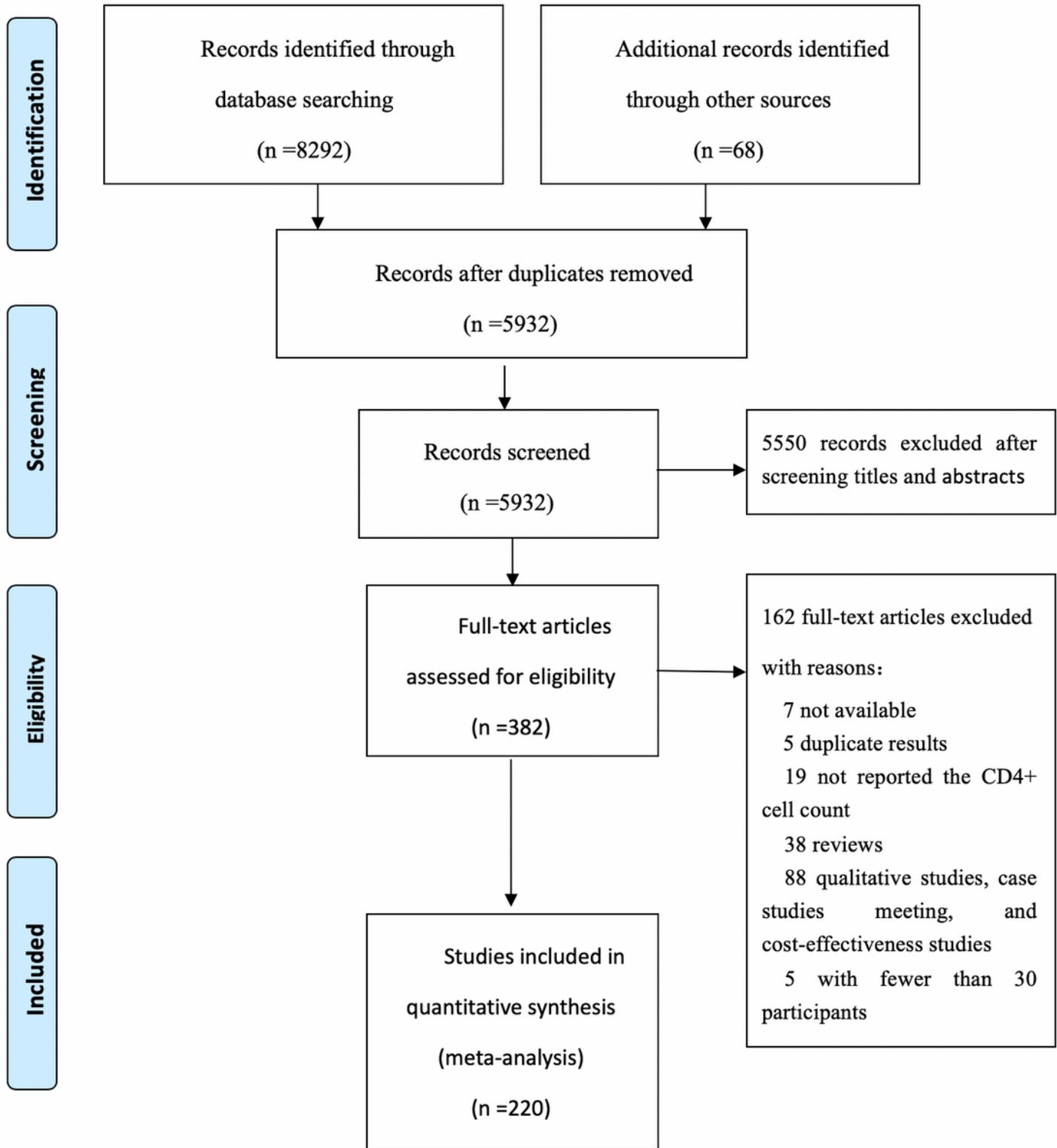


Figure 1

Prisma 2009 Flow diagram literature search and study selection. PRISMA diagram showing the different steps of systematic review, starting from literature search to study selection and exclusion. At each step, the reasons for exclusion are indicated. doi:10.1371/journal.pone.0052562.g001

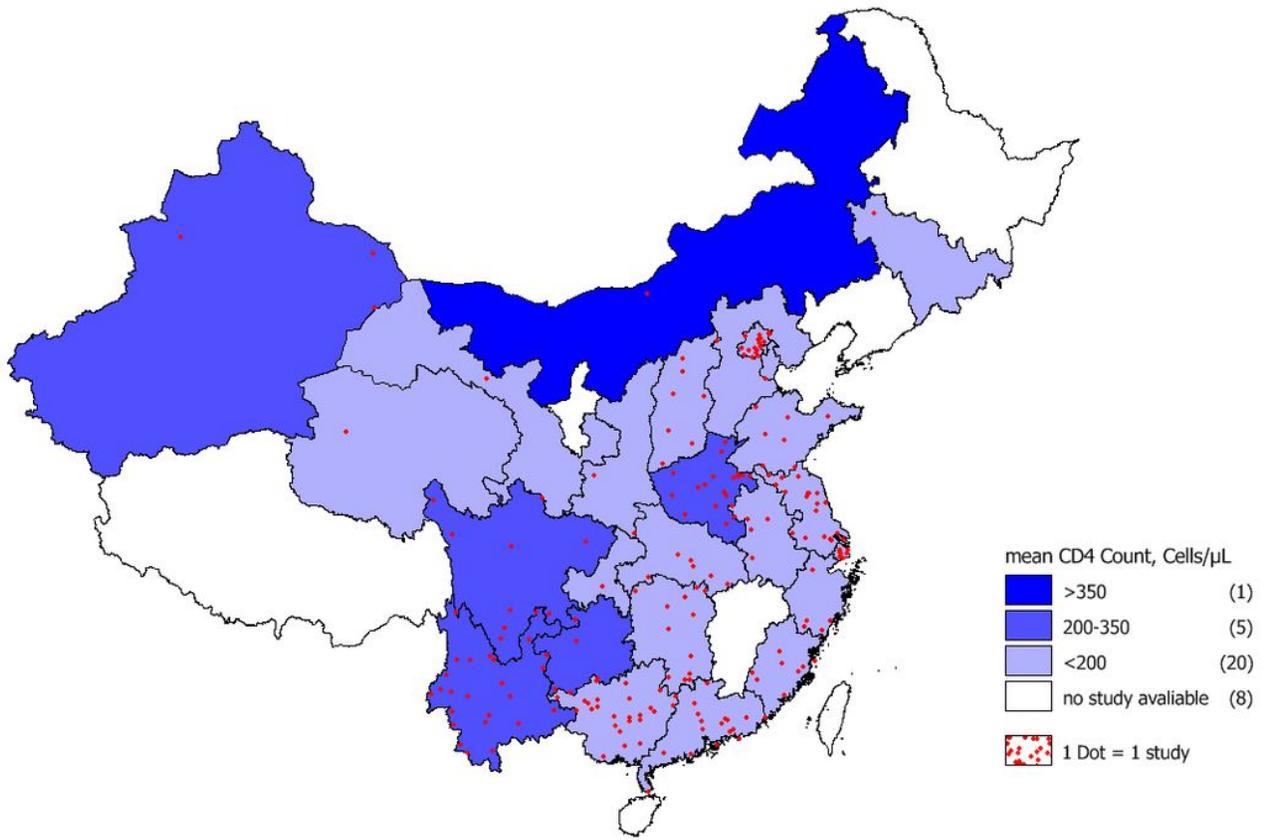


Figure 2

The regional disparity of mean CD4+ T cell counts. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

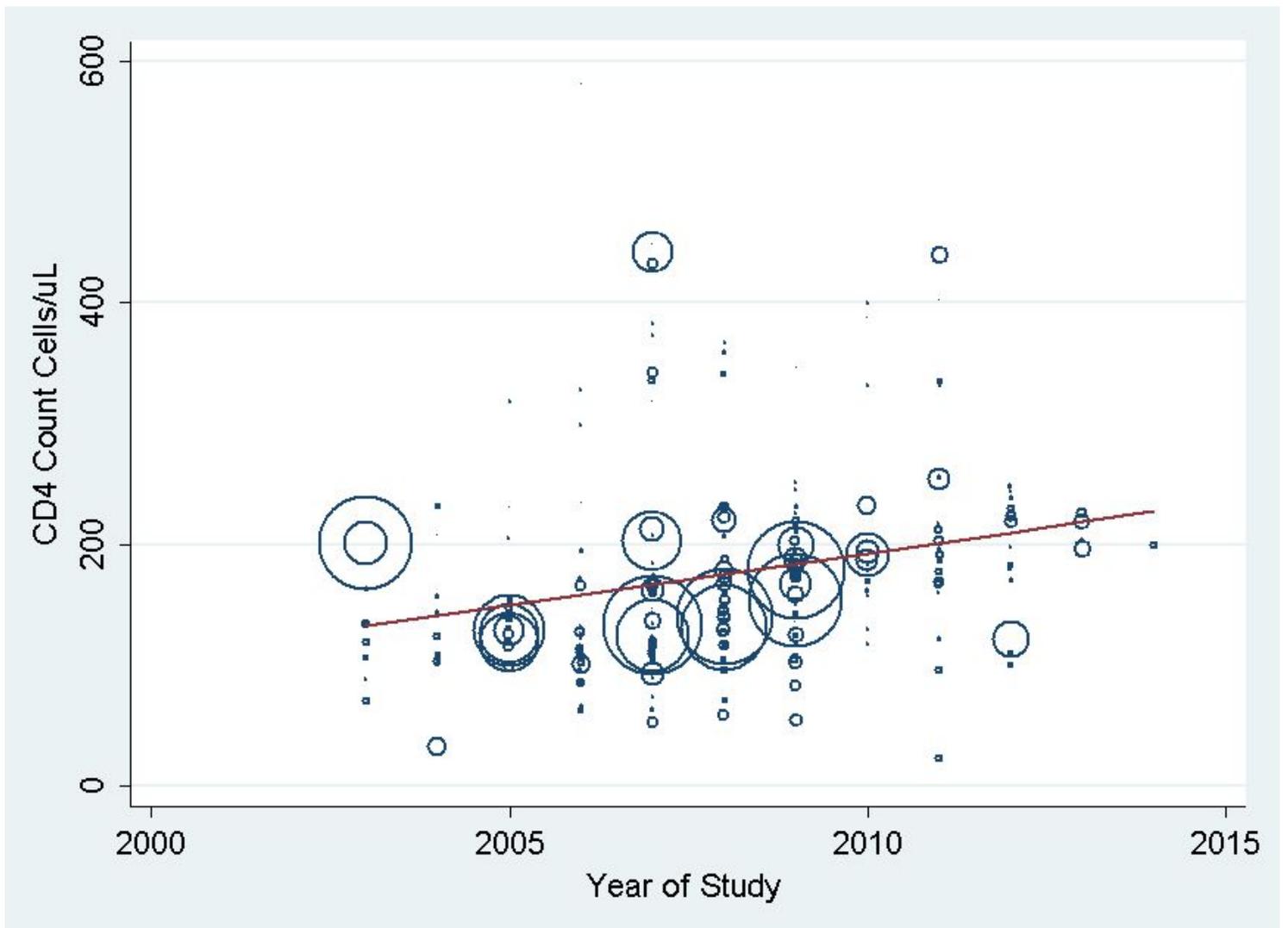


Figure 3

Temporal trends in CD4 count initiation of antiretroviral therapy (B) in China during 2003–2014.

Supplementary Files

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