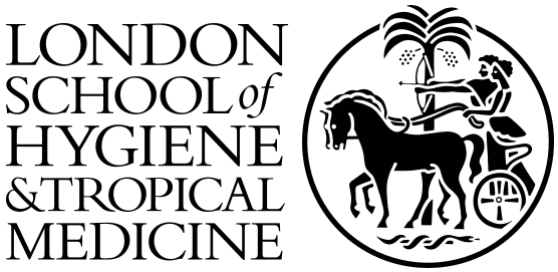

Point of care HbA1c for diabetes management and its accuracy among TB patients: a study in four countries

Running title: PoC/Lab HbA1c screening among TB patients

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Summary

Background

Diabetes (DM) is common among tuberculosis (TB) patients and often undiagnosed or poorly controlled. We compared point of care (POC) with laboratory glycated haemoglobin (HbA1c) tests among newly diagnosed TB patients to assess POC test accuracy, safety, and acceptability in settings where immediate access to DM services may be difficult.

Methods

We measured POC and accredited laboratory HbA1c (HPLC method) in 1942 TB patients aged over 18, recruited from Peru, Romania, Indonesia, and South Africa. We calculated overall agreement and individual variation (mean ± 2 standard deviations); stratified by country, age, sex, body mass index (BMI), HbA1c level and comorbidities (anaemia, human immunodeficiency virus (HIV)). We used an error grid approach to identify disagreement that could raise significant concerns.

Results

Overall mean POC HbA1c values were modestly greater than laboratory HbA1c by 0.14% units (95% confidence intervals 0.11 to 0.18), but there was a substantial discrepancy for those with severe anaemia (1.07% HbA1c, 95%CI 0.67 to 1.46). For 89.6% of 1942 patients, both values indicated the same DM status (no DM; HbA1c <6.5%) or had acceptable deviation (relative difference <6%). Individual agreement was variable, with POC values up to 1.84% units higher or 1.56% lower. For a minority, use of POC HbA1c alone could result in error leading to potential over-treatment (n=40, 2.1%) or under treatment (n=1, 0.05%). The remainder had moderate disagreement, less likely to influence clinical decisions.

Conclusion

POC HbA1c is pragmatic and sufficiently accurate to screen for hyperglycaemia and DM risk among TB patients.

Introduction

Globally, there is a high prevalence of diabetes (DM) among newly diagnosed tuberculosis (TB) patients, with estimated prevalence ranging from around 5-50% in different settings[1-7]. TB-DM patients have been shown to have higher early mortality rates (death within 100 days of starting TB treatment)[8] and worse TB treatment outcomes[9, 10]. They are also likely to have poor control of their DM during TB treatment, possibly because of hypoglycaemic or hyperglycaemic effects of anti-TB chemotherapy[2], potential drug interactions and stress hyperglycaemia due to TB disease itself[2]. For these reasons, it is important to diagnose DM early on in TB treatment, and to assess the adequacy of glycaemic control, but this can be logistically difficult in low and middle income countries where TB-DM incidence is expected to be the highest. WHO and several countries have made recommendations to screen all TB patients for DM[11-13], but the optimal ways of achieving this in different settings have not been established[14].

The gold standard test for DM diagnosis is considered to be the Oral Glucose Tolerance Test (OGTT) as it is the most sensitive test available[15, 16]. However, in practice fasting plasma glucose (FPG) and glycated haemoglobin (HbA1c) (both acceptable for diagnosis) are more often used due to their convenience[17]. Urinary glucose tests and DM risk scores are cheaper alternatives used to identify DM status but both have lower sensitivity, and are not recommended for diagnosis[18-20].

HbA1c has been used widely to monitor DM control since the 1980s[21, 22] but it was only recommended as a diagnostic test for DM in 2011 by WHO[23]. Acceptance of HbA1c as a diagnostic test was delayed due to concerns about standardisation of HbA1c methods and assays internationally[24], and quality assurance[25, 26]. WHO therefore recommends the use of HbA1c for diagnosis of DM only when strict quality assurance measures are in place[23]. Only laboratories and manufacturers aligned to the "National Glycohemoglobin Standardization Program" (NGSP) or International Federation of Clinical Chemists (IFCC) laboratory networks and reference methods[27] are accredited to diagnose DM using HbA1c. Nevertheless, the HbA1c test has very important practical advantages, particularly as there is no need for fasting. A POC HbA1c test can be performed with limited facilities and space, being based on a single finger-prick (capillary) blood sample, which is then applied to a cartridge, and inserted into a desktop analyser; HbA1c is quantified and reported within just a few minutes. Therefore, POC HbA1c test could be administered by trained health care workers instead of relying on the presence of health care professionals, which would be beneficial for settings with limited personnel resources (e.g. nurse-led centres). Due to their practical advantages POC tests are becoming more widely used in TB clinics[7, 28, 29], both to screen patients for undiagnosed DM, and to identify those with poorly controlled DM who may require further management. However, to

our knowledge DM diagnosis using POC HbA1c has not yet been recommended by WHO or any regulatory bodies, and the implications of using POC tests, compared with laboratory alternatives, have not been extensively explored, particularly not among TB patients.

A recent review among DM individuals showed very high levels of agreement (correlation coefficient, 0.967; 95% CI 0.960–0.973) between laboratory and POC HbA1c[30]; however, included studies mostly took place with industry involvement, or were carried out under "optimal" conditions. Another review[31] among 60 studies comparing the performance of POC devices to laboratory testing in HbA1c showed a negative mean bias in pooled results (i.e. POC HbA1c < laboratory HbA1c) although with large variabilities between devices; but studies included were not restricted to specific participants' characteristics (e.g. people with or without co-morbidities). In this article, we explored the agreement between POC and laboratory HbA1c results among TB patients from four middle income countries[32]. We also assessed the field worker's perceptions of the ease of use and acceptability of each test, adapting a protocol previously set out for this purpose[33].

Method

Study overview and population

The TANDEM study was a multi-centred international study designed to identify optimal ways to screen and manage DM in TB patients[32]. Baseline screening was conducted between 2013 and 2017 in four countries: Indonesia, Peru, South Africa, and Romania. Participants aged 18 years or older were included if they were recruited within 72 hours of pulmonary TB treatment initiation. We included either newly diagnosed or previously treated cases, regardless of their HIV status. Appendices 1-2 showed further details of the sites and recruitment methods. For this study we included individuals with both a laboratory and POC HbA1c result regardless their DM status at the time of testing.

Measurements

POC HbA1c (analysed using Hemocue® HbA1c 501 Analyser)[34] was collected during the participants' clinic visits, and within 72 hours after TB diagnosis. In Romania, HemoCue® was not available so the QuoTest[35] HbA1c Analyser QTD (by EKF Diagnostics) was substituted for Hemocue®. Laboratory HbA1c was estimated from venous blood sample collection taken at the same time as the POC test. All laboratory HbA1c samples were analysed using the HPLC method as per WHO guidelines and were carried out in an accredited laboratory with NGSP certification[36].

Consent and ethical approval

All patients gave written informed consent. The study was approved by the Research Ethics Committee, London School of Hygiene & Tropical Medicine (LSHTM ethics ref: 6449, LSHTM amendment no: A473). Ethical permissions were also received from relevant local and/or national research committees.

Analyses

We compared the mean and 95% Confidence Intervals (CI) for HbA1c from POC and laboratory sources in the whole sample using paired t tests. We further explored the mean differences in subgroups stratifying by variables that could potentially affect HbA1c level, these variables include country (Indonesia, Peru, South Africa, and Romania), age group (<30 years, 30-39 years, 40-49 years, 50-59 years, and ≥60 years), sex (male or female), BMI (<18.5 kg/m^2, 18.5-24.9 kg/m^2, 25.0-29.9 kg/m^2, ≥30.0 kg/m^2)[37], anaemia (non-anaemia, mild anaemia, moderate anaemia, and severe anaemia, based on standard WHO definitions for men and women separately)[38], and HIV status (HIV positive or negative). We calculated robust standard errors to account for the clustering of data within four countries in our study. We also compared POC and laboratory HbA1c levels within different laboratory HbA1c ranges to explore whether the agreement between the two measures varied between specific HbA1c ranges (<5.7%, 5.7-6.4%, 6.5-8.9%, ≥9%). These ranges were chosen based on American Diabetes Association criteria[39]; they defined "pre-diabetes" as an HbA1c measurement between 5.70% and 6.49%). The cut-point of 9% for severe uncontrolled DM was based on the upcoming WHO guidelines and on previous research[40]. The intra-individual differences (mean ± 2 standard deviations i.e. range of agreement within which 95% of patients fall) were also calculated across subgroups, and Bland-Altman plots of agreement were produced for the whole sample and for all subgroups. We explored whether any key covariates (age group, sex, country, BMI level, laboratory HbA1c level, anaemia, and HIV status) could explain individual differences between the POC and laboratory values by running linear regression models with the unit difference between the two tests as the outcome, separately for each covariate. We also examined the overall differences across all levels for each covariate with over two categories using Wald test. Statistical analyses were performed using STATA version 12.0[41].

A priori, we determined that an acceptable level of agreement would be one that resulted in the same categorisation (DM, yes or no) and / or had a relative difference of less than 6%, chosen based on NGSP criteria of acceptable performance limits for manufacturers' methods[42]. An "error grid" was completed to assess the clinical relevance of findings, taking into account that the clinical importance of any particular difference in HbA1c, depends on the absolute levels of both values, and not simply the percentage or absolute difference[40, 43, 44]. We explored agreement across the standard

diagnostic cut-point (6.5%), and also at a threshold previously used for “severe uncontrolled” DM (9%)[40].

To assess the operational feasibility of implementing the tests in settings where TB patients were being treated, structured questionnaires were administered to nine health care workers performing the POC test and collecting blood for the laboratory HbA1c tests in Indonesia (n=5), Peru (n=3) and South Africa (n=1) at the start and end of the study. The tests were assessed for user-friendliness, self-reported training and performance time, acceptability by health care workers, perceived patient acceptability (possible reasons for non-compliance or unwillingness to have tests performed), sample and equipment quality, logistics of performing tests and reporting results, and perceived appropriateness. These domains were derived by adapting and expanding a previously developed scale that evaluated the characteristics of manual haemoglobin techniques alongside a reference method in Malawi[33]. The questionnaires were delivered by face to face interview with health care workers in all study countries[33].

Response options included a five-point Likert scale (strongly agree to strongly disagree) for user friendliness and several other approaches for all the domains. These included open-ended responses as well as closed-ended categorical options for agreement (yes/no), or frequency (never/only when outside normal range, always), and completing numeric values for predetermined units of quantity and time. Participant responses were entered into Excel (Microsoft Corporation, Redwood, WA, USA), where proportions and measures of central tendency were calculated for quantitative data. Thematic analysis was performed for open text responses by creating codes for the text. The coded text was arranged into categories, which were them used to generate themes that were incorporated into the existing domains. No internal consistency of questions was performed. All health care workers performing the DM tests in the TANDEM study were approached to participate in the operational feasibility study. At the start of the study all 14 health care workers participated, but at the end of the study the questionnaires were only administered to nine health care workers (64% response) due to some staff having already moved to other jobs.

Results

Out of 2345 TB patients, 1942 (734 from Indonesia, 542 from Peru, 416 from Romania, and 250 from South Africa) had both a baseline POC and laboratory HbA1c result available (see Table 1). A total of 157 patients had no POC test, mainly because of temporary equipment failure or shortage of cartridges affecting particularly one remote, rural site in Romania. Only 72 people (4.2%) were HIV positive, though 97 patients refused HIV testing , 91 did not have the test done, three had confirmed laboratory results missing, 17 did not have test done for unclear reasons, and further ten people had

laboratory results missing but for no known reason. The median age was 35 years, 61% of the study sample were men, 37% were underweight and 9% were overweight or obese. Almost half of the participants had anaemia of some extent: 29% with mild anaemia, 18% with moderate anaemia, and 1.4% with severe anaemia.

Mean agreement (population agreement)

Table 1 shows the baseline mean HbA1c results from POC and laboratory sources. In the total sample, POC HbA1c results were significantly greater than laboratory HbA1c level by 0.14% units (95%CI 0.11 to 0.18). We did not identify substantial differences in population level mean HbA1c by age group, sex, or BMI level.

POC HbA1c levels were higher than laboratory HbA1c results in patients with anaemia, and the largest difference was found among those with severe anaemia (1.07% (95%CI 0.67% to 1.46%) P=0.001) (see Table 2). POC HbA1c results were higher than laboratory values regardless of HIV status, although the difference was not significant amongst HIV negative (0.15% (0.11%, 0.19%)) compared to positive patients (0.30% (0.10%, 0.49%)). There was a small but significant difference in HbA1c results by country: POC HbA1c was found to be slightly higher than laboratory HbA1c in Indonesia (0.26% (95%CI 0.21 to 0.31)) and Peru (0.55% (95%CI 0.47 to 0.64)), but slightly lower in Romania -0.37% (95%CI -0.42 to -0.31) and South Africa (-0.23% (95%CI -0.32% to -0.13%). The difference in direction could reflect significantly higher mean POC HbA1c in Peru and Indonesia (6.1 and 6.2% HbA1c), compared with Romania and South Africa (both 5.6%). The greatest mean difference was found in Peru, where a batch of the POC test was subsequently manufacturer identified as inaccurate. In a sensitivity analysis, we removed values for the period of time in which this substandard batch were used (affecting 184 out of 542, 39% of tests in Peru), but this did not substantially alter the mean difference in Peru (0.59% (95%CI 0.48% to 0.69%, compared to 0.55% (95%CI 0.47 to 0.64) when including the faulty batch). The mean difference between POC and HbA1c increased with higher laboratory HbA1c level.

Individual variation in agreement

Overall, the mean ± 2 standard deviations for within individual agreement ranged from +1.84 to – 1.56% HbA1c, suggesting that individual TB patients could have a difference of up to nearly 2 units of HbA1c% higher or 1.5 units lower on the POC test (i.e. a POC measurement of 6.5% could be in the range 5.0% - 7.9% on the laboratory test) (see Table 2). Intra-individual differences were similar for most sub-groups but appeared widest for those with severe anaemia (-0.93 to +3.06 HbA1c %), though only a small number of individuals were included in this category (n=27). There were generally smaller but statistically significant differences in the unit discrepancy between the two tests for other covariates

including age and level of laboratory HbA1c (Table 2), and Bland-Altman plots of agreement were shown in Appendix 3 for each covariate. The POC test was on average higher than the laboratory test at low levels (HbA1c < 5.7%), but this reversed and became more variable (greater intra-individual differences) at higher levels of HbA1c.

Error grid analysis (see Figure 1 and Table 3)

For the majority of individuals their POC and laboratory HbA1c value were either both below 6.5% (n=1574, 81.1%) or only deviated from one another by less than 6% (relative difference) (n=86, 4.4%). A small number of patients (n=79; 4.1%) had greater than 6% relative deviation, but would still be assigned a concordant DM status using the standard diagnostic cut-points. Thus for 1739 patients (89.5%) there was no important difference between the two tests (see Zones A and B in Table 3 and Figure 1).

However, for 10.5% of individuals, POC and laboratory HbA1c values indicated differences in DM control status. N=1 (0.1%) had a POC HbA1c estimate greater than 9% when the laboratory HbA1c estimate was between 6.5% and 8.9%; the POC suggesting severe hyperglycaemia when the laboratory test suggested more moderate hyperglycaemia (Zone C1 in Figure 1). For n=188 (9.7%) TB patients the POC value was between 6.5% and 9% when the laboratory value was <6.5%; suggesting moderate to high levels of hyperglycaemia when this was not present on the laboratory measurement (Zone D1). This could also result in possible over-treatment, most likely to arise for the lower proportion (n=28, 1.4%) of patients with POC ≥8%, whilst the laboratory test was <6.5%. For 0.6% of individuals (n=11) the POC HbA1c was > 9% when the laboratory HbA1c was less than 6.5%, leading to a substantial risk of over-treatment (Zone E1). Overall, 40 patients (1 in Zone C1, 28 in Zone D1, and 11 in Zone E1, 2.1%) could risk unnecessary treatment or referral based on the POC test result. Only one individual (0.05%) had a POC <6.5% when the laboratory HbA1c was >9.0% and could thus be incorrectly classified as below this threshold when they had very severe hyperglycaemia.

Operational feasibility

At both time points for the operational feasibility study the POC was assessed by health care workers as more user friendly than the laboratory HbA1c, particularly because of the direct and rapid result. In terms of perceived appropriateness of tests, health care workers were initially hesitant about adopting a new test and on average their self-assessment for training time was that it took them four and a half working days (range of 30 minutes to seven working days) to feel that they could proficiently perform the POC test, but by the end of the study their perception was that less time (only one and a half working days; range 30 minutes to three working days) was needed, having performed the test consistently for an average of two years during the TANDEM study. After two years' experience, the

average time estimated to perform a POC test (6.4 minutes) was slightly more than the time estimate to perform the blood draw for the laboratory HbA1c (4.5 minutes). The POC test was generally perceived to be more acceptable by patients than a venous blood draw, though 13% of respondents indicated that some patients were unwilling to have their fingers pricked. The quality of the POC machines was also a concern for the health care workers, as whilst they did not break down often, the down time when a repair was needed was perceived to increase from 12 to 16 hours after two years. However, this corresponded with a decrease in the daily quality control checks of the machines from 64% to 38%, demonstrating potential reduced equipment maintenance over time as the test became more familiar.

Discussion

Overall, the vast majority of patients (89.6%) were classified by both tests as having the same DM status or the differences were within an acceptable margin of error. Mean differences were also very small for most patients (except for those with severe anaemia), suggesting that the POC test can be used to monitor DM prevalence at a population level. It is well-known that anaemia can affect HbA1c level; a recent systematic review[45] suggested that HbA1c can be over-estimated in the presence of iron deficiency anaemia, and may be under-estimated in the presence of other forms of anaemia. We had previously analysed the relationship between laboratory HbA1c and anaemia in our study, and found no overall statistically significant difference in HbA1c across anaemia categories (especially among non-, mild-, and moderate anaemia) on HbA1c levels in TANDEM study, although for those patients with severe anaemia HbA1c did appear lower[14]. Another Indian study among TB patients recently showed little difference in HbA1c by level of anaemia[4]. Nevertheless, our data suggests that it might not be appropriate to use HbA1c for screening in TB patients with severe anaemia, but due to the small sample size we could not analyse this further.

Despite good mean (population level) agreement for most patients, at an individual level there were substantial differences between laboratory and POC HbA1c, with POC HbA1c ranging from almost 2 units higher to about 1.5 units lower than laboratory HbA1c values. For just under 2.5%, the POC test substantially over-estimated the laboratory test in a clinically important range. However, clear guidance to TB clinics to repeat POC HbA1c tests for those with severely raised initial levels (≥8%) but no previously known DM, or to use an alternative fasting glucose test, should help mitigate against this risk. In our study this would have resulted in 70 repeated tests (<5%). After the initial stages of treatment when the patient is no longer infectious, it may be appropriate to refer to DM services. For more severe, uncontrolled DM, specialist advice should be sought including the need for hospital admission, particularly if HbA1c is over 10%. For those with moderate hyperglycaemia, specialist

advice should also be sought including intensifying glucose treatment, monitoring, and management. Local expertise, availability of DM medications and monitoring, will all determine the precise thresholds at which urgent referral or advice might be required. Specific guidance on management targets for DM among TB patients aimed at front line health care workers is currently under review and expected to be published by the International Union Against Lung Disease later this year. We also suggest that all patients potentially newly identified with DM should be followed up towards the end of TB treatment and referred to DM services where appropriate, and this guidance should prevent over-diagnosis and treatment in the longer term.

The strength of our study is the relatively large number of patients with both laboratory and POC HbA1c test results from four continents. Our analyses also addresses a pressing need, since following initiatives to support screening for DM in TB patients[11, 12, 46, 47], capillary POC tests are being introduced in TB clinics. In our study, the tests were performed at the same time during the initial clinic visit. We also used field-based rather than laboratory trained staff, and assessed patient/field worker satisfaction of use of POC. Our results are thus more likely to reflect potential agreement in practice, compared with manufacturer or laboratory based studies which often use highly skilled testers in near optimal conditions. Laboratory measurements of HbA1c were all performed in accredited laboratories, certified to NGSP standards. Missing data were very low for most covariates and tests, except in one remote site where some POC HbA1c tests had not been taken. Overall, 93% of eligible patients had the POC test performed. We also used an error grid approach to explore the agreement in key clinical areas where treatment or referral decisions might be made, rather than simply calculating diagnostic accuracy at a set cut-point. The key limitations are some missing data for HIV status, and the use of a different POC test in Romania, where Hemocue® was not available. The overall pattern of results in Romania is, however, consistent with the other countries included. We found quality control problems with the POC HbA1c cartridges, clearly affecting some tests. This would likely not have been identified outside of a research setting, in which we were using other DM tests simultaneously. After noticing the discrepancy at an early stage in one site (Lima, Peru) we approached the manufacturer for advice, but retained the apparently inaccurate POC batch values in our main analyses, as this reflects what would be most likely to happen in practice.

Other studies comparing POC and laboratory HbA1c values among TB patients are rare. A study amongst 400 adults with suspected TB reported poor agreement between POC and laboratory HbA1c results in Nigeria[48]. Their POC for HbA1c showed low sensitivity (50%) and moderate specificity (74.5%) compared with the laboratory based HbA1c test. The study population had a high HIV prevalence and no further details of the agreement between the two tests (such as the actual

discrepancy in HbA1c estimated), or the training and experience of those undertaking the POC test were provided.

The key benefit of using POC tests among TB patients is the potential for rapid diagnosis and better management to improve clinical outcomes among those with TB-DM. Overall, there was a high acceptance of POC HbA1c for use in real world settings in both remote and non-remote clinics, especially as there is no need for repeat visits or for individuals to be fasting. Field workers found the test generally acceptable to use, though the initial training time estimated, down time, and diminution in quality control checks over time stress the importance of initial training and suggest that regular re-training and assessment would be required in practice. The cost of POC testing is much lower than other types of HbA1c test, due to its immediate result-reading, which would be ideal for low-middle income countries with limited resources in local primary care centres. Potentially, the cost of POC HbA1c could be reduced further by limiting its use to TB patients with an initial raised non-fasting (random) capillary glucose level, which in our study would have reduced the need for the POC test by around 70%[14]. However, the financial assistance and educational support from local government and international public health promoters (e.g. WHO, NGO) in collaboration with test manufacturers would likely still be required to facilitate the process, especially in more remote and disadvantaged communities. A recent study in South Africa suggested that POC HbA1c test significantly improved the glycaemic control in less advantaged local DM clinic and increased the accessibility for DM patients in the community[49]. POC HbA1c tests are generally thought to be stable at room temperature for many months, and some studies have found good agreement with laboratory results even in more extreme temperatures[50], but this has not been widely assessed. POC HbA1c is ideal for measuring hyperglycaemia at a population level, since mean differences with laboratory HbA1c were small. POC HbA1c provides feedback on risk of DM amongst TB patients to health care professionals and patients. It can also highlight those potentially at risk of poor TB outcome, who may need additional management. Overall, for most patients agreement with the laboratory measure was either good or would not affect clinical decisions. Patients with a significantly raised POC HbA1c (e.g. $\geqslant$8%) and without known DM could be assessed clinically including evaluating whether they have known DM risk factors (e.g. family history of DM), and offered a repeated HbA1c test or fasting blood glucose test to confirm the level of hyperglycaemia. In our population, this would have resulted in repeat testing for only 5% of patients. Ideally, those with severe anaemia (1.4% of our study) should also receive an alternative test, since POC HbA1c performed poorly in this group. Newer technologies should also be assessed in similar studies as they enter the market, but all potential pragmatic and feasible tests may suffer some limitations in terms of accuracy[51]. POC HbA1c is sufficiently accurate and likely the test of choice for screening among most TB patients at present.

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Competing Interests:

The authors declare that no competing interests exist.

Author Contributions:

DG and JAC conceived of the idea and developed analysis plans with input from CUG, BA, DAJM, RvC and PH. PH performed main statistical analyses and drafted the paper. YL designed, performed and analysed operational feasibility assessments with input from UG, JAC, SRK and FP. JAC, DG and FP helped with manuscript drafting. All other authors contributed to the development of the overall project, data collection and reviewed the manuscript. All authors approved the final version of the manuscript.

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Table 1 Baseline mean HbA1c (%) results from POC and lab in TANDEM study[*]

Variables		N (%)	Mean (95%CI)	
			POC HbA1c	Lab HbA1c
Total sample		1942 (100.00)	6.00 (5.94, 6.06)	5.85 (5.80, 5.91)
Sex	Female	752 (38.74)	6.06 (5.96, 6.16)	5.84 (5.74, 5.95)
	Male	1189 (61.26)	5.96 (5.89, 6.03)	5.86 (5.80, 5.93)
Age group	<30yrs	701 (36.10)	5.74 (5.69, 5.79)	5.55 (5.51, 5.59)
	30-39yrs	444 (22.86)	5.93 (5.83, 6.03)	5.66 (5.60, 5.72)
	40-49yrs	363 (18.69)	6.05 (5.89, 6.20)	6.05 (5.88, 6.22)
	50-59yrs	254 (13.08)	6.46 (6.21, 6.71)	6.44 (6.19, 6.69)
	60yrs+	180 (9.27)	6.44 (6.17, 6.71)	6.31 (6.07, 6.56)
BMI[†]	Underweight	714 (36.88)	5.89 (5.82, 5.97)	5.77 (5.70, 5.84)
	Normal range	1055 (54.49)	5.99 (5.91, 6.08)	5.85 (5.77, 5.93)
	Overweight	142 (7.33)	6.42 (6.14, 6.70)	6.17 (5.87, 6.47)
	Obese	25 (1.29)	6.91 (5.97, 7.85)	6.75 (5.77, 7.73)
Country	Indonesia	734 (37.80)	6.23 (6.11, 6.35)	5.96 (5.84, 6.08)
	Peru	542 (27.91)	6.14 (6.03, 6.24)	5.59 (5.51, 5.66)
	Romania	416 (21.42)	5.62 (5.54, 5.70)	5.99 (5.90, 6.08)
	South Africa	250 (12.87)	5.64 (5.53, 5.75)	5.87 (5.77, 5.96)
Anaemia[‡]	Non-anaemia	1003 (51.67)	5.96 (5.87, 6.05)	5.85 (5.76, 5.93)
	Mild anaemia	557 (28.70)	6.03 (5.92, 6.13)	5.92 (5.82, 6.02)
	Moderate anaemia	354 (18.24)	6.02 (5.91, 6.14)	5.82 (5.71, 5.93)
	Severe anaemia	27 (1.39)	6.39 (6.02, 6.76)	5.32 (5.11, 5.54)
Lab HbA1c	<5.7	1123 (57.83)	5.71 (5.66, 5.76)	5.34 (5.32, 5.36)
	5.7-6.4	659 (33.93)	5.91 (5.86, 5.95)	6.01 (6.00, 6.02)
	6.5-8.9	99 (5.10)	6.31 (6.12, 6.51)	6.91 (6.79, 7.02)
	9+	61 (3.14)	11.81 (11.35, 12.28)	11.95 (11.44, 12.46)
HIV status	HIV-	1654 (95.82)	6.03 (5.96, 6.09)	5.88 (5.81, 5.94)
	HIV+	72 (4.18)	5.95 (5.74, 6.16)	5.66 (5.49, 5.82)

[*] Participant numbers reported here vary slightly from some other TANDEM consortium analyses owing to minor differences in inclusion criteria and/or recruitment period

[†] Underweight: <18.5 kg/m^2; normal range: 18.5-24.9 kg/m^2; overweight: 25.0-29.9 kg/m^2; obese: ≥30.0 kg/m^2.

[‡] Anaemia categories were defined according to WHO. Among non-pregnant women (>15 years) non-anaemia defined as haemoglobin levels >120g/L, mild anaemia defined as 110-119g/L, moderate anaemia was defined as 80-109g/L, and severe anaemia was defined as <80g/L; among men, non-anaemia defined as >130g/L, mild anaemia was defined as 110-129g/L, moderate anaemia defined as 80-109g/L, and severe anaemia defined as <80g/L. Among women, there were five people pregnant and their anaemia level was defined differently as below: non-anaemia >110g/L, mild anaemia is 100-109g/L, moderate anaemia is 70-99g/L, and severe anaemia is <70g/L.

Table 2 Intra-individual difference for HbA1c from POC and laboratory sources stratified covariates

Variables		Mean	Intra-individual difference (POC-Lab) mean-2SD, mean+2SD	P value
Total sample		0.14	-1.56, 1.84	<0.001
Sex	Female	0.21	-1.48, 1.90	Ref
	Male	0.10	-1.60, 1.80	0.136
Age group[§]	<30yrs	0.19	-1.36, 1.73	Ref
	30-39yrs	0.27	-1.79, 2.33	0.340
	40-49yrs	-0.001	-1.54, 1.54	0.017
	50-59yrs	0.02	-1.39, 1.43	0.010
	60yrs+	0.13	-1.71, 1.97	0.704
BMI[**]	Underweight	0.12	-1.33, 1.58	Ref
	Normal range	0.14	-1.70, 1.98	0.931
	Overweight	0.25	-1.54, 2.04	0.566
	Obese	0.16	-1.03, 1.34	0.846
Country	Indonesia	0.26	-1.10, 1.62	Ref
	Peru	0.55	-1.48, 2.58	<0.001
	Romania	-0.37	-1.47, 0.74	<0.001
	South Africa	-0.23	-1.70, 1.25	<0.001
Anaemia[††]	Non-anaemia	0.12	-1.58, 1.82	Ref
	Mild anaemia	0.11	-1.55, 1.78	0.920
	Moderate anaemia	0.20	-1.45, 1.85	0.523
	Severe anaemia	1.07	-0.93, 3.06	0.038
Lab HbA1c	<5.7	0.37	-1.33, 2.07	Ref
	5.7-6.4	-0.11	-1.32, 1.11	0.014
	6.5-8.9	-0.60	-2.16, 0.97	0.011
	9+	-0.13	-3.09, 2.82	0.020
HIV status	HIV-	0.15	-1.43, 1.73	Ref
	HIV+	0.30	-1.34, 1.93	0.940

[§] Wald test was used to test overall differences across all categories; P>0.100 for all tested variables except for country (P<0.001) and Lab HbA1c groups (P=0.035).

[**] Underweight: <18.5 kg/m2; normal range: 18.5-24.9 kg/m2; overweight: 25.0-29.9 kg/m2; obese: ≥30.0 kg/m2.

[††] Anaemia categories were defined according to WHO. Among non-pregnant women (>15 years) non-anaemia defined as haemoglobin levels >120g/L, mild anaemia defined as 110-119g/L, moderate anaemia was defined as 80-109g/L, and severe anaemia was defined as <80g/L; among men, non-anaemia defined as >130g/L, mild anaemia was defined as 110-129g/L, moderate anaemia defined as 80-109g/L, and severe anaemia defined as <80g/L. Among women, there were five people pregnant and their anaemia level was defined differently as below: non-anaemia >110g/L, mild anaemia is 100-109g/L, moderate anaemia is 70-99g/L, and severe anaemia is <70g/L.

Table 3 Error grid analysis zones and clinical interpretation

Zone #	Definition	Comparison with reference standard	N (%)	Clinical interpretation
A	POC<6.5 & Lab<6.5 Or Lab-6%<POC< Lab+6%	POC deviates from reference by ≤6% or both values are <6.5	1660 (85.5) (1574 HbA1c<6.5 in both POC and Lab results; 86 POC values deviates from Lab results by less than 6%)	A: POC and reference value both <6.5, or POC values deviates from reference values by ≤6%
B1	POC> Lab+6%	POC deviates from reference by >6%	12 (0.6)	B1 and B2: POC deviates from reference by >6%, but would lead to no treatment or no erroneous treatment i.e. does not cross diagnostic cut-points
B2	POC< Lab-6%	POC deviates from reference by >6%	67 (3.5)	
C1	POC≥9* and Lab≥6.5	Overestimation	1 (0.1)	C1: poor glycaemic control was identified instead of moderate control
C2	POC<6.5 and 8<Lab<9	Underestimation	2 (0.1)	C2: tight glycaemic control was identified instead of moderate control
D1	6.5≤POC<9 and Lab<6.5	Overestimation	188 (9.7)	D1: moderate glycaemic control was identified instead of normoglycaemia
D2	6.5≤POC<9 and Lab≥13	Underestimation	0 (0)	D2: moderate glycaemic control was identified instead of tight glycaemic control
E1	POC≥9 and Lab<6.5	Overestimation	11 (0.6)	E1 poor glycaemic control was identified instead of normoglycaemia
E2	POC<6.5 and Lab≥9	Underestimation	1 (0.05)	E2 normoglycaemia was identified instead of poor glycaemic control
Total			1942 (100)	

*the stringent cut off of 9% is used as an indicator for poor control. This is based on the level of hyperglycaemia at which TB outcomes are thought to worsen

See Figure 1 below for graphical representation of the Zones.

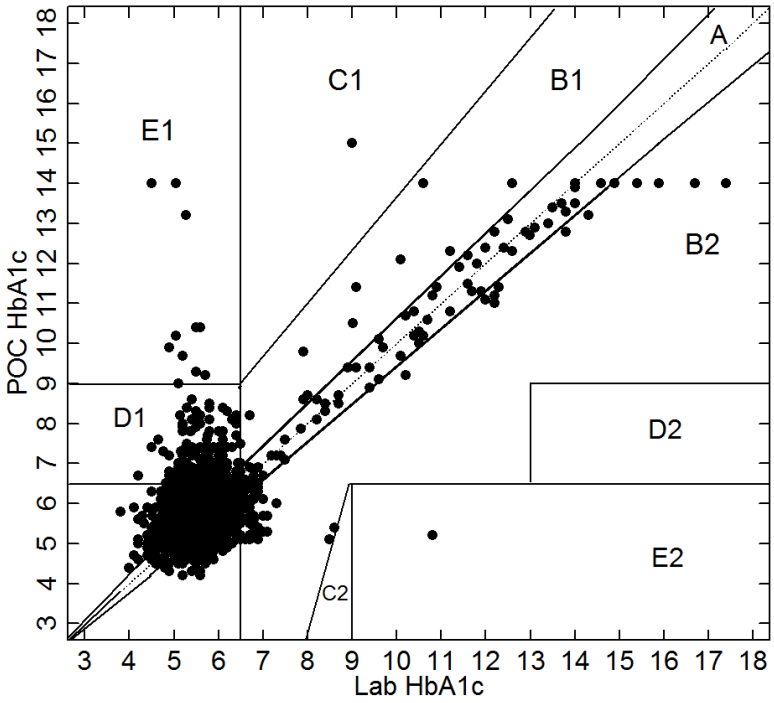

Figure 1. Error grid demonstrating agreement between the laboratory and POC HbA1c measurement

Appendices

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Appendix 1 Site locations for TANDEM study

Summary - Study site locations

In Bandung, Indonesia, suspected TB patients were recruited in 44 community health centres (CHCs) and from a district and a referral hospital. In Lima, Peru, patients were recruited at three primary health facilities and one secondary level hospital. In Romania, patients with TB were recruited from two secondary level hospitals, in two counties (Gorj and Dolj). In South Africa, patients were recruited at six community health care clinics in the northern Cape Town metropolitan area.

Country and site selection

For the TANDEM study, it was important to select countries from different geographic regions so that diverse cultural, health system structures and population demographics could be represented. The burden of TB and DM also needed to be sufficiently high so that there would be sufficient TB-DM burden within the populations to be able to detect a causal effect. The countries also needed to be typical of settings where economic improvement and changes in lifestyles would be likely to increase the risk of DM substantially. During the TANDEM proposal development in 2011, current data indicated that Peru and Romania had some of the highest TB incidence rates in the South American and European regions respectively (106 and 159 per 100,000 population respectively) and an expected increase of DM between 90% and 160% (WHO, 2010a). With a TB incidence of 189 per 100,000 population (WHO, 2010a), Indonesia's burden was well above the recommended screening threshold for TB in people with DM of 100 per 100,000, as recommended by the WHO/Union Framework (The Union and WHO, 2011), even though it was not one of the highest in the South-East Asia region at that time.

The feasibility of conducting the studies was also an important criterion in the country selection and this was largely informed by long-term pre-existing research relationships between the TANDEM project principal investigators and research institutions within the countries as well as the collaborators' capacity to recruit, test and treat patients for TB and DM and their access to potential participants. Given these considerations, Indonesia, Peru, Romania, and South Africa each with a high burden of TB and an increasing prevalence of DM, were selected.

The research team based in the Universitas Padjadjaran (UNPAD) in Bandung, Indonesia has a pre-existing research relationship with the main public tertiary teaching Hospital (RSHS), thus the DOTS and Endocrinology clinics at RSHS were selected for recruitment of people with TB and DM,

respectively. The CHCs with the greatest number of patients with TB in Bandung were contacted and asked to participate in the TANDEM study, with the permission and endorsement of the City Health Office. Patients with TB were recruited from those facilities along with the 14 additional satellite CHCs. Recruitment of patients with TB was lower than expected, particularly from CHCs in the east. Therefore, the second hospital, Ujung Berung District Hospital, was later added so that patients with suspected TB at CHCs in east Bandung could be sent to Ujung Berung hospital for confirmation and enrolment in TANDEM.

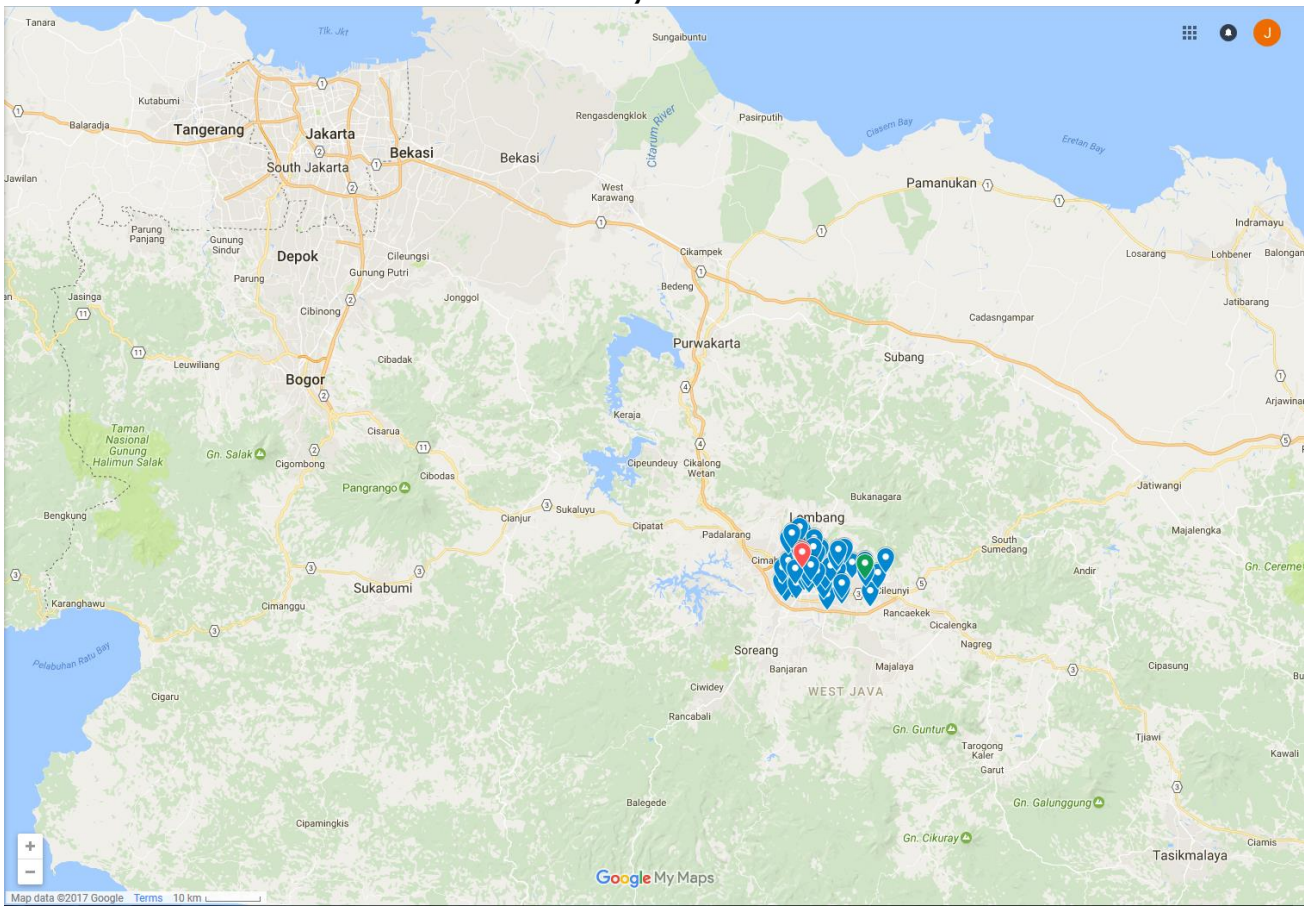
In Peru, TANDEM made a request to the Ministry of Health to get permission and access to health facilities in Lima to conduct the studies in WP1 and WP2. The Ministry of Health then provided a list of facilities with sufficient patient volume to meet the Peru recruitment targets and that were not already involved in another research project, conducted by any other local or international institution. HAMA, the reference hospital for almost one million people in South Lima, was chosen for recruitment of people with DM since the Endocrinology Department and the daily DM clinic are the most accessed DM services in the area, particularly by uninsured people with DM. To recruit people with TB, four health facilities with a high or medium prevalence of TB in the Metropolitan area of Lima were chosen.

In Romania, sites were also purposively selected based on pre-existing research collaborations with the country principal investigator in Dolj and Gorj counties as well as a high volume of patients with TB at the Victor Babes Hospital and the Runcu Hospital, and patients with DM at the two general hospitals.

In South Africa, all clinical sites used for recruitment were located in the northern part of the Cape Town metropolitan area. The facilities were selected because they are relatively close to Stellenbosch University's Faculty of Medicine and Health Sciences and cater for people with low- to lower-middle income for whom interventions are most needed. The areas have previously been reported to have a high prevalence of TB and diabetes, and the study team have a longstanding relationship with the personnel due to previous research activities. Diabetes patients were recruited from 3 Community Health Centres, under the management of Western Cape Provincial Health Department. Tuberculosis patients were recruited from 6 Primary Health Centres, under the management of City of Cape Town Health Department.

TANDEM – GLOBAL LOCATIONS (See tandem-fp7.eu)

TANDEM - SITES IN BANDUNG, INDONESIA



- **Site 1**
  - Endocrine outpatient-clinic
  - DOTS outpatient-clinic
- **Site 2**
  - TB Research Clinic
  - Arcamanik Community Health Centre
  - Astanaanyar Community Health Centre
  - Babakan Sari Community Health Center
  - ... 42 more
- **Site 3**
  - Kemuning (in-patient) building
- **Site 4**
  - Kota Bandung District Hospital

TANDEM - SITES IN LIMA, PERU

Capa sin título

- Centro de Salud Fortaleza
- Hospital Huaycan
- Centro de salud San Cosme
- Centro Materno Infantil San Jose

TANDEM – SITES IN CRAIOVA ROMANIA

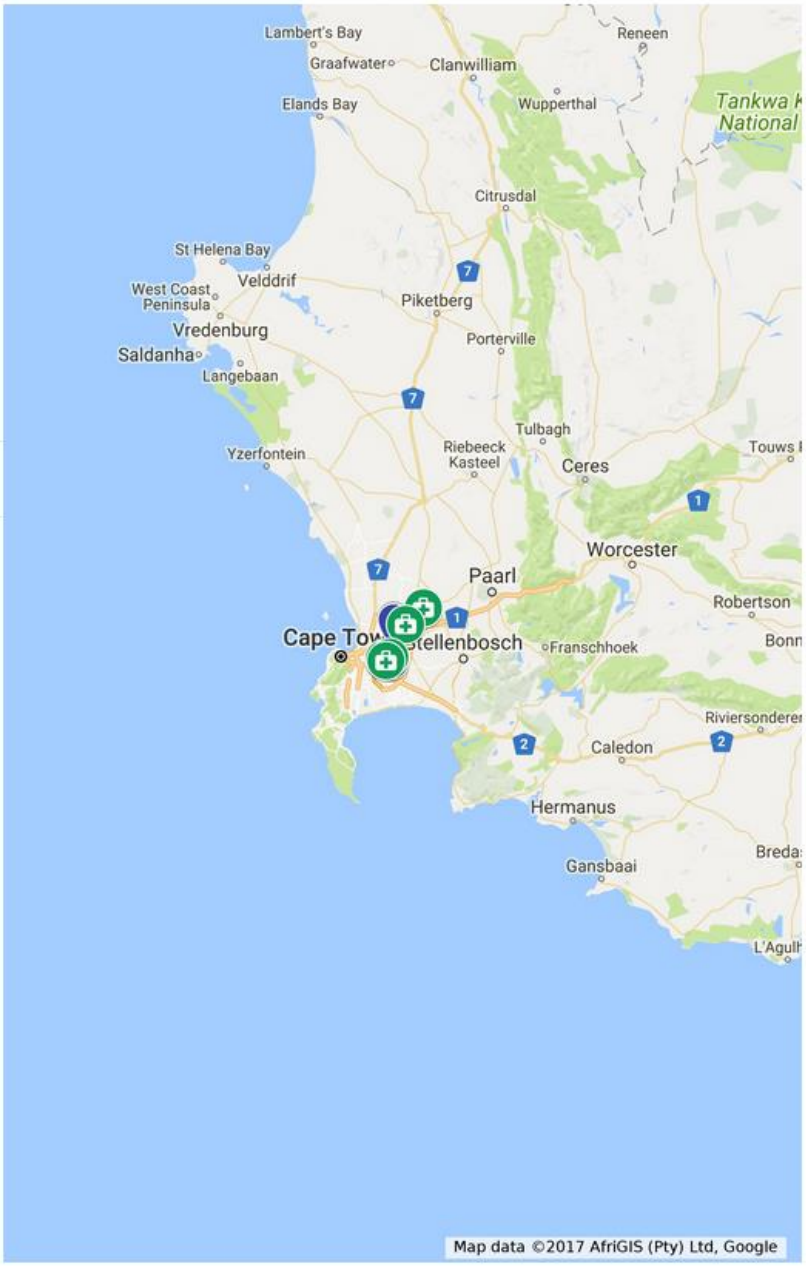
TANDEM - SITES IN STELLENBOSCH, SOUTH AFRICA

TANDEM sites in South Africa

Faculty of Medicine and Health Sciences, Stellenbosch University

- Fisantekraal Health Clinic
- Uitsig Clinic
- Elsies River Day Hospital
- Durbanville Day Hospital
- Ravensmead Public Clinic
- Adriaanse Baby Clinic

Untitled layer



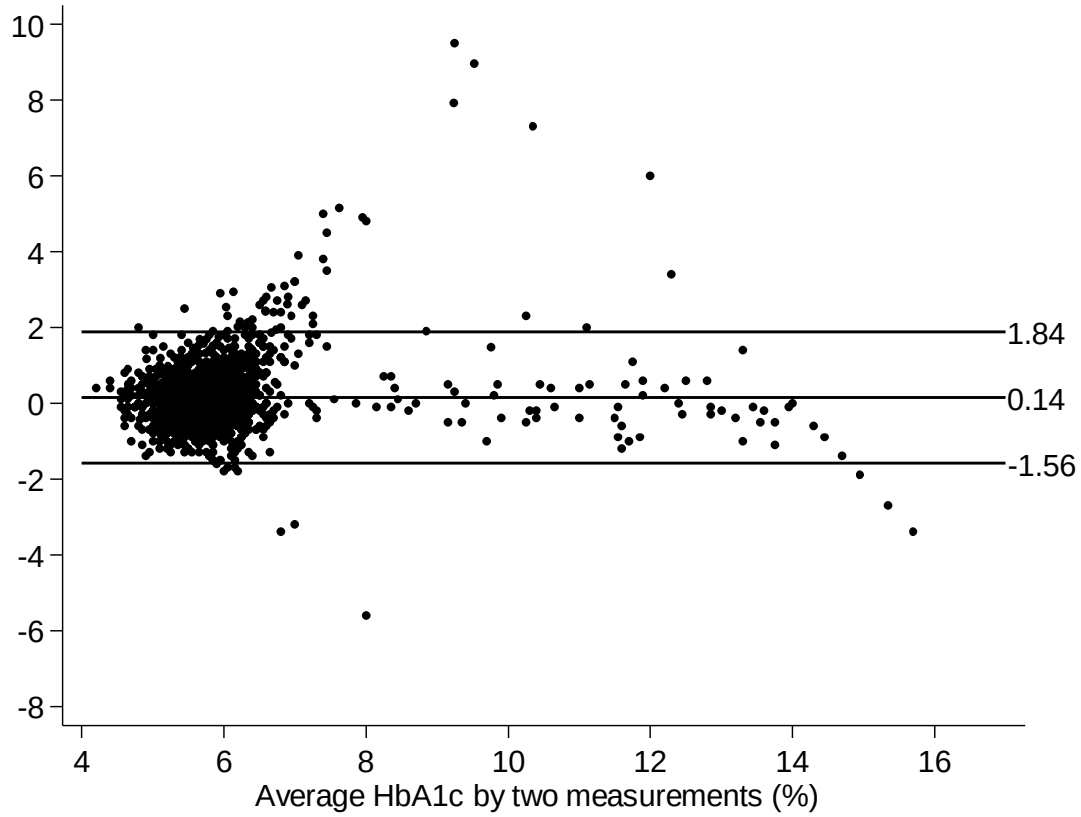
Appendix 2 TANDEM TB diagnosis algorithm

Case Definition	Criteria	
Definite TB	Culture or GeneXpert positive	With or without: Suggestive TB on X-ray Possible TB on X-ray TB symptoms
Probable TB	Smear Positive	And either: Suggestive TB on X-ray Possible TB on X-ray and TB Symptoms
Possible TB	Smear Positive	And either: Possible TB on X-ray TB symptoms
	TB Symptoms	And either: Suggestive TB on X-ray Possible TB on X-ray
No TB	Does not fulfil any of the above criteria	

In Indonesia and Peru, in order to obtain a positive result using the microscopic observation drug susceptibility assay (MODS) two colony forming units must be observed. Negative results require no growth. Indeterminate results occur when only one colony forming unit is observed, but is insufficient for bacterial confirmation. Indeterminate results are ignored by the case definition algorithm and are by default treated as negative[1].

[1] Moore DA, Mendoza D, et al. Microscopic observation drug susceptibility assay, a rapid, reliable diagnostic test for multidrug-resistant tuberculosis suitable for use in resource-poor settings. J Clin Microbiol. 2004;42:4432–4437.

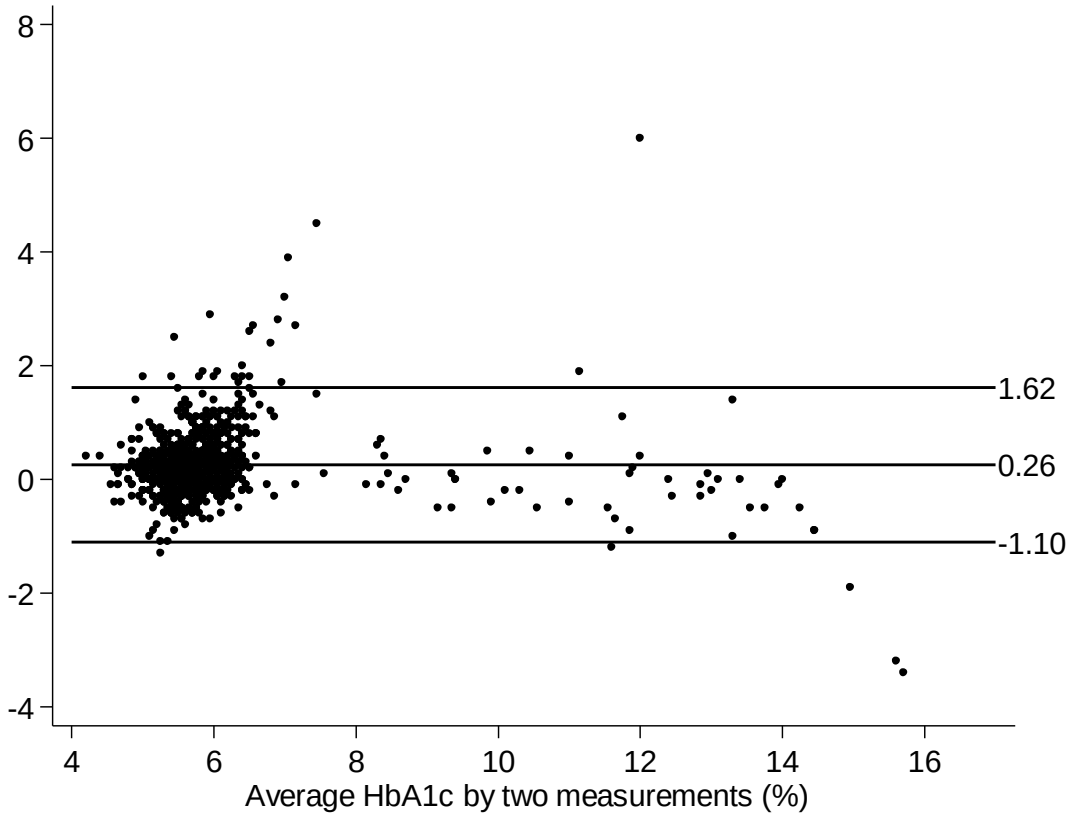
Appendix 3. Figures showing individual agreement between POC and laboratory HbA1c in the TANDEM study



Total sample HbA1c difference

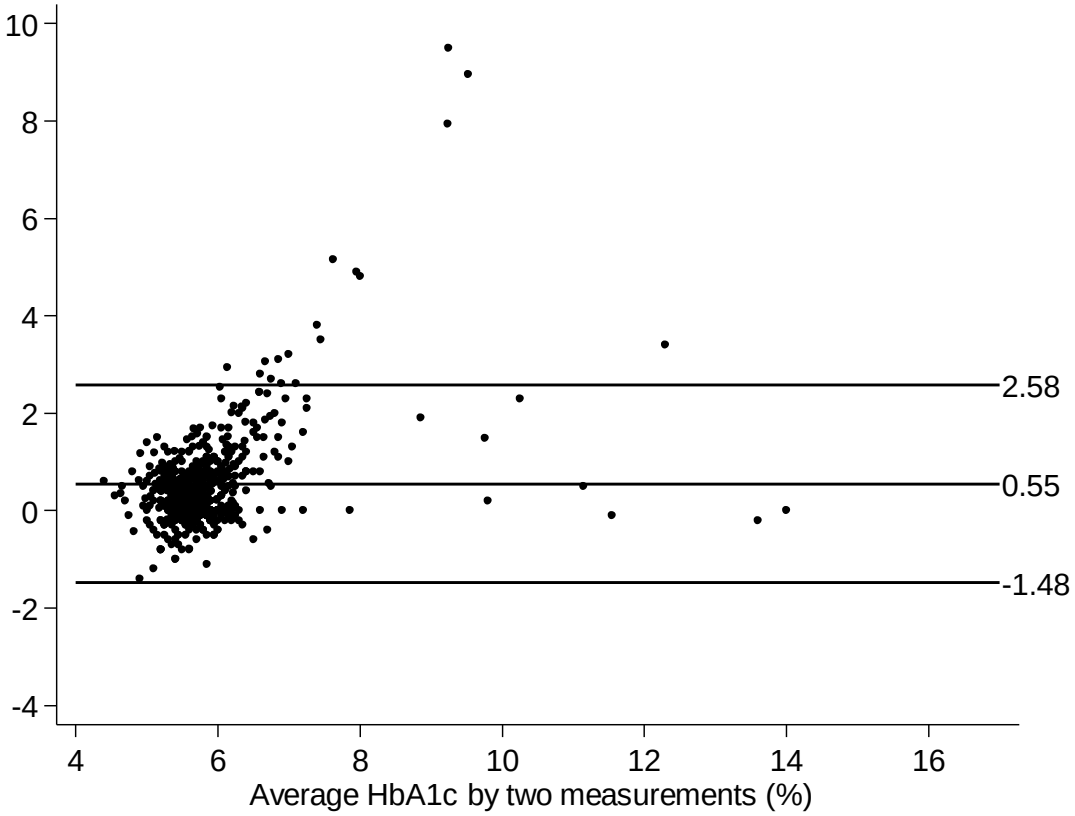
POC was 0.14% (95%: 0.11, 0.18) greater than lab values (P<0.001)

By study country:



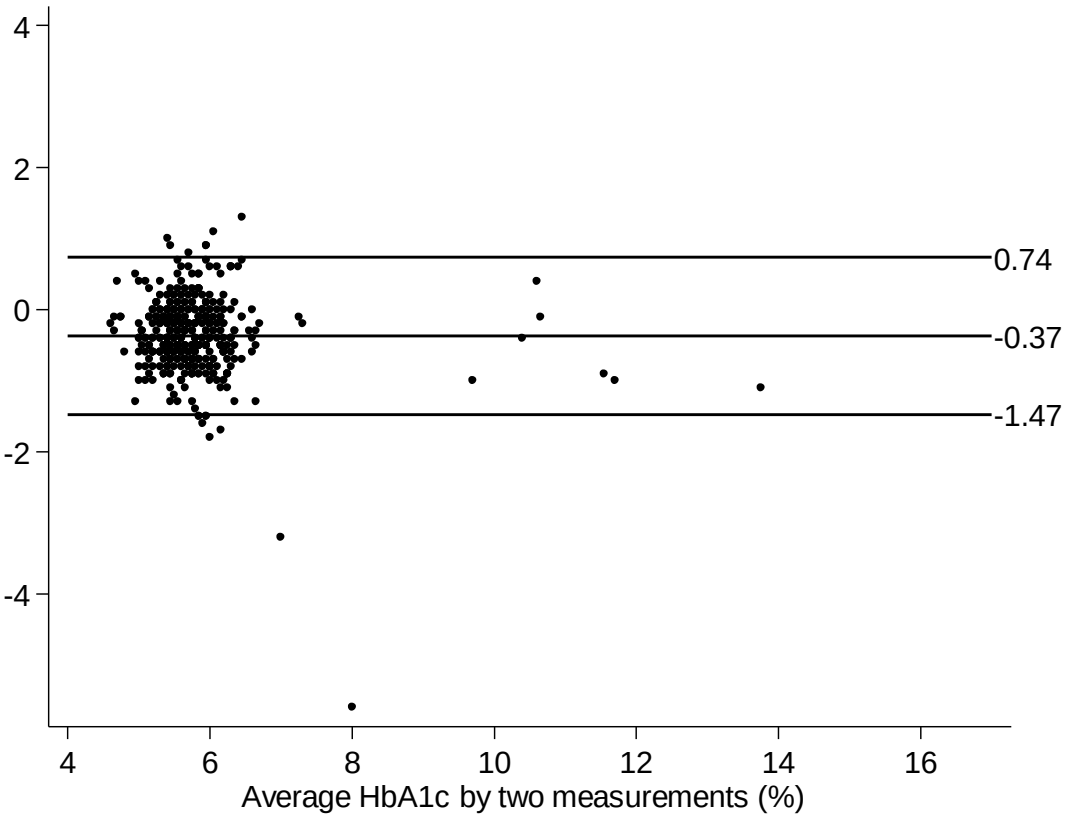
Among Indonesian sample

POC was 0.26% (95%: 0.21, 0.31) greater than lab values (P<0.001)



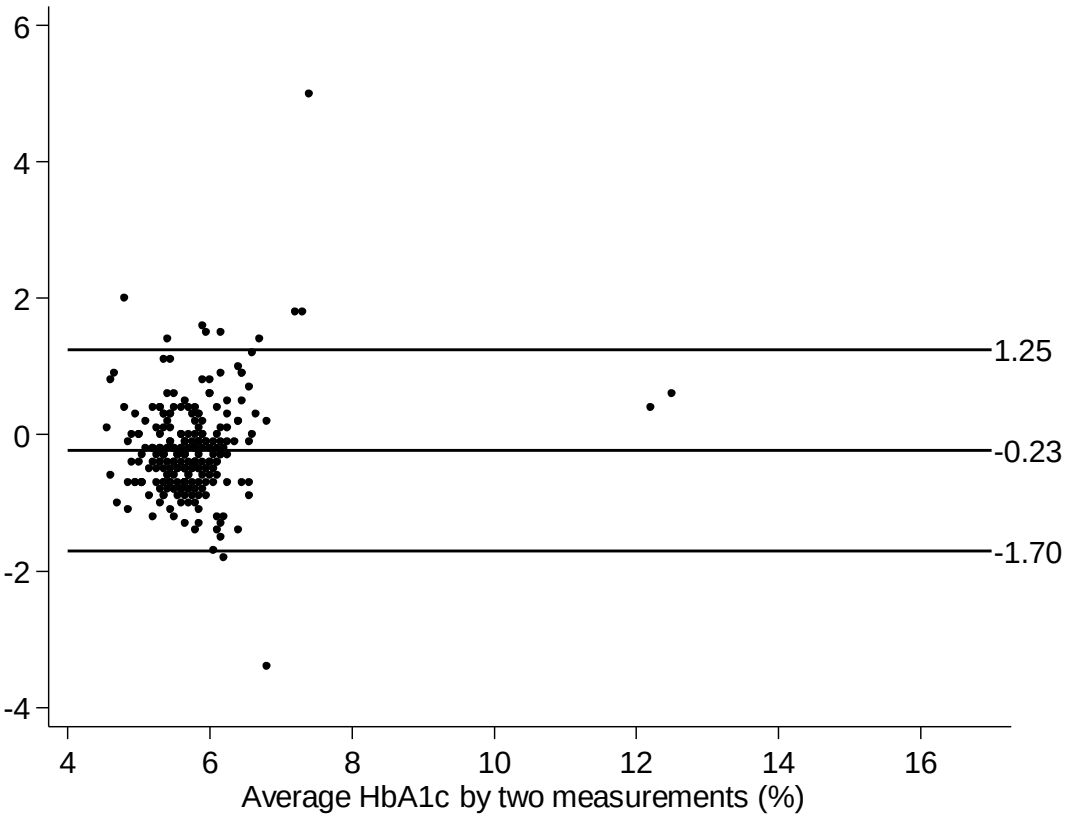
Among Peruvian sample

POC was 0.55% (95%: 0.47, 0.64) greater than lab values (P<0.001)



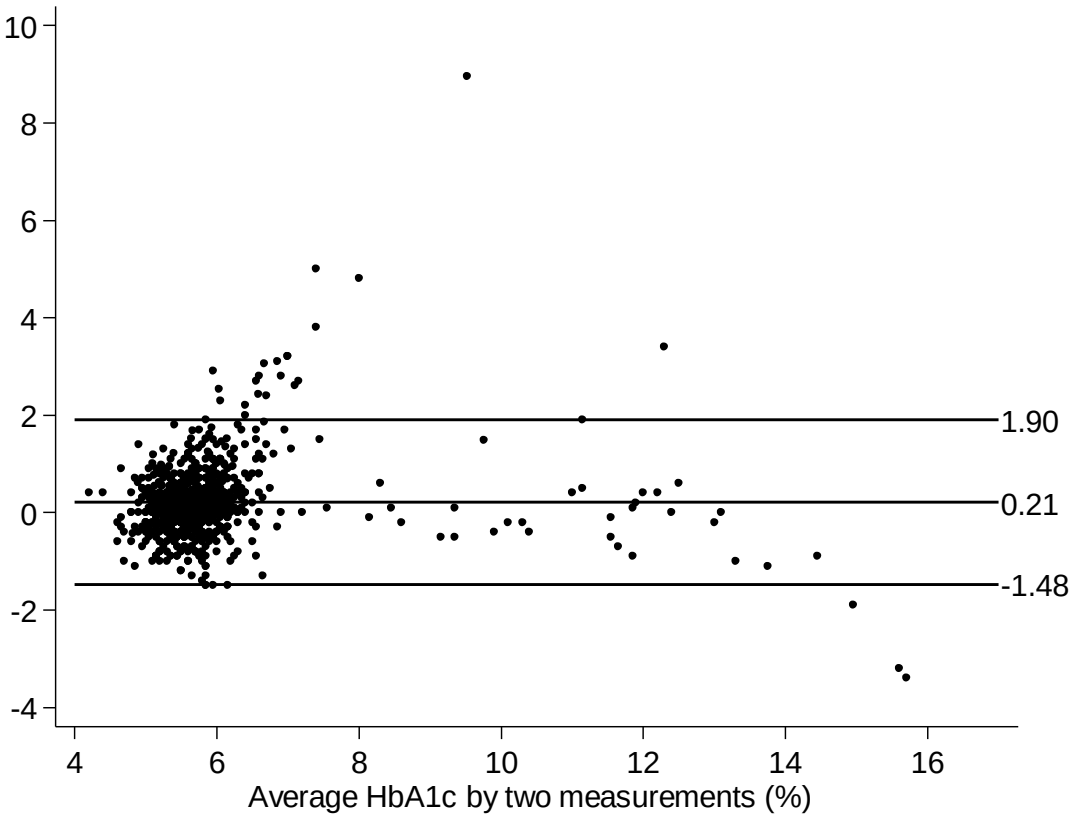
Among Romanian sample

Lab HbA1c was -0.37% (95%: -0.42, -0.31) greater than POC values (P<0.001)



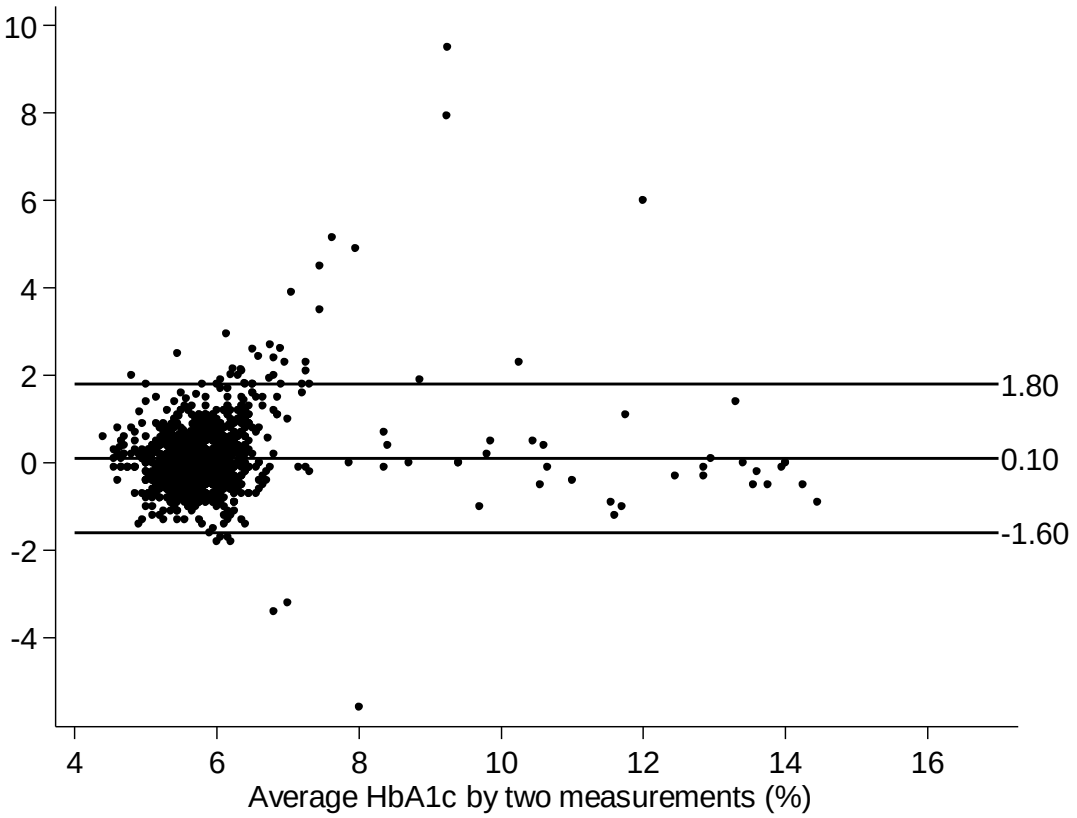
Among South African sample
Lab HbA1c was -0.23% (95%: -0.32, -0.13) greater than POC values (P<0.001)

By sex:



Among women only

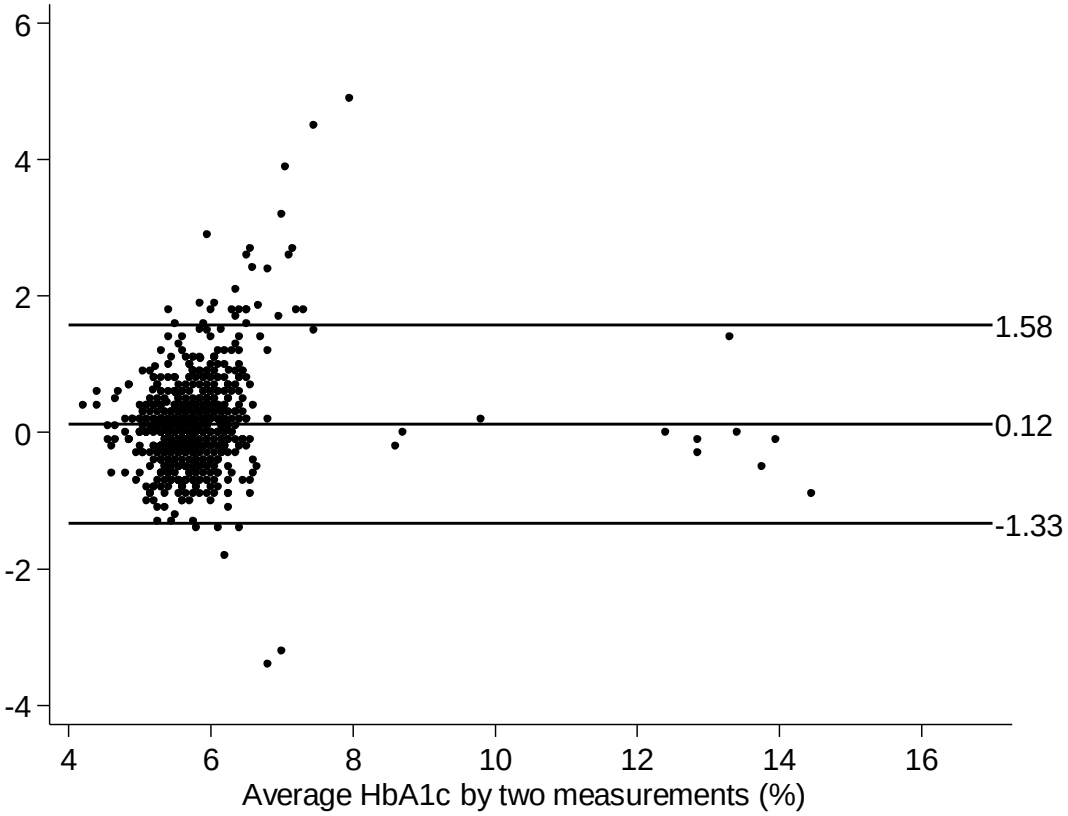
POC value was statistically greater than lab values by 0.21 (95%CI: 0.15, 0.27)



Among men only

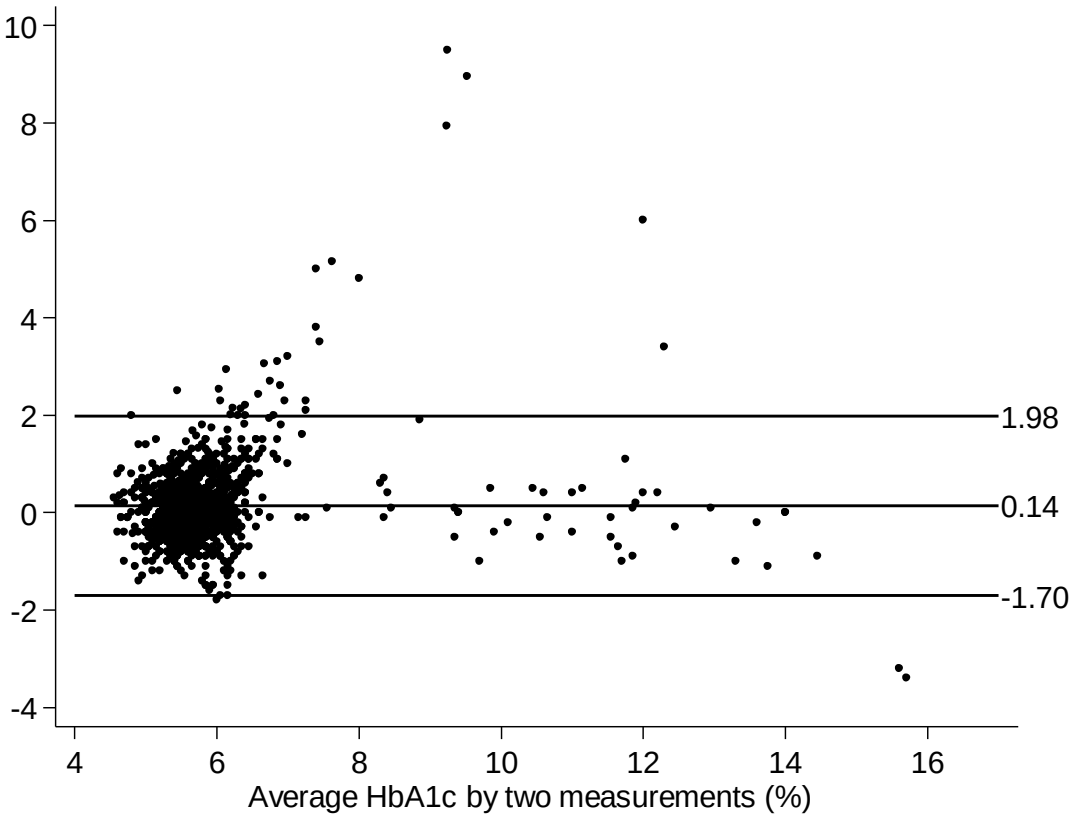
POC value was statistically greater than lab values by 0.10 (95%CI: 0.05, 0.15)

By BMI groups:



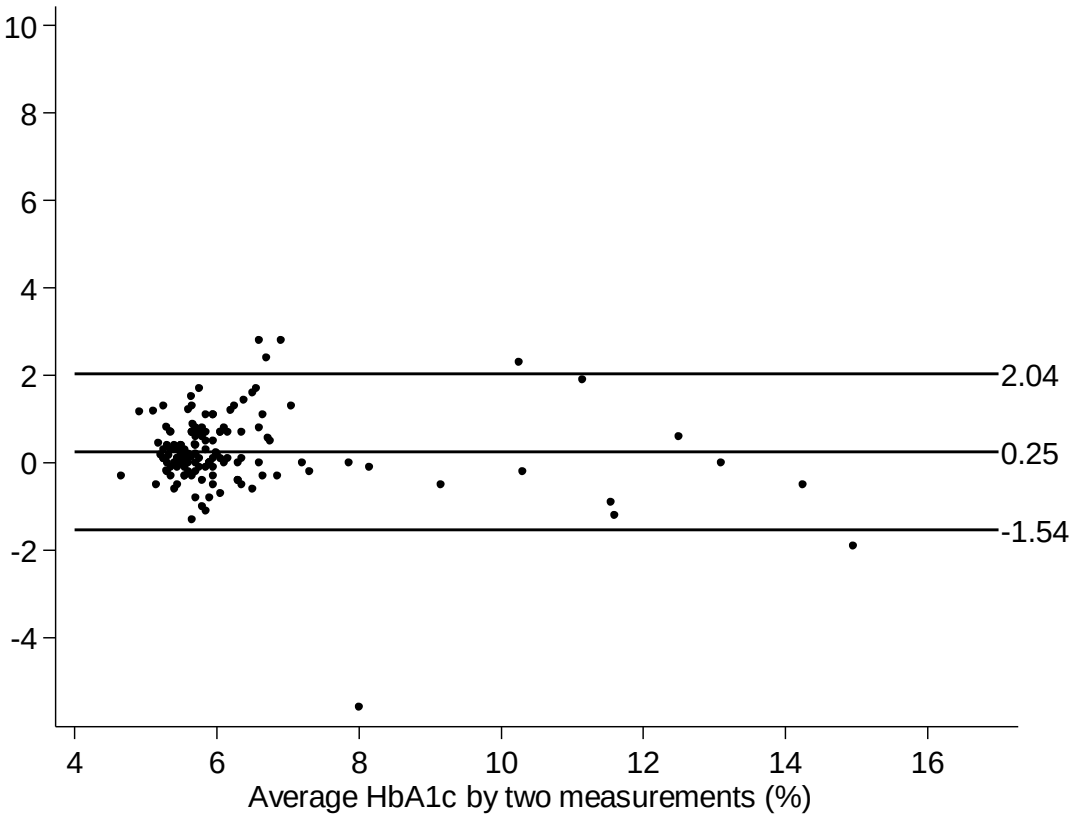
Among underweight group only

POC values were significantly greater than lab values by 0.12 (0.07, 0.18)



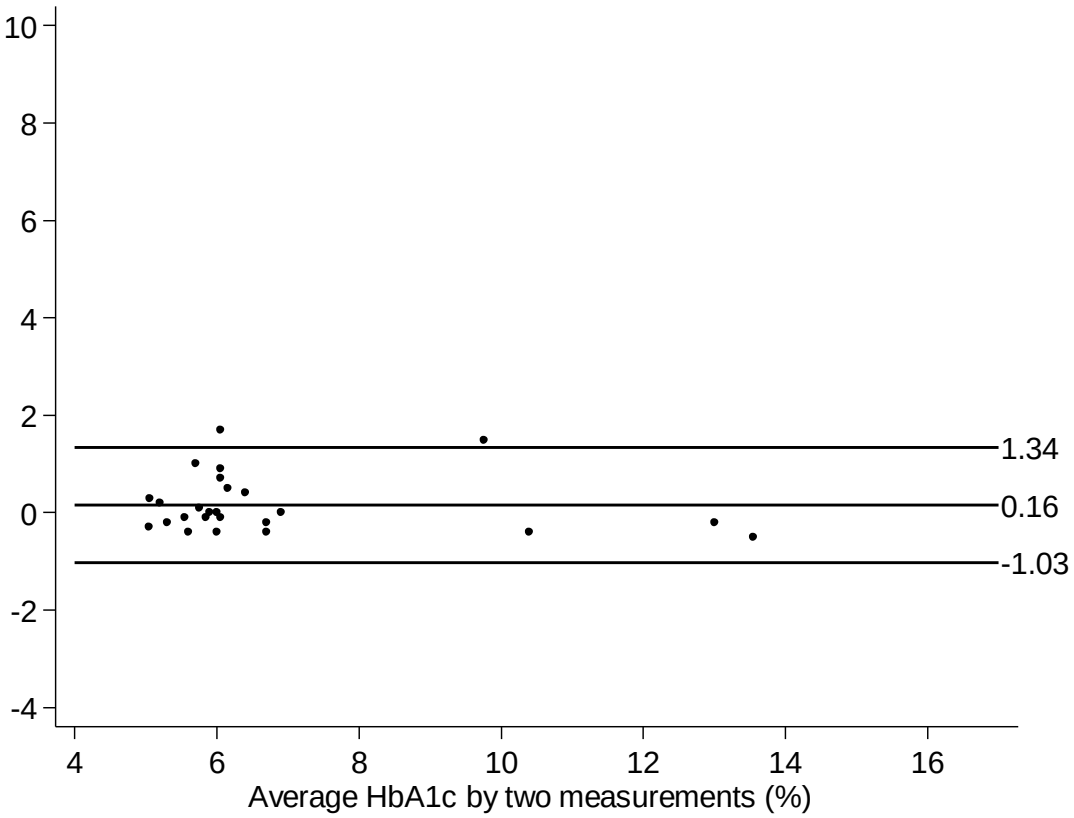
Among normal weight group

POC values were significantly greater than lab values by 0.14 (0.09, 0.20)



Among overweight group (143 people)

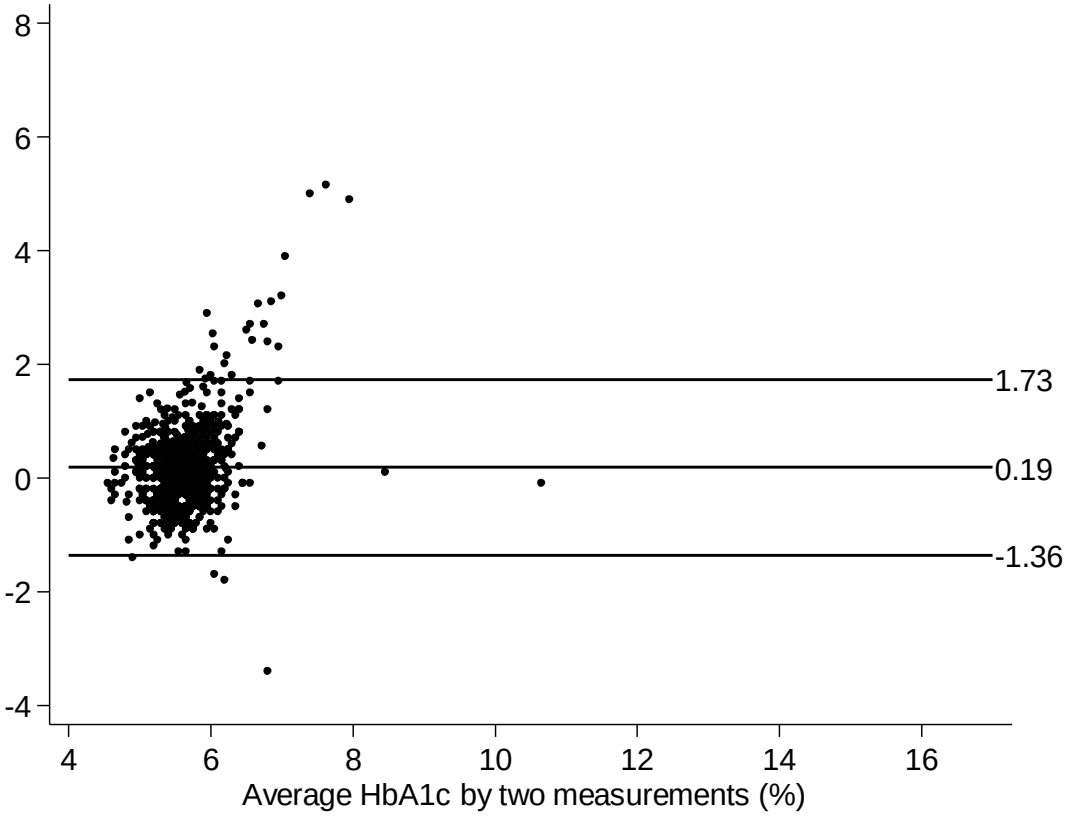
POC values were significantly greater than lab values by 0.25 (0.10, 0.40)



Among obese group (25 people)

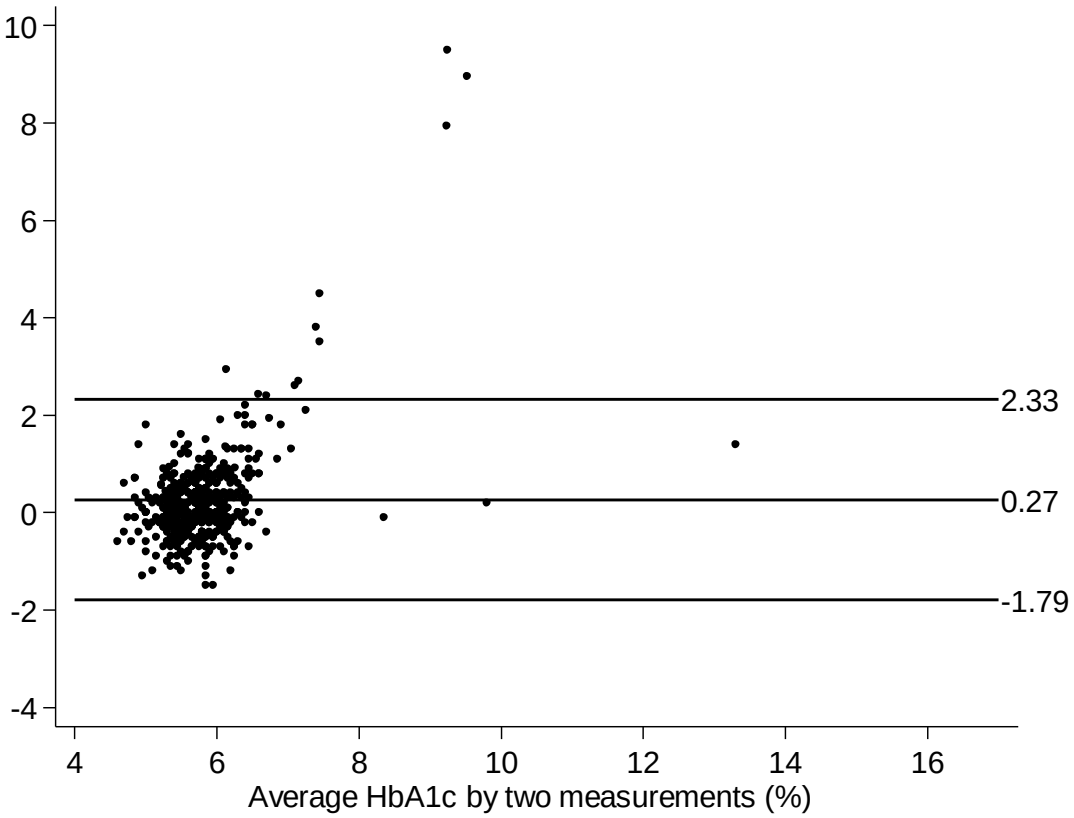
There is no statistical difference between POC and lab values 0.16 (-0.09, 0.40)

By age groups:



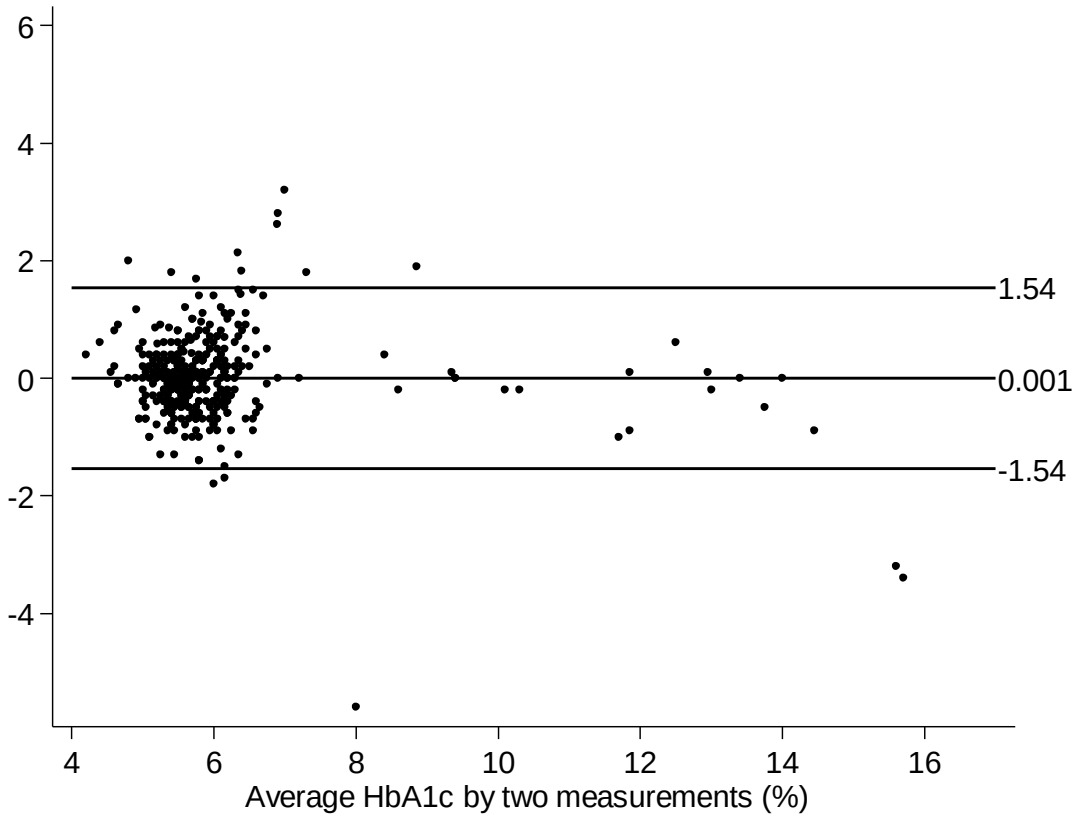
Among <30 years

POC values were significantly greater than lab values by 0.19 (0.13, 0.24)



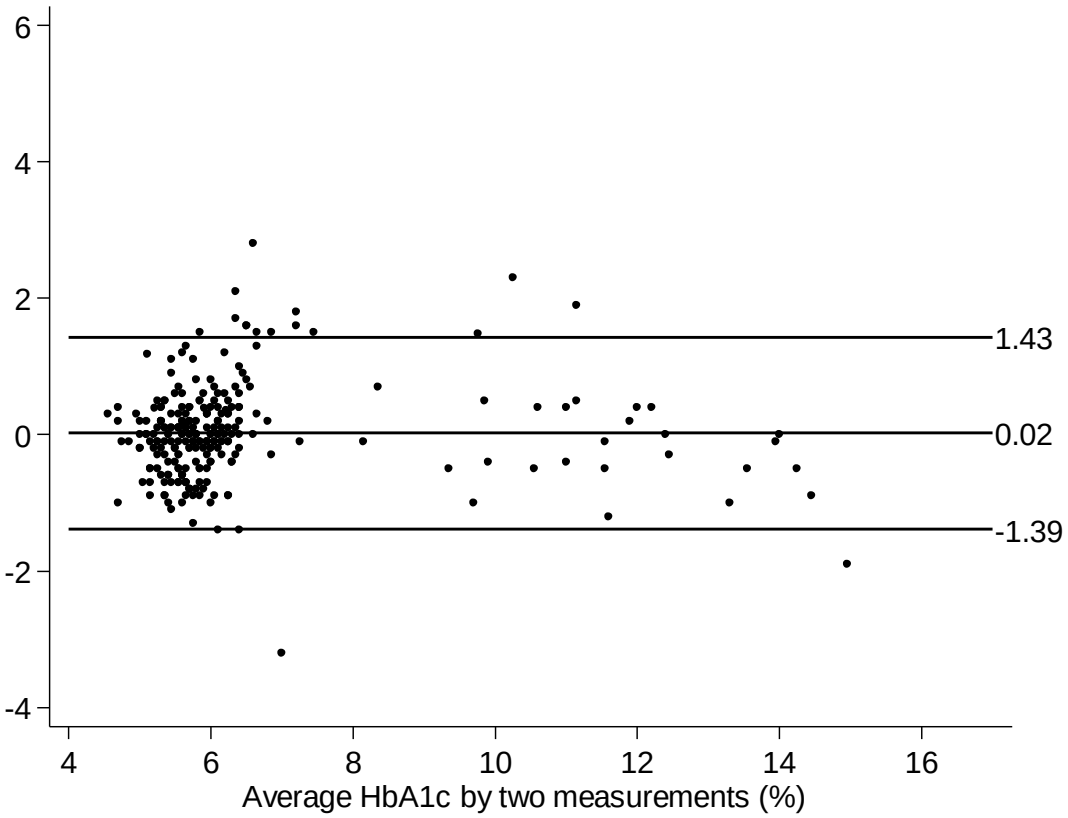
Among 30-39 years

POC values were significantly greater than lab values by 0.27 (0.17, 0.36)



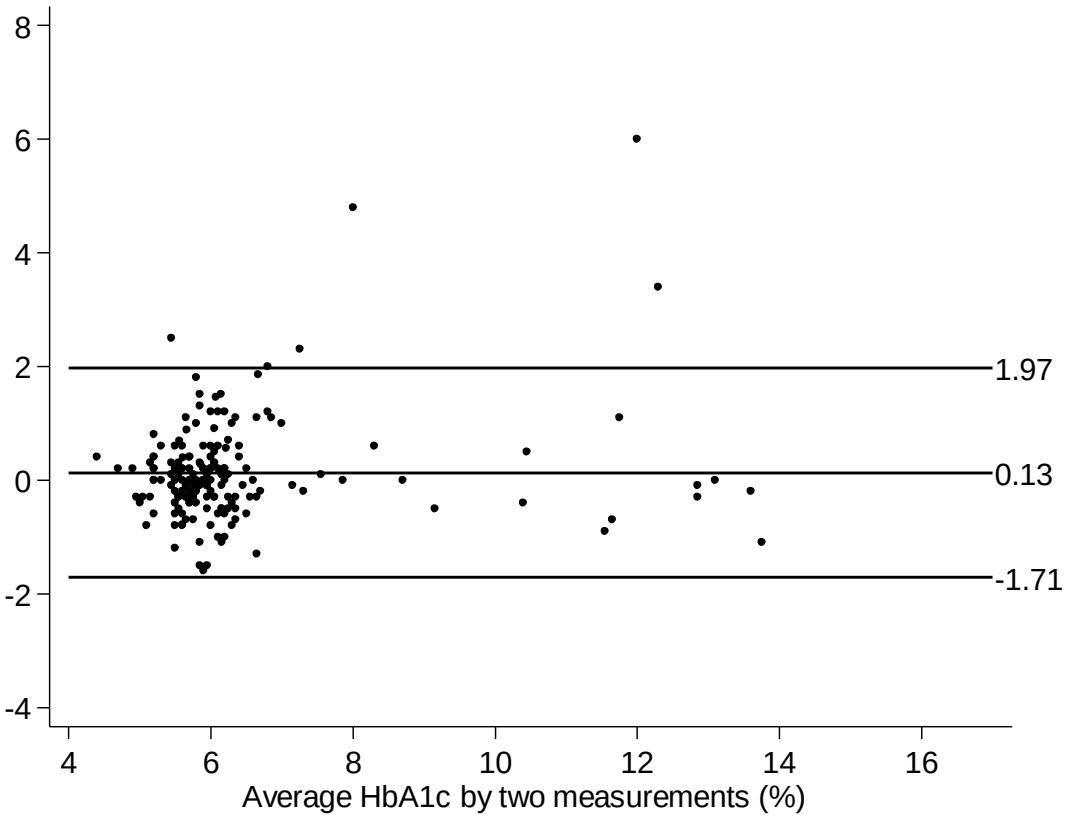
Among 40-49 years (375 people)

There is no statistical difference between POC and lab values -0.001 (-0.08, 0.08).



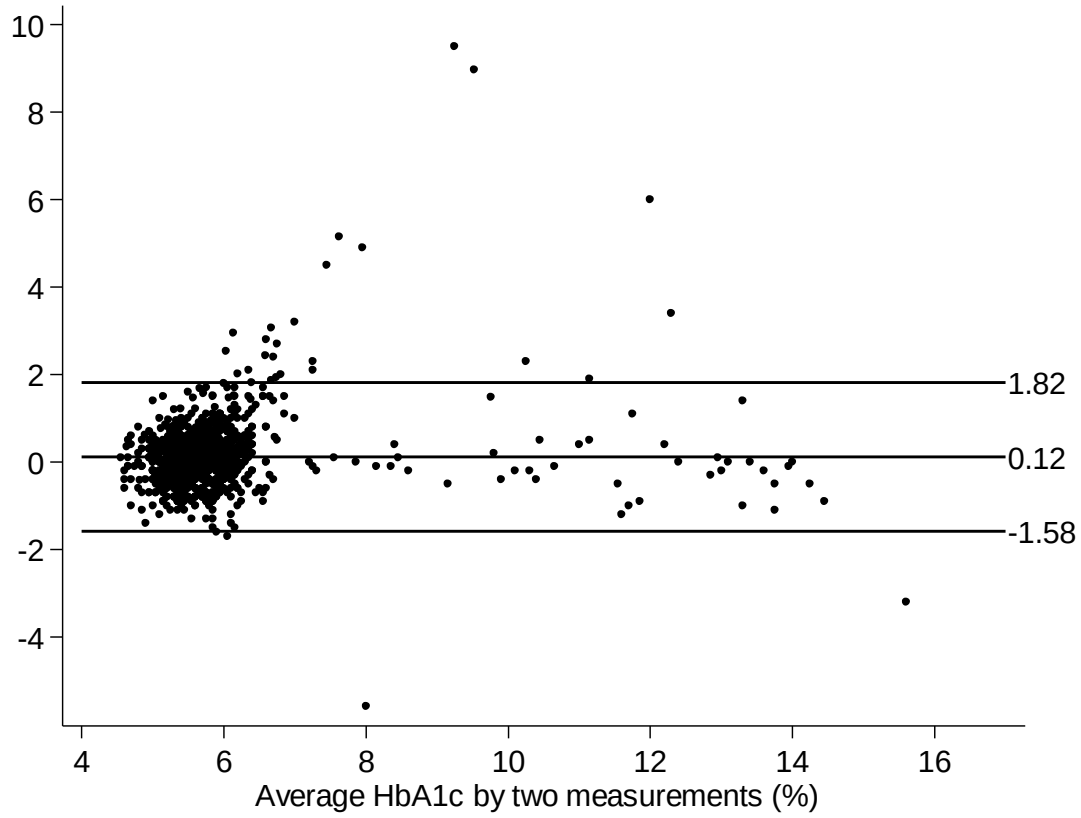
Among 50-59 years (251 people)

There is no statistical difference between POC and lab values 0.02 (-0.07, 0.11)



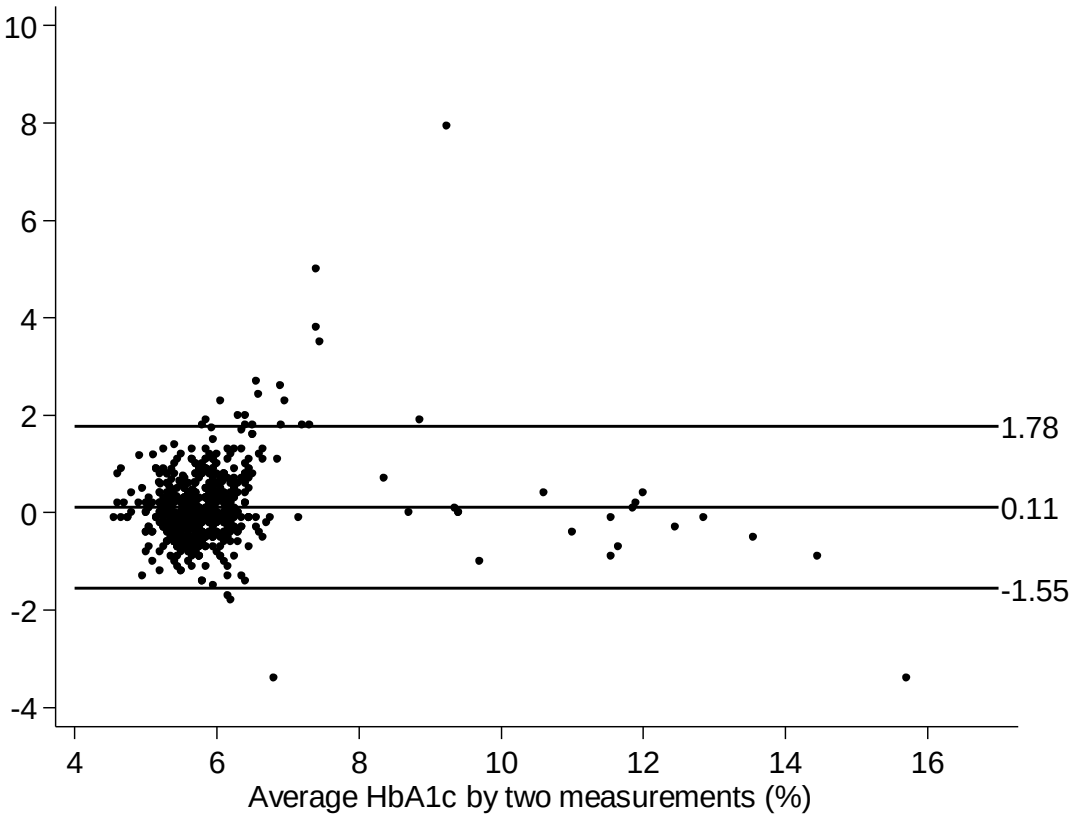
Among >60 years (188 people)
Borderline significant: 0.13 (-0.01, 0.27) P=0.06

By anaemia status:



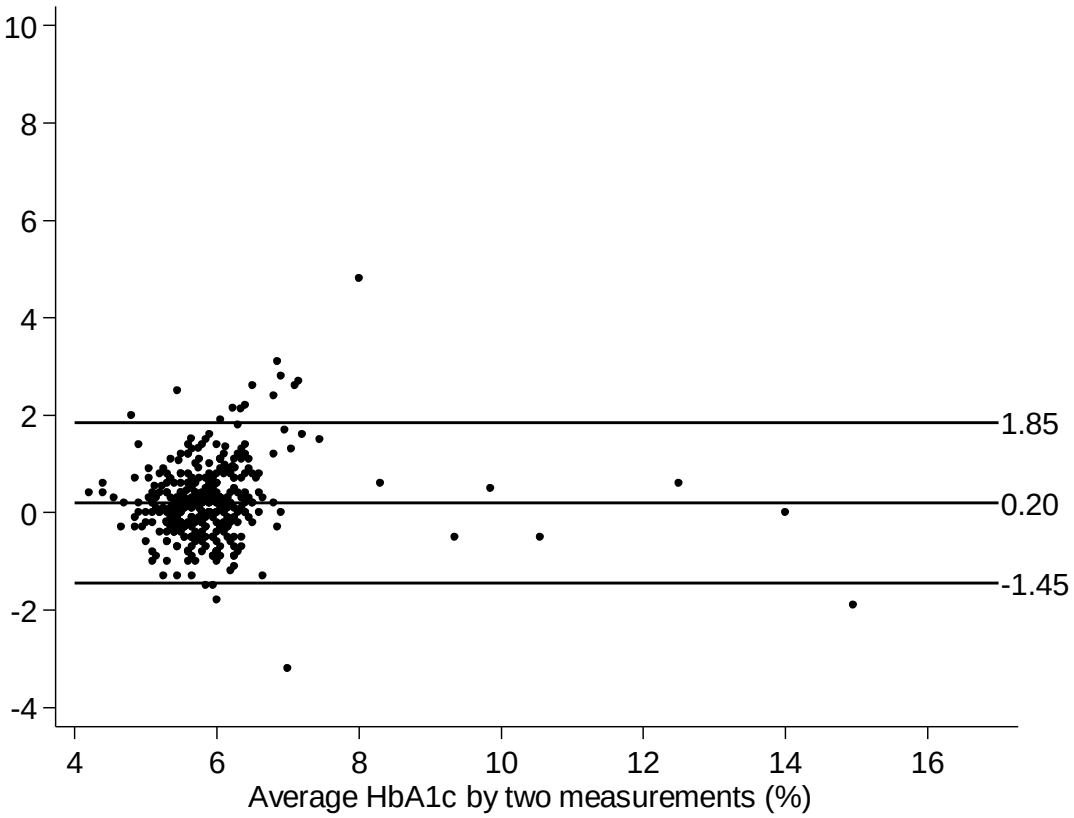
Among non-anaemic group

POC was significantly greater than lab values by 0.12 (0.06, 0.17).



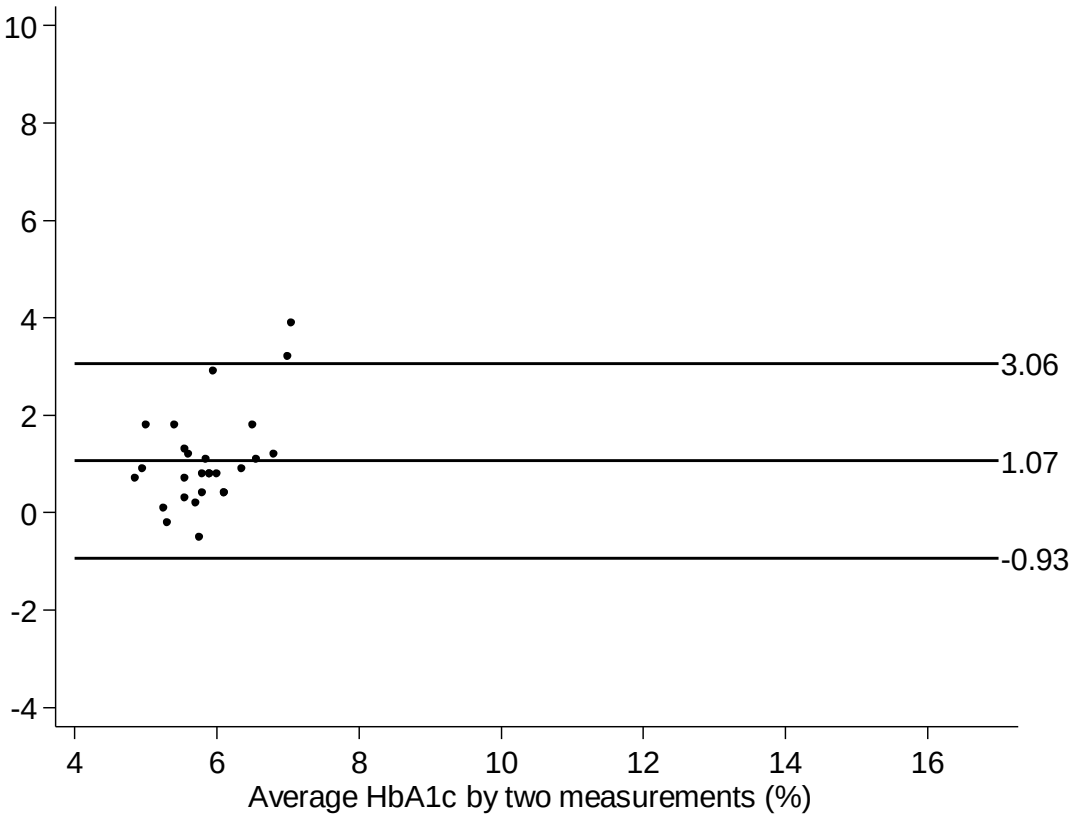
Among mild anaemic group

POC values were significantly greater than the lab values by 0.11 (0.04, 0.18)



Among moderate anaemic group (352 people)

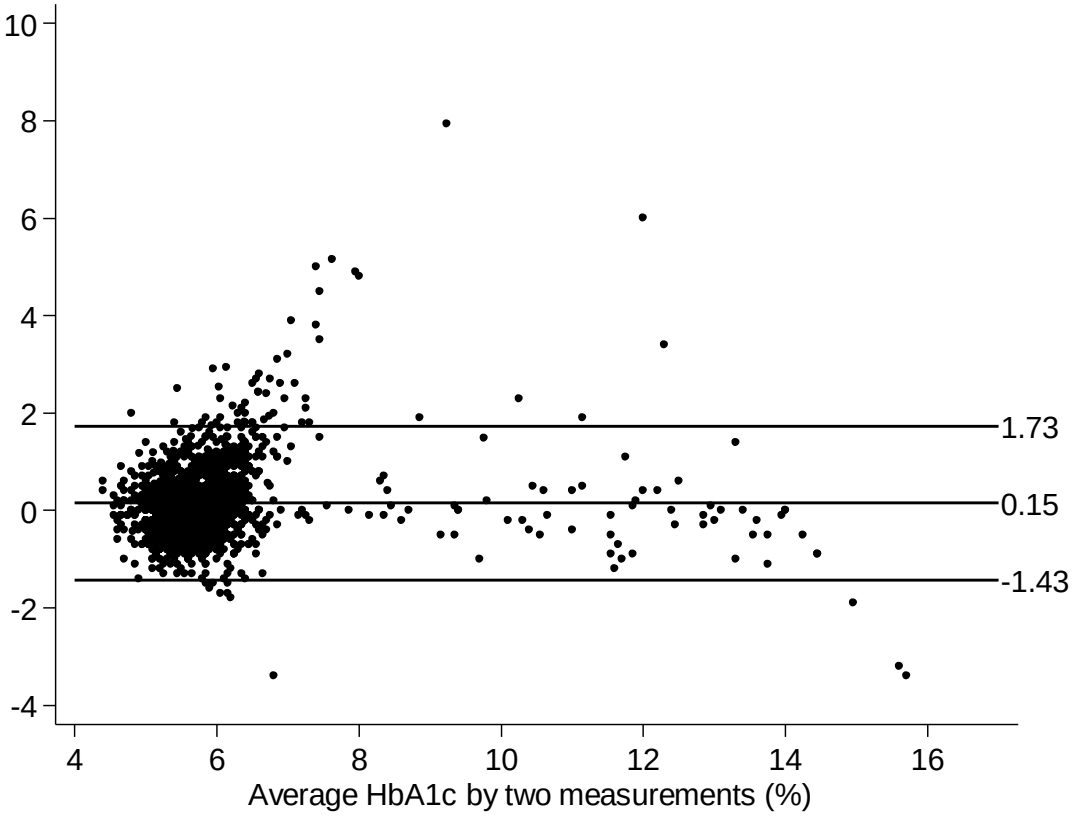
POC values were significantly greater than lab values by 0.20 (0.12, 0.29)



Among severe anaemic group (27 people)

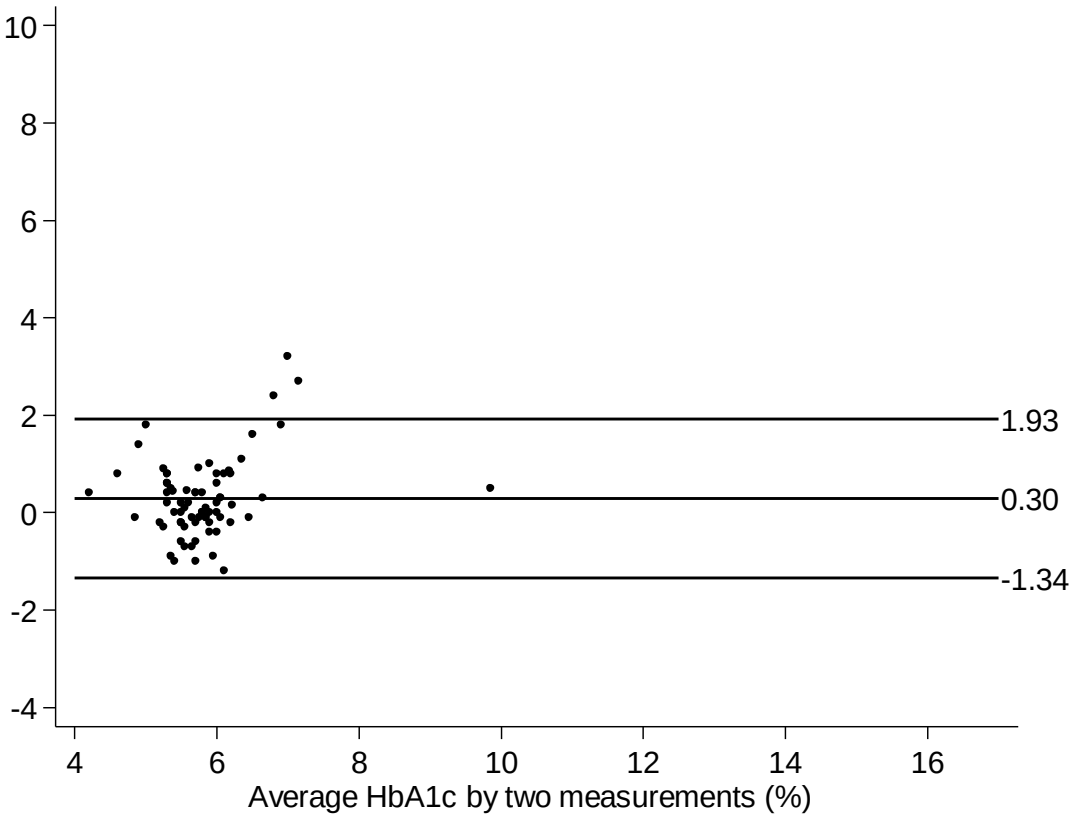
POC values were significantly greater than lab values by 1.07 (0.67, 1.46), P<0.001

By HIV status:



Among HIV- group (1652 people)

POC values were significantly greater than lab values by 0.15 (0.11, 0.19), P<0.001



Among HIV+ group (72 people)

POC values were significantly greater than lab values by 0.30 (0.10, 0.49), P=0.003