

Title: The Effect of Co-Trimoxazole on Serum Potassium Concentration: Safety Evaluation of a Randomised Controlled Trial

Running Title: Effect of Co-Trimoxazole on Serum Potassium

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Structured Summary

Aims

Co-trimoxazole maintains a well-established role in the treatment of *Pneumocystis jirovecii* and *Toxoplasma gondii*, as well as urinary tract infections. Observational studies report hyperkalemia associated with co-trimoxazole which may stem from an amiloride-like potassium sparing effect. Our study reports on changes in serum potassium on patients without acute infections, and the influence of concomitant anti-kaliuretic drugs on this effect.

Methods

Post-hoc analysis of a randomised controlled trial in patients with interstitial lung disease who were assigned to placebo or 960 mg twice daily co-trimoxazole. Serum potassium and creatinine were measured at baseline, six weeks, 6, 9 and 12 months. Primary outcome was difference in mean serum potassium concentrations between co-trimoxazole and placebo at six weeks.

Results

Mean serum potassiums were similar at baseline, 4.24 (\pm 0.44) mmol/L in the 87 co-trimoxazole group participants and 4.25 (\pm 0.39) mmol/L in the 83 control participants. Co-trimoxazole significantly increased mean serum potassium at 6 weeks, difference between means compared to placebo of 0.21 mmol/L (95% Confidence Intervals [CI] 0.09-0.34; $p=0.001$). This significant increase in serum potassium was detectable even after exclusion of patients on anti-kaliuretic drugs, difference between means for co-trimoxazole compared to placebo 0.23 mmol/L (95% CI 0.09-0.38, $p=0.002$). There were 5/87 (5.7%) patients on co-trimoxazole whose serum potassium reached concentrations ≥ 5.5 mmol/L during the study period.

Conclusions

Co-trimoxazole significantly increases serum potassium concentration, even in participants not using anti-kaliuretic drugs. Whilst the magnitude of increase is often minor, a small proportion in our outpatient cohort developed hyperkalaemia of clinical importance.

What is already known about this subject

- Co-trimoxazole has an established role in treating urinary tract, Pneumocystis jirovecii and Toxoplasma gondii infections.
- Observational studies have suggested combination of co-trimoxazole and anti-kaliuretic medications is associated with sudden death through the mechanism of severe hyperkalaemia.
- There are no placebo-controlled randomised trials with serum potassium results to demonstrate these changes.

What this study adds

- Our trial demonstrates significant serum potassium rise in co-trimoxazole users compared to placebo.
- These findings remained in a separate analysis accounting for patients prescribed concomitant anti-kaliuretic medications.
- The magnitude of increase was not large, however would be of importance to patients with serum potassium at the higher end of normal.

Introduction

Co-trimoxazole (a combination antibiotic of trimethoprim and sulfamethoxazole) is a commonly used treatment in the United States for urinary tract infections[1] and a reported 4000 prescriptions a month are dispensed in Canada. Following concerns in the United Kingdom of antibiotic-related Clostridium difficile colitis from other broad-spectrum antibiotics, co-trimoxazole is regaining favor[2] and maintains a well-established role in the

treatment and prophylactic measures for *Pneumocystis jirovecii* and *Toxoplasma gondii* infection[3].

Its link to hyperkalaemia lies in trimethoprim's mechanism of action, which has been described by laboratory and animal studies as that akin to the potassium sparing effect of amiloride, where sodium channel activity is inhibited [4-6]. Earlier studies identified that those with more inherent defects in potassium homeostasis, had a higher risk of exacerbating this antidiuretic effect, these included patients with acquired immunodeficiency syndrome[7] and acutely unwell hospitalized patients with mild renal insufficiency [4, 5, 8]. Recently there has been a significant focus of literature on evaluating the effects of concomitant medication such as inhibitors of renin-angiotensin system [9, 10], spironolactone [11] and beta-adrenoceptor antagonists [12] on precipitating sudden, severe hyperkalaemia, which might be a mechanism behind increased risk of sudden death in co-trimoxazole users, especially in elderly patients. It is speculated that the drug interaction with co-trimoxazole may exacerbate the amiloride-like inhibition of sodium channels in the luminal membrane of the distal tubule resulting in impaired potassium secretion.

However, much of the data are observational in nature[9, 11], and few studies have had access to or reported serum potassium levels obtained through protocolised long-term follow-up in a high quality randomised controlled trial. We undertook a post-hoc analysis of a placebo-controlled randomised controlled trial with 12 months follow-up to evaluate the effect of standard dose co-trimoxazole on the serum potassium concentrations. We also aimed to evaluate the change in serum potassium concentrations in separate subgroups of participants according to baseline history of concomitant medications that can increase serum

potassium concentrations, namely angiotensin converting enzyme inhibitors (ACE I), angiotensin II receptor blockers (ARB) and potassium sparing diuretics.

Methods

This study is a post-hoc analysis of a multicenter randomised placebo-controlled double-blinded parallel arm trial of the use of co-trimoxazole for the treatment of idiopathic pulmonary fibrosis. Briefly, the trial recruited patients from 28 university and district hospitals in England and Wales between January 2008 and 2009. Patients randomised to the treatment arm received the standard dose of 960 mg (two tablets of 480 mg each) twice daily of co-trimoxazole (320 mg trimethoprim, 1600 mg sulfamethoxazole) plus folic acid.

Controls were supplied identical placebos and folic acid. Laboratory testing, including urea and electrolytes were performed at baseline and assessed at 6 weeks, 6, 9 and 12 months as part of the safety monitoring of the study. The full methodology is reported in Shulgina et al. [13]. Research ethics was obtained from the Cambridgeshire 4 Research Ethics Committee [reference number: 07/MRE05/45]. The study was adherent to the Declaration of Helsinki and conducted in accordance with good clinical practice. Safety of the trial was monitored by independent oversight committees (Data Monitoring and Ethics Committee (DMEC) and Trial Steering Committee (TSC)) who had access to all serious adverse events (SAEs) reporting and withdrawals. All patients gave written informed consent. Age, gender, co-morbidities and concurrent medications were recorded at baseline.

The primary outcome of the trial was change in forced vital capacity (FVC) after 12 months.

For this post-hoc analysis, the main outcome of interest was the first follow-up serum potassium measurement at six weeks after study entry. Secondary outcomes included serum potassium concentrations at later time points, as well as serum creatinine concentrations.

A. Statistical analysis

All analyses were conducted using IBM SPSS Statistics 22. We calculated mean values and standard deviations (SD) for serum potassium and creatinine concentrations over the study period at each measurement point. We assessed homogeneity of variance using Levene's test and used the independent t-test to evaluate differences between the two intervention arms.

For categorical adverse events, we used the chi-squared test to evaluate differences between groups. Pearson's correlation coefficient was used to describe the relationship between two continuous variables in the trial participants.

The main outcome was the difference in mean potassium concentrations between the treatment and placebo groups at the 6-week follow-up. We also calculated change in potassium concentrations against baseline at all time points for each individual patient, and compared the mean change between the two groups.

In a pre-planned analysis, we evaluated the primary outcome in subgroups of patients who were, or were not using drugs that retain potassium (ACE I, ARB and potassium sparing diuretics) at baseline.

Results

One hundred and eighty-one patients were enrolled onto the original study. Eighty-six patients were randomised into the placebo group and ninety-five into the treatment group.

These groups were stratified for azathioprine and mycophenolate mofetil use only. **Table 1** summarizes the baseline characteristics of patients included in the complete case analysis, where both baseline and 6-week follow-up potassium were available in included patients.

Appendix 1 lists the baseline characteristics of the entire treatment and placebo group.

Baseline mean potassium, serum creatinine and the number of patients taking medications which could alter potassium homeostasis were in equal distribution. All patients enrolled in the study provided a serum potassium and creatinine level at baseline. The availability of follow-up data diminished as the study progressed, due to adverse events, discontinuation of interventions and withdrawal of consent, n=83, 65, 57 and 54 in the placebo group at 6 weeks, 6 months, 9 months and 12 months respectively whilst in the treatment group n= 87, 63, 51, 53 were available at those time points. Blinded interim analysis showed no significant difference in the percentage of patients dying, average number of adverse or serious adverse events between the two groups.

A. Main Outcome: Difference in Means Between Groups

At the six-week follow-up, the mean serum potassium concentration in the treatment group (4.46 ± 0.41 mmol/L) was significantly higher than the mean in the placebo group (4.24 ± 0.40 mmol/L), which represents a difference between means of 0.21 (95% CI 0.09-0.34) mmol/L, $p=0.001$.

The mean serum potassium concentrations recorded at the four study follow-up visits are shown in **Figure 1** and **Appendix 2**. The change from baseline serum potassium data are shown in **Figure 3** and **Appendix 3**, and indicate significant incremental rises in serum potassium with co-trimoxazole compared to placebo at all follow-up points.

The largest increase in the serum potassium of the entire trial was 1.7 mmol/L, which was recorded in a patient receiving co-trimoxazole. We found that 15/87 (17%) patients on co-trimoxazole experienced a change of $\geq +1$ mmol/L serum potassium at any point in the study compared to 3/83 (3.6%) in the control arm. The relative risk of a rise $\geq +1$ mmol/L serum potassium with co-trimoxazole is 4.77 (95% CI 1.43 – 15.88) compared to placebo.

We found that 25/87 (29%) of patients in the treatment group had a peak serum potassium ≥ 5.0 mmol/L at any point of follow up, compared to 15/83 (18%) patients in the control arm.

The relative risk of serum potassium ≥ 5.0 mmol/L at any point in the trial was 1.59 (95% CI 0.90 – 2.80) with co-trimoxazole compared to placebo.

Overall, 5/87 (5.7%) patients in the co-trimoxazole arm had serum potassium ≥ 5.5 mmol/L, compared to 1/83 (1.2%) in the control arm. There were no reports of hyperkalemia as a cause of a serious adverse event or a reason for patient withdrawal.

A pre-planned analysis on mean serum potassium at baseline to 6 weeks was performed on a subgroup of patients where we excluded baseline users of ACE inhibitors (ACEI), Angiotensin II receptor blockers (ARB) or Potassium sparing diuretics (n=28). **Figure 2** illustrates our finding of a significant increase in serum potassium concentrations in the treatment group compared to placebo, 0.23 mmol/L (95% CI 0.09-0.38, p=0.002), even in the absence of concomitant use of drugs that have been implicated in hyperkalemia. When we

considered the small subgroup comprising users of ACEI, ARB or potassium sparing diuretics, the difference in mean potassium concentrations between co-trimoxazole and placebo arms was not statistically significant (0.14 mmol/L (95% CI -0.10-0.38) $p=0.24$).

B. Secondary Outcomes

Figure 3, Appendix 2 and Appendix 3 illustrate the mean serum creatinine concentrations in treatment and placebo group at 6 weeks, 6, 9 and 12 months. At the six-week follow-up, the mean serum creatinine concentration in the treatment group (105.79 ± 33.43 mmol/L) was significantly higher than the mean in the placebo group (89.81 ± 18.10 mmol/L), which represents a difference between means of 15.99 (95% CI 7.88-24.09) mmol/L, $p=0.005$. The elevation in creatinine was persistent at further follow-up measurements. (**Appendix 2 and 3**). We found a moderate positive correlation between change from baseline in potassium and creatinine concentrations at 6 weeks, $r(168)=0.383$, $p<0.0005$.

C. Renal Adverse Events

On reviewing reported adverse events in patients in the co-trimoxazole group, 10/95 patients (11%) of patients were reported to have a deterioration in renal function compared to 3/86 (3.5%) in the placebo group ($p=0.78$). Here, 7 of the 10 patients in the co-trimoxazole group went on to complete the study whilst 3 of the 10 patients were unable to continue after the 6-week follow-up. Serum creatinine was on a downward trend for these patients on follow-up testing up to 2 months later. Renal impairment was specifically mentioned in the original study publication, however individual electrolytes have never before been published.

Discussion

Main Findings

In this post-hoc analysis of a blinded, placebo-controlled, randomised controlled trial we demonstrate a significant increase in measured serum potassium at 6 weeks in patients taking co-trimoxazole as compared to those on placebo. We note that the significant increase in serum potassium concentrations occurred even in patients who were not taking concomitant ACEI, ARBs or potassium sparing diuretics with co-trimoxazole, thus indicating that this adverse effect is not due to a specific drug interaction. While the magnitude of increase was clinically modest in most patients, we found that about 1 in 7 patients in the treatment group were affected by increases of ≥ 1.0 mmol/L. About 1 in 25 patients receiving co-trimoxazole had a peak serum potassium that exceeded 5.5 mmol/L, which is a concentration that we would consider to be of major clinical concern. We also noted a concurrent increase in serum creatinine with co-trimoxazole therapy within the first six weeks of starting treatment.

Comparison with Literature

Co-trimoxazole has been linked to sudden death through the postulated mechanism of precipitating life-threatening hyperkalemia. The exact renal mechanism has been previously described[4], through human and animal studies. Trimethoprim inhibits renal potassium excretion by blocking sodium channels in the distal nephron and decreasing the electrical driving force favoring potassium secretion. We report findings which can be attributed to the described mechanism. There is a significant rise in mean serum potassium at 6 weeks followed by a sustained increase from baseline at the further three points of serial potassium

measurements. This trend appears to be replicated in serum creatinine. Rise in serum creatinine is secondary to a well described mechanism related to the trimethoprim component of co-trimoxazole which competitively inhibits tubular creatinine secretion[14]. Previous studies have demonstrated a rise in serum creatinine with concomitant fall in creatinine clearance and no significant change in glomerular filtration rate (GFR) [15]. The mechanism of the moderate correlation between increase in potassium and creatinine concentrations are not clear, and further research into the possibility of a nephrotoxic effect may be indicated.

Four large population studies have examined this life-threatening complication of hyperkalemia, thought to be induced by a drug-interaction with co-trimoxazole. Antoniou et al. has reported the highest risk of hospital admission[11] with hyperkalemia or sudden death [16] in patients concurrently taking spironolactone. The same group has also reported a higher risk of hospitalization with hyperkalemia and sudden death in patients taking co-trimoxazole alongside inhibitors of renin-angiotensin system in comparison to patients prescribed other antibiotics. This reaction is thought to be linked to the amiloride properties of trimethoprim, which are further perpetuated by the antagonistic effects of ACEI, ARB and potassium sparing diuretics on aldosterone. In contrast, our study has not demonstrated evidence of life threatening serum potassium concentrations across all patients, even in those taking medications whose mechanisms of action involve aldosterone.

The strength of previous studies lies in their large numbers captured in electronic databases over a significant period of time. However, none of these studies had access to serum potassium measurements. There also remains an important question of whether confounding has been entirely accounted for in the previous observational datasets.

Strengths and Limitations

Unlike our current work, few studies have had access to serial serum potassium measurements in a protocolised manner with a randomised controlled trial. A large analysis of 6162 patients prescribed high and standard dose co-trimoxazole[17] has been reported, however serum potassium measurements in this study were recorded if available at variable times up to 30 days after the initial prescription was made, making it difficult to comprehend what context the serum potassium was measured in. Similarly a retrospective analysis of 53 patients' serum potassium whilst on co-trimoxazole[18] has shown significant ($p=0.017$) increase of serum potassium to mean of 4.67 mmol/L. Again, serum potassium recordings were taken within 5 days of prescription or as close to, with no knowledge of the patient's medical situation at the time. To our knowledge, there has only been one randomised controlled trial with prospective serum potassium measurements[19]. This was an un-blinded randomised controlled trial of 97 outpatients where patients randomised to the control group were those treated with other antibiotics. All patients in this study had one follow up serum urea and electrolyte measurements on day 5 of treatment. Only 6% ($n=3$) of their cohort developed severe hyperkalemia ≥ 5.5 mmol/L, which is comparable to the 2.6% of patients in the Gentry et al.[17] study who developed grade 1 hyperkalemia (5.6-6.0 mmol/L). Unlike our study, this study was not blinded, and patients were receiving active control drugs rather than placebo.

Our study's results are comparable to those who have reported on serum potassium measurements in an outpatient setting. This study builds on those previously described as it has been performed on well patients, with no acute infections, in a blinded, randomised, placebo-controlled setting. We are able to individually account for all potassium-altering

medications in each patient and for the first time report on the sustained, longer term effects of co-trimoxazole on a patient's serum potassium and creatinine. We recognize our study is limited by the smaller sample size, time-varying effect and losses to follow-up that led to fewer available serum potassium measurements as the study progressed. However, we are able to definitively report that the withdrawal of patients has not been precipitated by clinically relevant hyperkalemia. Only 3 of the 10 patients with reported renal deterioration were unable to complete the study after 6 weeks. It was also reassuring to note the improvement in their renal function after withdrawal from treatment, confirming the reversible nature of the impairment. Finally, we did not have sufficient numbers of patients with markedly elevated potassium concentrations for us to be able to reliably identify the patient risk factors that predispose to this adverse effect. The mean age of the co-trimoxazole group was 72.38 (SD 8.45); we were unable to investigate the effect of age on the increase in serum potassium. As the study population was older, this may be in itself a contribution to a larger increase in serum potassium, independent of concomitant anti-kaliuretic medication use. It is possible that there is an underlying genetic predisposition that renders some patients susceptible to hyperkalemia with co-trimoxazole, but this trial was not designed to investigate such pharmacogenetic markers.

Conclusion

Over our study, we did not identify a significant risk of patients developing life-threatening hyperkalemia, even with up to a year's exposure; nor did we find evidence of an interaction with anti-kaliuretic agents. However, we are conscious that a small minority of patients experienced potassium elevations to a degree that may raise clinical concern. Therefore, there

should be far greater caution in those who already have serum potassium concentrations at the top end of the normal range.

TIPAC investigators are listed in alphabetical order in **Appendix 4**.

Statement of competing financial interests: APC (a TIPAC investigator) is an employee of GlaxoSmithKline but has no conflict of interest to declare.

Table of Links:

TARGETS	
G-protein-coupled receptor [21]	Enzymes [24]
<u>Angiotensin Receptor</u>	<u>Angiotensin Converting Enzyme</u>
<u>β1-adrenoceptor</u>	<u>Cyclooxygenase 1</u>
Nuclear Hormone Receptor [22]	<u>Cyclooxygenase 2</u>
<u>Glucocorticoid receptor</u>	<u>Dihydrofolate Reductase</u>
<u>Mineralocorticoid receptor</u>	<u>Thymidylate Synthetase</u>
Transporters [23]	Ion channels [25]
<u>Kidney-Specific Na-K-Cl symporter</u>	<u>Calcium-activated potassium channel subunit alpha-1</u>
<u>Na-Cl symporter</u>	

These Tables list key protein targets in this article that are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [20], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [21-25].

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Table 1: Baseline Characteristics of complete case analysis

Characteristic		Placebo (n=83)	Co-trimoxazole (n=87)
		Mean/number (SD/%)	Mean/number (SD/%)
Age, years	Mean \pm SD	70.86 (8.25)	72.54 (8.45)
Number of women (%)		20 (24.1)	29 (33.3)
Number of patients with hypertension (%)		22 (26.5)	19 (21.8)
Number of patients taking potassium-altering drugs (%)		66 (76.7)	61 (64.2)
	ACE inhibitor	13 (15.7)	13 (14.9)
	Angiotensin Receptor Blocker	8 (9.6)	15 (17.2)
	Potassium Sparing Diuretics	0 (0)	1 (1.1)
	Potassium Supplement	0 (0)	1 (1.1)
	Loop Diuretics	10 (12.0)	15 (17.2)
	Thiazide Diuretics	5 (6.0)	7 (8.0)
	Aspirin	27 (32.5)	33 (37.9)
	NSAID (not including aspirin)	1 (1.2)	1 (1.1)
	Beta-adrenoceptor antagonists	15 (18.1)	13 (14.9)
	Prednisolone	51 (61.4)	49 (56.3)
Mean K ⁺ concentration, mmol/L (SD)		4.25 (0.39)	4.24 (0.43)
Mean serum creatinine level, mmol/L (SD)		89.0 (21.8)	88.96 (25.0)
SD - standard deviation, CI - Confidence Intervals			
NSAID - non-steroidal anti-inflammatory drug, ACE - angiotensin converting enzyme			

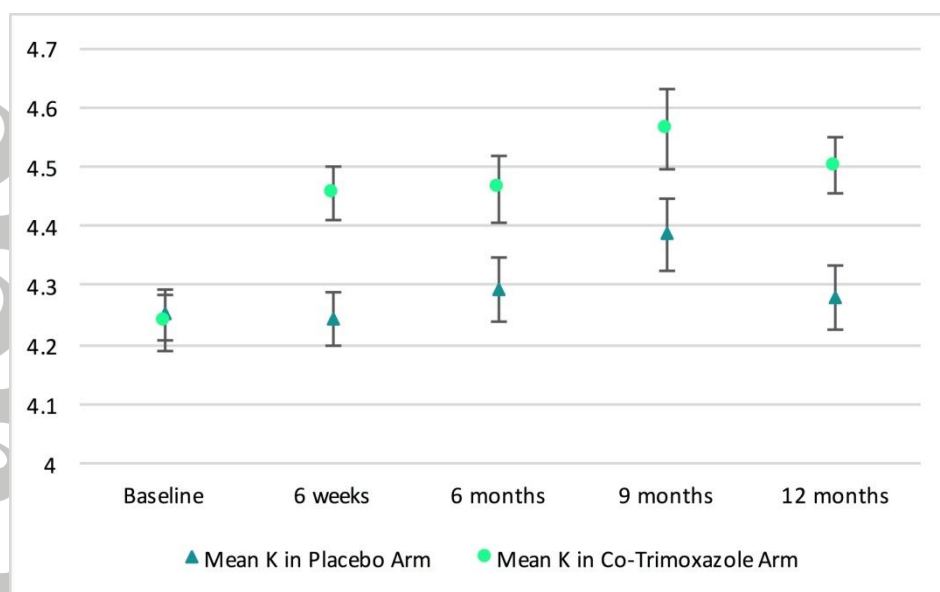


Figure 1: Mean Serum Potassium in Co-Trimoxazole and Placebo Arms

Illustrated error bars depict the standard error of each measurement.

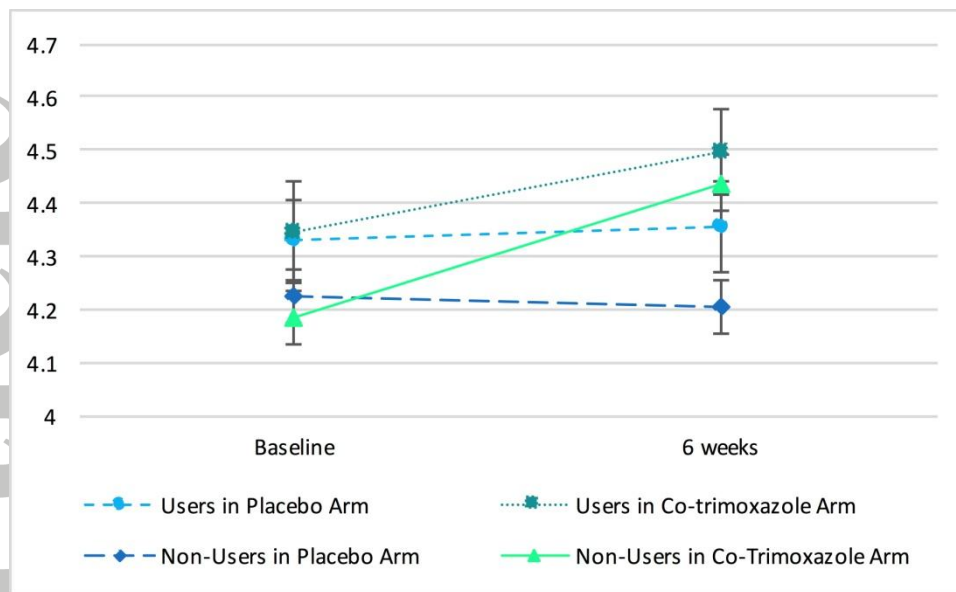


Figure 2: Mean Serum Potassium in users and non-users of ACEi, ARB or K⁺ sparing diuretic users at baseline and 6 weeks.

Illustrated error bars depict the standard error of each measurement

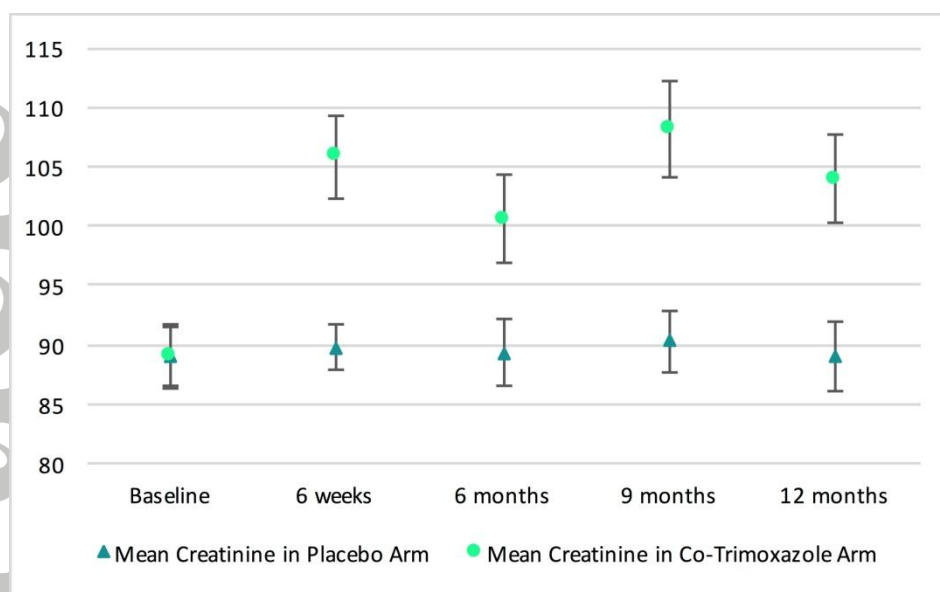


Figure 3: Mean Serum Creatinine in Co-Trimoxazole and Placebo Arms

Illustrated error bars depict the standard error of each measurement