

Correspondence

Concentrate on iron and folic acid along with vitamin B12

We read with interest the National Iron Plus Initiative Guidelines for 2013 onwards.¹ We feel that these guidelines have an important defect and hope they can be corrected.

We were surprised that there is no mention whatsoever of vitamin B12 deficiency. We feel that it is a major mistake to concentrate on the replacement of iron and folic acid alone without considering vitamin B12 deficiency. A community study of slum dwellers in Pune² showed that 61% of the slum dwellers and over 80% of those in the urban area around Pune were suffering from vitamin B12 deficiency and, consequently, raised homocysteine levels. The figure for the rural area was 68%. These figures are higher than those reported for anaemia, including for pregnant women. In a private hospital-based study,³ we found that homocysteine levels were elevated (almost always due to vitamin B12 deficiency) among 80% of all patients with strokes, among a similar percentage of those with myocardial infarction and among 36.5% of persons who had no vascular disease (arterial or venous), nor any reason to think of vitamin B12 deficiency.⁴ Only 9.4% were found to have folic acid deficiency. Vitamin B12 deficiency is far more common than folic acid deficiency among Indians, yet all gynaecologists in India give pregnant women iron and folate but completely neglect vitamin B12 deficiency, to the detriment of the child's intelligent quotient and development. Yagnik *et al.*⁵ pointed out that maternal vitamin B12 deficiency is an important cause of small-for-date babies, premature babies, and a multitude of problems in pregnancy, during the neonatal period and up till 6+ years of age. For a national programme to concentrate only on iron and folic acid is a complete mistake, and it perpetuates the misconception that we grew up with in medical college in the 1950s–1980s that vitamin B12 deficiency is uncommon in India. We thought that this problem had been addressed long ago, but on examining the National Iron Plus programme, we found that we were completely wrong. In our opinion, the strategy of the National Iron Plus initiative needs to be formulated anew, keeping vitamin B12 deficiency in mind, even if it is costlier to provide vitamin B12 than iron and folic acid. Besides anaemia, vitamin B12 deficiency causes a host of complications of the central nervous system, including stroke and coronary artery disease.⁴

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Authors' Reply

We are most grateful for the comments received from the eminent scientists who have made outstanding contributions in the field of vitamin B12 deficiency and associated disorders in India.

The published paper was based on the guidelines of the Ministry of Health and Family Welfare, Government of India, which have been developed on the basis of experience with the previous National Anaemia Control Programme.¹ These guidelines, which have been under implementation since 1970, adopt a comprehensive approach to incorporate all high-risk groups in the preventive strategy against anaemia caused by iron deficiency.

Iron deficiency is the most common cause of anaemia in India, but anaemia can also be caused by other nutritional deficiencies (including folate, vitamin B12 and vitamin A), acute and chronic inflammation, parasitic infections, and inherited or acquired disorders that affect haemoglobin (Hb) synthesis, or the production or survival of red blood cells.² There is an abundance of scientific evidence, in the form of randomized controlled trials (RCTs), systematic reviews and meta-analysis, to prove the usefulness of iron and folic acid supplementation, either oral or parenteral, or daily or weekly, in improving Hb synthesis. However, we do not have adequate scientific evidence on the impact of the administration of vitamin B12 along with iron and folic acid on the improvement of Hb.

Although isolated studies have provided excellent information and data regarding the benefits of vitamin B12 on cognition, neurological functions and pregnancy outcomes, the quality and strength of the evidence will be considered low.³ To gather high-quality evidence so as to ascertain whether vitamin B12 has a place in the Iron Plus Initiative, we need more RCTs on the impact of the administration of iron and folic acid with vitamin B12 on improvement in Hb.

The Iron Plus Initiative guidelines were intended solely to provide evidence-based national guidelines for preventive and therapeutic interventions against anaemia among different high-risk groups. The major emphasis was on iron-deficiency anaemia. The guidelines also recommend dietary diversification to fulfil the requirement of iron, folic acid, vitamin C and vitamin B12 to prevent anaemia.⁴

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Hiccups as an unusual manifestation of tuberculosis-associated immune reconstitution inflammatory syndrome

Tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) in HIV is the paradoxical worsening of an existing lesion or condition after initiation of highly active antiretroviral therapy (HAART) due to dysregulated augmentation of immune responses, despite an effective virological suppression.¹ The incidence has risen to nearly 54% with concomitant treatment of both diseases.² Persistent hiccups, as a manifestation of TB-IRIS is extremely rare, and we present probably the first case reported from India.

A 38-year-old man with HIV-1 presented with fever and productive cough of 3 months duration with no other important medical history. Physical examination revealed few crepitations at the right infrascapular region. Chest X-ray showed minimal bilateral hilar node enlargement. A sputum smear examination revealed acid-fast bacilli and cultures grew *Mycobacterium tuberculosis* (Mtb) sensitive to antituberculosis drugs. Random plasma sugar, liver and renal

function tests, and abdominal ultrasonogram were within normal limits. His baseline CD4 count was 69 cells/cmm and HIV plasma viral load was 438 000 copies/ml.

He was started on four drug antituberculosis therapy (ATT) daily under supervision, along with HAART after 20 days, as per the national guidelines.³ On day 16 post-HAART, he complained of hiccups as the sole symptom without any overt abnormality on physical examination. Pantoprazole, metoclopramide and antacids were administered orally. Two days later he was febrile (38.5 °C) and X-ray chest showed minimal mediastinal enlargement. Quantitative buffy coat analysis for malarial parasite and urine cultures were negative. Compared to the baseline values, there was a 2.3-times log₁₀ decline in plasma HIV viral load, an increase in CD4/CD8 ratio and elevated levels of interleukin-6 and C-reactive protein (Table I). He became afebrile after 3 days of receiving acetaminophen, but the hiccups persisted, warranting hospitalization.

Baclofen 10 mg (oral) twice a day was added. Ultrasonogram (repeated) revealed multiple enlarged abdominal lymph nodes (Fig. 1). Cytopathological examination of a left cervical node, that appeared

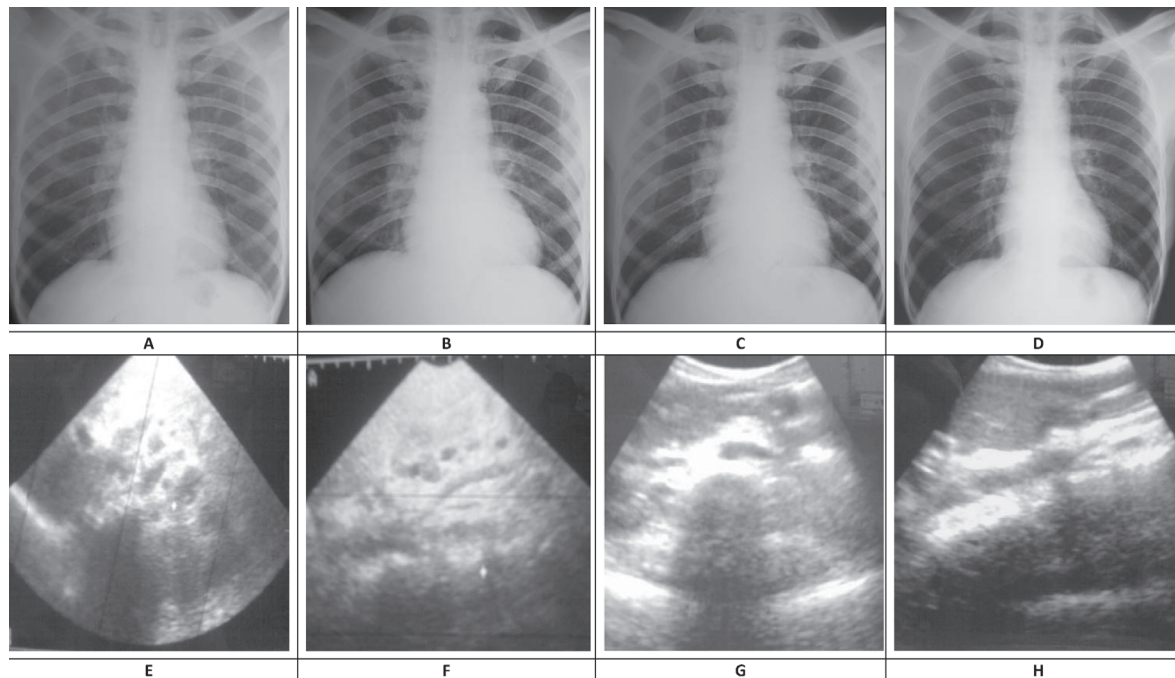


FIG 1. Chest X-ray (A-D) and ultrasonogram abdomen (E-H). A: Before starting antitubercular therapy (ATT); B: Day 3 of immune reconstitution inflammatory syndrome (IRIS) event; C: Day 25 of IRIS event; D: End of ATT; E and F: Day 9 after IRIS event; E: Extensive mesenteric adenitis; F: enlargement of lymph nodes along the portal vein; G and H: End of ATT after steroid therapy showing clearance; G: mesenteric and para-aortic region; H: along the portal vein.

TABLE I. Haematological parameters serially evaluated (including immune markers)

Parameter	Pre-ART	Antitubercular therapy				
	15/07/2011	IRIS episode 29/08/2011	2nd month 19/09/2011	6th month 20/01/2012	12th month 27/07/12	18th month 11/01/13
Haemoglobin (g/dl)	9.2	8.3	9	10.2	12.2	14.1
Red blood cells (cells/ml)	3.55	2.9	3.21	3.26	3.63	4.13
White blood cells (cells/ml)	6400	5300	6000	5000	3300	3200
Packed cell volume (%)	26.4	24.2	27.4	30.4	33.0	39.8
Platelets ($\times 10^3$ /ml)	156	200	186	368	179	264
CD4 (cells/ml)	69	50	66	107	142	174
CD8 (cells/ml)	1096	226	409	528	305	344
CD4/CD8 ratio	0.06	0.22	0.16	0.2	0.47	0.51
Viral load (copies/ml)	438 000	1973	<400	<400	Not done	Not done
C-reactive protein (mg/L)	25.4	86.5	20.1	2.3	Not done	Not done
Interleukin-6 (pg/ml)	12.6	35.7	18.1	1.5	Not done	Not done

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simultaneously, revealed granulomatous lymphadenitis that was culture negative for Mtb. A diagnosis of IRIS was made by an independent panel of doctors (CC, SSe, SSw) based on the INSHI criteria (International Network for the Study of HIV associated IRIS).¹

He was started on steroids and his hiccups resolved in 5 days even though the abdominal nodes persisted on the ultrasonogram for several weeks. HAART and ATT were continued uninterrupted. At the end of ATT (month 6), ultrasonogram of the abdomen and X-ray chest were normal.

TB-IRIS presenting as hiccups is extremely rare with few cases reported with sarcoidosis,⁴ histoplasmosis⁵ and after steroid therapy in patients with lymphoma.⁶ That steroids alleviated hiccups, rather than aggravating it, aided in diagnosing IRIS.⁶ Resolution of hiccups (that correlated with decreases in levels of immune markers) despite persistent abdominal nodes signified an inflammatory pathology rather than mere physical compression.⁷ The importance of recognizing IRIS does not end solely with appropriate medication, but requires continued reassurance in the wake of frustrating symptoms, thus ensuring patient's compliance to life-long therapy of HAART.

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Erratum

In the Correspondence titled 'Team-based learning in a medical centre in Malaysia: Perspectives of the faculty' by Salam *et al.* (*Natl Med J India* 2014;**27**:350), the Acknowledgement should read: 'We received UKM ethics committee grant PTS-2013-161 for this research' and not '... grant PTS-2012-161. . .'. We regret the error.—Editor