Growth failure in HIV-infected children

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Consultation on Nutrition and HIV/AIDS in Africa: Evidence, lessons and recommendations for action

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Contents

1. Introduction

Abnormalities in growth and metabolism are common in children infected with HIV. Poor growth was among the first manifestations of HIV infection to be recognized in children and had a significant effect on short-term survival (*1,2*). More recently alterations in body fat distribution and lipid, glucose and bone metabolism were described that may place HIV-infected children at increased risk for future morbidities.

2. Growth failure

Poor growth is both a manifestation of HIV as well as an independent risk factor for death. Numerous studies performed in children in a variety of settings including the United States and Africa demonstrate that poor growth is a sensitive indicator of disease progression and an independent risk factor for death. Studies conducted largely in industrialized countries have identified multiple primary and secondary factors involved in growth.

2.1. Classification of growth disorders in HIV

The importance of growth to HIV infection has long been appreciated and is reflected in the nearly universal inclusion of growth measures as study endpoints in therapeutic trials as well the inclusion of growth abnormalities as criteria for severe disease in both the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) classification systems. Children with growth failure (e.g., attained weight for age <60%) meet WHO Stage III (severe) disease criteria. Abnormal growth is also included in the criteria diagnosis of AIDS wasting, which is a category C criterion (AIDS-defining illness) within the CDC classification system for HIV-infected children. AIDS wasting is defined as weight loss of 10% or more of body weight or deceleration in weight gain resulting in downward crossing of 2 or more of the percentile lines for age (e.g., 95th, 75th, 50th, 25th, 5th) in a child older than 1 year or in the 25th percentile of weight for height on consecutive measurements separated by more than 30 days in addition to the presence of chronic diarrhoea or chronic fever.

Nearly every clinical trail conducted by the Pediatric AIDS Clinical Trial Group has included growth, most commonly as weight-for-age *Z*-scores, as a study outcome measure. An important

limitation of weight-based definitions is that they fail to identify children with compromised statural growth, which in some populations is the most common growth abnormality. Compromised statural growth is arguably superior to weight-based criteria as an indicator of disease progression. Benjamin et al. (*3*) recently reported that height velocity was more strongly associated with disease progression than was weight velocity. Other terms such as growth faltering, failure to thrive, growth retardation and growth failure, which indicate declining weight for age, height for age or both, have also been used in some studies of children with HIV infection

2.2. Prevalence of growth abnormalities

Diminished growth is highly prevalent in HIV-infected children. Estimates of growth failure vary by study population and according to the criteria used. Studies from Europe performed with children receiving antiretroviral drugs (ARVs) of modest efficacy (before the availability of potent multiclass combination ARV regimens) reported a failure-to-thrive prevalence of approximately 50% in children surviving to age 5 years (*4*). Fewer data are available from birth cohorts in developing countries. Bailey et al. (*5*) reported growth retardation, defined as length-for-age *Z*-score greater than -2 SD based on U.S. National Center for Health Statistics references, in more than 60% of HIV-infected children surviving to age 20 months in a study performed in the Congo. High levels of stunting were also observed in noninfected children born to HIV-positive mothers as well as children born to HIV-negative mothers.

2.3. Intrauterine growth

Prospective cohort studies performed in Haiti and Africa indicated that maternal HIV infection affects pregnancy outcomes adversely (*6–10*). However, findings of studies performed in industrialized countries, where confounding by other maternal factors is more of a problem, are less consistent (*11,12*). Whether maternal HIV per se has an independent effect on intrauterine growth apart from established obstetrical factors is not certain. Many but not all studies report that infants born to HIV-positive mothers have significantly lower mean birth weight and length than do infants of HIV-negative mothers regardless of whether HIV transmission has occurred. The disparate findings likely reflect the underlying differences in the prevalence and types of obstetrical risk factors in the study samples. High rates for reterm births and small-for-gestational age infants are reported among

samples of HIV-positive women in the United States, but most adverse outcomes are attributable to low socioeconomic status, suboptimal prenatal care and drug use (*13*). In contrast, a prospective study in semirural Rwanda reported that intrauterine growth retardation but not prematurity was associated with HIV infection (*14*). The influence of maternal nutritional status on birth outcomes are discussed in greater detail in this report by Papathakis (*15*).

Intrauterine exposure to ARVs either as a maternal therapy or as chemoprophylaxis to prevent mother-to-child HIV transmission does not appear to significantly affect birth outcomes (e.g., length of gestation and birth size) or subsequent growth (*16,17*). Intrauterine and postnatal growth in HIV-negative children with in utero and neonatal azidothymidine exposure is normal (*18*). No effect on weight, height, head circumference or cognitive or developmental function up to age 4 years has been reported among those exposed to azidothymidine (*19*). Birth outcomes and subsequent growth related to ARV treatments introduced more recently for use during pregnancy have been less well studied. Low birth weight was reported in association with protease inhibitors in an initial study (*20*) but this was not confirmed in subsequent larger studies with better capacity to adjust for potential confounding (*21*). No studies have evaluated the effect of multiclass antiviral regimens on birth outcomes in malnourished women.

Although some evidence suggests that fetal HIV infection affects fetal growth, much of the data show no differences in birth size between HIV-positive and -negative newborns of infected mothers. In a prospective study performed in the United States, Moye et al. (*22*) found that the effect of intrauterine acquired HIV infection on weight of newborns was -0.28 kg and on length was –1.64 cm compared with HIV-exposed but -negative controls. Differences in birth weight and height remained after the effects of maternal drug and alcohol exposure were controlled for. An effect on head circumference at birth (mean difference 0.7 cm) was also observed.

Most studies, however, including those from Europe (*23,24*), Haiti (*9*), the United States (*11*) and the Congo (*5*), failed to detect differences. Because in utero HIV transmission appears to occur late in gestation, the effect on fetal growth would not be anticipated to be substantial. These findings are also comparable with observations in HIV-1 transgenic mice of no effect of infection on embryonic or fetal growth (*25*).

The reasons for the discrepancy among some of the studies is not known. Difficulties in controlling for confounding by factors such as severity of maternal disease, which is associated with the risk of mother-to-child transmission of HIV as well as birth size, may be partially responsible. In addition, population differences in rates of prematurity, socioeconomic factors and other prenatal factors that influence birth outcomes may also be involved (*26*).

2.4. Postnatal growth of HIV-infected infants and children

The negative effects of HIV infection on postnatal growth have been consistently observed and well documented in studies performed in both industrialized and developing countries. Disturbances in growth are detectable well before the onset of opportunistic infections or other manifestations. Growth faltering by age 3–4 months was observed in studies performed in the United States, Europe and Africa. Height and weight impairment increases with age. Moye et al. (*22*) observed that HIV-infected children were 0.7 kg lighter and 2.2 cm shorter than children 18 months of age exposed to but not infected with HIV.

Sub-Saharan African children with HIV also have growth retardation early in life. An effect on length for age and weight for age by age 3 months compared with values for seroreverters was reported in a South African urban cohort (*27*). In some studies among sub-Saharan African children, wasting (e.g., disproportionate effect on weight versus height) becomes prominent after 1 year (*5*). Nonetheless, although the effect on weight is disproportional, effect on length is still severe in this cohort—50% with length-for-age *Z*-score below –2 SD by 1 year.

Data for beyond age 4 years are more limited but an average weight deficit of 7 kg and height deficit of 7.5 cm by age 10 years was reported in the European Collaborative Study (*23*). Progressive stunting (i.e., proportionately decreased statural and ponderal growth) is more typical than wasting (disproportionate decrease in weight for length) in postnatal growth. Only a single study reports growth beyond age 2 years in sub-Saharan Africanchildren in which the HIV effects on growth are diminished compared with earlier in life (*10*). This finding may reflect the early mortality of the most severely affected. Overall, sexual maturation is delayed in perinatally HIV-infected children, although precocious puberty is also occasionally noted (*28–30*).

2.5. Fat-free or lean body mass is decreased in HIV-associated growth failure

Alterations in body composition accompanying paediatric HIV infection were reported in studies performed in Europe and North America. Inclusion of measurements of body composition either with simple methods such as body skinfold thickness and circumference measurements (e.g., anthropometrics) or more sophisticated approaches such as dilutional methods for determination of total body or intracellular water, imaging methods such as dual x-ray absorptiometry or indirect estimation methods such as bioimpedance analysis provide a means of quantitating fat and fat-free or lean tissue stores. More specifically, body cell mass (the metabolically active portion of lean tissue) can be estimated by counting total body potassium.

Lean body mass is lower in HIV-infected children than in HIV-negative control children when assessed by arm muscle circumference (*31*). Reductions in fat-free mass and body cell mass were also documented using laboratory-based methods, including dual x-ray absorptiometry, bioimpedance analysis and whole-body potassium counting (*32,33*).

In children with HIV-associated growth failure, fat-free or lean body mass decreases preferentially and body fat is relatively spared (*32,34*). This body composition pattern is distinct from that of children with strictly nutritionally based stunting (*35*,*36*) and is comparable with that of HIV-positive adults with HIV infection and other wasting disorders and supports the involvement of preferential catabolism or deranged anabolism (*35,37*).

2.6. Growth, body composition and survival

The poor growth and decreases in amount of fat-free or lean mass are significantly linked to survival. Studies performed in perinatally HIV-infected children from the United States, Europe and Africa and HIV-infected children with hemophilia indicate that poor growth is independently associated with poor survival. Studies performed early in the U.S. HIV epidemic identified poor growth as an independent risk factor for death, with a relative risk of 2.0 in children receiving zidovudine as monotherapy (*38*). Similarly, HIV-infected Ghanaian children with poor weight gain in infancy have a fivefold increase in the risk for death by age 2 years (*39*). Fontana et al. (*33*) estimated that the relative risk of death was increased fivefold in HIV-infected children with the lowest quantities of fat-free mass.

In the United States, where adequate sources of nutrition are readily accessible, somatic growth is also a sensitive indicator of prognosis during treatment with ARVs (*40*). Recently, Benjamin et al. (*3*) determined that statural growth velocity (height-for-age *Z*-score) was the growth index most closely associated with clinical progression, immune reconstitution and declines in viral replication among U.S. children receiving potent ARV therapies. The relationship between survival and height growth is reported to be independent of age, viral load and CD4+ cell count (*41*). Height growth may also be an important predictor of survival regardless of HIV status.

2.7. Etiology of HIV-associated growth failure

A number of causal factors suggest that the genesis of growth disturbances in HIV-infected children is multifactorial. Poor growth is often attributable to recognizable illnesses and secondary conditions that accompany HIV infection. Secondary causes of growth faltering or failure, many of which are potentially preventable, reversible or modifiable, are involved. These include dietary insufficiency, diarhheal illnesses, and anemia. Poor growth is also encountered in HIV-infected children with no discernible secondary illnesses (i.e., much of the variance in growth appears to be independent of HIV infection and suppression of viral replication with ARVs is an importance means of enhancing growth). Research in this area has also provided insight into several potentially important mechanisms involved in impairment of normal growth.

2.8. Studies of energy balance and viral replication

Undernutrition appears to play an important role in HIV-associated growth failure (*42,43*). Even in settings where food sources are adequate and readily accessible, dietary intake is lower in HIV-positive children than HIV-negative control children (*37*,*44*). In addition HIV-infected children with growth failure have lower intake than do HIV-infected children with normal growth (*45*). Anorexia or comorbid conditions that impede food intake, such as oral candidiasis, are presumed to cause this lower intake. Tumor necrosis factor-α, which is found at increased levels in HIV infection, could be involved in appetite inhibition (*46*).

In contrast to some studies of HIV-positive adults, no increases in basal metabolic rate were reported in HIV-infected children in the absence of secondary infections (*34,44*,*45*). Nonetheless energy balance studies performed in U.S. children found energy deficits in children with HIV-

associated growth (*45*), suggesting that dietary intake for children with growth failure is not sufficient to meet metabolic demands and sustain normal growth. In contrast, children with normal growth were found to have an energy surplus (*45*).

A deficiency in dietary intake, however, is unlikely the sole source of growth failure in these children. Several studies performed before potent ARVs were available showed that increasing the nutritional intake in children with HIV-associated growth failure with supplemental enteral and tube feedings improves weight but does not affect linear growth or lean body mass (i.e., arm muscle mass) (*47*). The experience reported with megestrol, a progestational agent used as an appetite stimulant, is similar (*48*).

Several studies observed that the level of HIV replication is closely associated with both the rate of growth and the quantity of lean tissue stores. Viral load measurements were greater in infants and children with poor growth than in infected children with normal growth (*45,49*); both growth velocity and fat-free mass were inversely related to HIV viral load. Results from multiple regression analysis indicate that once viral load is considered, dietary intake accounts for little of the variance in growth. Dietary intake also varies inversely with level of virus, suggesting that viral replication directly or indirectly suppresses appetite. The temporal relationships between growth and viral load are uncertain. Chantry et al. (*41*) found no association between growth at 24 weeks and viral load 12 weeks after starting therapy with azidothymidine, dideoxyinosine or both. The mechanism by which HIV replication impedes growth has not been established. Even without secondary infection, whole-body protein kinetics are altered with increased protein catabolism and synthesis of acute phase reactants, thus diverting energy away from accrual of fat free mass and growth (*37*). Disturbed energy use is also potentially important. Studies performed in HIV-positive adults indicate that inappropriate use of substrate, such as persistent de novo lipogenesis under fasting conditions, which in children could shunt energy away from growth.

HIV-associated micronutrient deficiencies with the potential to adversely affect growth and disease course are reviewed in this report by Friis (*43*). A study performed in infants born to HIV-positive mothers in Malawi, where vitamin A deficiency is highly prevalent, found that maternal vitamin A deficiency influenced infant ponderal and linear growth during the first year of life (*50*). By

age 12 months, infants of vitamin A–deficient mothers weighed approximately 8% less and were approximately 2% shorter than infants born to vitamin A–replete mothers irrespective of the infants' HIV status. Villamor et al. (*51*) reported significant improvements in length in HIV-positive children younger than 18 months who were given 200 000 IU vitamin A after being hospitalized with pneumonia. A potentially important mechanism by which vitamin A affects growth is by preventing diarrhoeal and respiratory illnesses (*52*). The prevalence of vitamin A deficiency and the degree to which growth retardation and disease progression are attributable to vitamin A deficiency in older children or children from more developed countries has not been established (*49,50,53–55*).

Additional studies of trace minerals in HIV-infected children have failed to detect a consistent pattern of deficiency. No differences in serum and erythrocyte zinc and selenium concentrations have been documented in HIV-infected children (*35*), including children with growth failure (*49*). The studies of zinc were limited by the lack of a valid means of assessing zinc status (*57*). Tissue levels of zinc may be normal even in severe zinc deficiency and serum zinc may actually increase under starvation conditions (*58*). In addition, zinc is an acute phase reactant; during infection zinc is redistributed from the serum to other tissue compartments, which makes interpretation of serum zinc levels particularly problematic in HIV infection. Perhaps the most valid way to establish zinc deficiency would be to evaluate the response to zinc supplementation, but such studies have not been undertaken.

Glutathione, the principle intracellular antioxidant, was reported to be reduced in children with HIV infection, with lowest concentration in children with growth failure (*59*). Use of cysteine and *N*-acetyl cysteine for restoration of glutathione stores has been advocated (*60)* but not evaluated in clinical studies.

2.9. Neuroendocrine disorders and growth

A number of neuroendocrine abnormalities with the potential to affect growth were identified in HIV-infected children, although no single endocrine abnormality is consistently encountered in HIV-associated growth failure. Estimates of the occurrence of primary and secondary thyroid abnormalities vary widely from 18% to none (*61*). Abnormalities in the circadian secretory pattern of thyroid-stimulating hormone also were reported (*62*). Data concerning adrenal function are from small

studies and are inconsistent; several investigators reported normal basal cortisol levels. Lala et al. (*63*) found 1 of 25 children to have primary adrenal insufficiency. In contrast, Oberfield et al. (*64*) observed elevated mean basal and stimulated cortisol levels that were associated with hippocampal atrophy, considered an indication of chronic exposure to elevated cortisol. Adrenal suppression was also documented in association with megestrol acetate, which is used as an appetite stimulant (*65*). A small study in nine children found that one third had elevated glucagon and that hyperglucagonaemia was associated with linear and ponderal growth (M. Ronadelli et al., unpublished data, 1999).

Direct and indirect evidence suggest that growth hormone insensitivity is causally involved in HIV-associated growth failure (*46,66,67*). Van Rossum et. al. (*46*) report normalization of growth hormone sensitivity in association with effective ARV therapy. Decreased growth hormone secretion was also reported, but primary growth hormone deficiency is encountered only occasionally (*68,69*). Basal growth hormone and stimulated growth hormone levels are normal in most children with HIV. Insulin-like growth factor (IGF)-1 was variably reported as normal or reduced (*70,71*), but in these studies overall nutritional status, which influences IGF-1 levels, was not taken into account. Matarazzo et al. (*72*) found that decreased IGF-1 levels were associated with disease progression and in some children with poor growth. Altered tissue sensitivity to IGF-1 may also be a factor. Geffner et al. (*67*) demonstrated in vitro resistance to IGF-1 and growth hormone in erythroid progenitor cells. Frost et al. (*66*) suggested that proteolysis of IGF-1 binding protein 3 (IGFBP-3) may diminish IGF-1 function. In this study, levels of IGF-1 and IGFBP-3/ternary complex were reduced in children with growth failure. Similarly, the relatively high IGFBP-3 with low IGF-1 reported by Van Rossum (*46*) is consistent with reduced growth hormone sensitivity. Improvements in growth observed in some children on highly active ARV therapy were shown to be due to the restoration of growth hormone sensitivity.

2.10. HIV, diarrhoea, malabsorption and growth

Gastrointestinal infections, a common cause of childhood malnutrition and growth retardation, also contribute significantly to poor growth in HIV-infected children. Children infected with HIV appear to be especially vulnerable to diarrhoeal diseases. In a longitudinal study of HIV-infected children in Kinshasha, Republic of Congo, Keuch et al (*73*) found that HIV-infected children

had increased rates of acute and chronic diarrhoea: 90% of infected children had one or more episodes of acute diarrhoea and chronic diarrhoea was 6 times as likely to develop in HIV-infected children as in uninfected children.

Diarrhoea is strongly associated with decreased growth and increased mortality. Thea et al. (*74*) reported an 11-fold increased risk of death in HIV-infected children in Kinshasha with persistent diarrhoea. During the ages of 6–11 months, the mean growth for HIV-infected infants with one or more episodes of diarrhoea per year was 1.4 cm/year less that infants with less than one episode (*75*). Additional episodes result in further decrements in growth

Thus in many regions of sub-Saharan Africa, diarrhoeal diseases represent an important and potentially modifiable factor involved in growth disturbances in HIV-infected children. Few studies, however, have evaluated whether the weight loss and growth retardation related to acute and chronic diarrhoea is reversible. Few studies have evaluated means of nutritional support for malnourished HIV-infected children recovering from acute diarrhoea.. This question has implications for treatment guidelines now being widely adapted throughout the nations of sub-Saharan Africa, many of which call for initiation of ARVs for children meeting WHO HIV Stage III criteria. Although data are not available, it is anticipated that attained weight for age of less than 60% will be among the most common findings among children meeting criteria for initiation of ARVs. Some children who otherwise are without HIV-related illnesses or reduced CD4+ counts may benefit from nutritional rehabilitation; ARVs can be deferred for these children. Further studies on the effect of prevention, early detection and management of diarrhoea on HIV disease progression are warranted.

Studies performed in the United States and Europe have reported detectable malabsorption during diarrhoea-free periods in HIV-infected children. Altered nutrient absorption is highly prevalent and can affect growth adversely. Surprisingly, this has not been established in studies in HIV-positive children. Approximately 30–60% of children infected with HIV are reported to malabsorb carbohydrates, 30% to malabsorb fat and 32% to malabsorb protein, typically without clinical symptoms (*76–78*). How HIV affects nutrient absorption independently of increasing risk of enteric infections is not known; primary HIV enteropathy may be involved (*79*). Most studies of

gastrointestinal function in children with HIV have had a cross-sectional design and have failed to find an association with malabsorption and growth.

A study of ritonavir, an HIV protease inhibitor drug, reported restoration of intestinal function and improved growth (*80*) but did not determine whether the improved growth was due to improved intestinal function or suppression of viral replication. Thus, the clinical significance of intestinal dysfunction and its contribution to growth disturbances remain to be determined.

3. Effect of ARVs on growth

A key remaining question concerns the extent to which suppression of viral replication and immune reconstitution normalizes the anabolic milieu and restores energy homeostasis and growth as described in detail in this report by Raiten (*81*). Studies of the effect of potent multiclass ARV regimens in reversing height deficits and body composition abnormalities are becoming available; results, although generally favourable, are mixed. Treatment with ARV regimens containing protease inhibitors significantly affected weight and weight-for-height ratio and had a marginal effect on height (*77*). Conversely, two studies found no overall improvement in growth in children receiving ARVs containing protease inhibitors despite improvements in viral load (*82*). Children with a very high entry viral load (e.g., >200 RNA copies/cc^3) who subsequently experienced a decline of more than 2.0 log had an improved height-for-age *Z*-score (*83*). A potentially important issue in studies of this nature is whether HIV treatments, many of which have significant gastrointestinal toxicities (e.g., nausea, vomiting, diarrhoea), negatively affect appetite and dietary intake, resulting in a blunting of growth improvement potentially achieved through viral suppression. Only Miller et al. (*84*) were able to account for this through measurement of dietary intake.

Virtually all experience to date has been in settings where food is readily accessible and underlying levels of undernutrition are negligible. Evaluating the impact of potent ARVs on somatic growth in children in developing countries is an important area of future research.

4. Effect of psychosocial factors on growth

Level of maternal education has also been found at least in one study to be an important predictor of growth in HIV-infected children. Villamor (75) in a study performed in Dar es Salaam,

Tanzania, found that children of mothers who did not complete grade school had decreased annual growth compared with those who had.

Maternal health, emotional and psychological status, and the characteristics of the caregiver–child interaction have a strong influence on growth. Infants of depressed mothers are at greater risk for growth failure. Little research on the effect of maternal depression and anxiety on childhood has been performed in resource-constrained nations and none has been published specific to HIV-positive mothers and their infants. Evaluating these issues in HIV infection is especially important area of research given the high rates of depression among women in general and mothers of young infants in particular that are reported in high HIV-seroprevalent periurban and rural areas of South Africa.

5. Research gaps

The following are research priorities:

- Evaluation of the growth and nutritional consequences of rapid weaning strategies related to avoidance of HIV transmission via breastfeeding.
- Development and evaluation of the effect of nutritional interventions on growth, body composition, immune function and disease progression in malnourished HIV-infected children.
- Evaluation of food intake, growth, body composition, lipid insulin and bone metabolism in malnourished HIV-infected children receiving ARVs.
- Evaluation of effective means of prevention of diarrhoeal illnesses as a means of preserving growth in children with HIV infection.
- Evaluation of long-term cardiovascular risk associated with observed changes in lipid and insulin metabolism and interventions to modify these changes..
- Evaluation of long-term risks associated with altered bone metabolism observed in HIV-infected children and adolescents and interventions to modify these changes.

6. Programatic challenges and considerations

The following are programatic priorities:

- Integrating nutritional monitoring into HIV medical care programs.
- Including weight as well as length or height in measurements monitored.

- Developing nutrition training and education programs for health services personnel involved in care of HIV-infected children.
- Including nutrition in health education activities for caregivers of HIV-infected children.
- Developing interventions to promote early detection and management of childhood illnesses, especially diarrhoea, among children infected with HIV.
- Targeting children with suboptimal growth for assessment and treatment of potentially reversible causes of poor growth
- Adapting algorithms for assessment and management of HIV-infected children with poor growth.

7. Summary

Poor growth is common in HIV-infected children and has a significant adverse effect on survival independent of the degree of immune deficiency. The cause of abnormal growth is multifactorial. Intrauterine growth may be compromised in children born to HIV-infected women. Traditional risk factors such as insufficient food intake and diarrhoea contribute to poor growth in children with HIV. However, in children not receiving ARVs, energy supplementation alone improves weight gain but does not reverse deficits in height.

Other factors associated with impaired ponderal and linear growth include level of HIV replication and use of ARVs for suppressing viruses and improving immune status. Results of studies also suggest that prevention, early detection and treatment of diarrhoeal illnesses may be effective targets for enhancing childhood growth and survival in children with HIV. A number of abnormalities in body fat, lipid, insulin and bone metabolism have been identified in populations receiving ARVs.

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