



Effect of Zhen Qi Fu Zheng granules on the bone marrow depression model induced by Zidorf



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ABSTRACT

Zidorf is a commonly used drug for the treatment of AIDS, the most common side effects of AZT was bone marrow depression. Therefore, we investigated the effects of Zhen Qi Fu Zheng (AQFZ) granules on the model of bone marrow depression induced by AZT. We showed that the high, medium and low doses of AQFZ granules could increase the number of WBC in the mice model induced by AZT, and the difference was significant ($P < 0.01$) compared with the model group. Each dose of AQFZ granules can increase the thymus cortex thickness, the number of thymus lymphocytes, spleen nodule size, the number of lymphocytes in the spleen ($P < 0.01$). The medium dose of AQFZ granules can also significantly improve the number of BMC in the bone marrow depression model ($P < 0.01$). As well as, the low dose of AQFZ granules can clearly increase the number of nucleated cells in a bone marrow ($P < 0.05$) and IL-2/blood serum. So, AQFZ granules can improve and regulate the hemogram, bone marrow and immune level of bone marrow depression model induced by AZT.

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1. Introduction

Acquired immune deficiency syndrome (AIDS) is a chronic infectious disease with high mortality caused by Human Immunodeficiency Virus (HIV) (The Lancet HIV, 2016; Chen et al., 2016). At present, the treatment of AIDS mainly includes Anti-HIV virus and the reconstruction or recovery of immune system to being damaged. Anti-HIV drugs have an important role in the treatment of AIDS, but due to the emergence of tolerance and untoward effect affect the smooth progress of AIDS treatment. For example, because AZT can cause the adverse effects of bone marrow depression, so the use of treating AIDS were interrupted (Currier et al., 2008; Dash et al., 2016). Natural products such as plant-originated compounds and plant extracts have enormous potential to become drug leads with anti-HIV and neuroprotective activity (Kurapati et al., 2016). Thousands of herbs have been screened for anti-HIV activity, and new compounds have been discovered from the extracts, many of which demonstrate inhibitory activity

against HIV (Chu et al., 2011; Amy et al., 2016). Against this backdrop, the World Health Organization (WHO) suggested the need to evaluate ethno-medicines for the management of HIV/AIDS. Traditional Chinese medicine (TCM) in the treatment of AIDS showed an advantage.

Although experimental studies on reducing the side effects of anti-HIV drugs are still not many. We can get inspiration from the combination of traditional Chinese and Western medicine for the treatment of tumor. Some of the drugs that treat AIDS, such as AZT, are also anti-tumor drugs (Han et al., 2015a). It is still used as first-line anti-AIDS drugs in clinical use, in the use of AZT or combined with other antiviral drugs in the treatment of AIDS also appear the adverse effects of bone marrow depression (Ma et al., 2016; Han et al., 2015b). Traditional Chinese medicine in the treatment of cancer has accumulated considerable experience in combination with Western Medicine (Lin et al., 2016; Liu et al., 2012). For example, we often used the method of dissipating dampness and strengthening spleen with acupuncture to ease the digestive tract reaction after chemotherapy. Used the method of dispelling wind invigorate the circulation of blood and acupuncture to treat cutaneous and mucous reactions of Kaposi's sarcoma patients after taking AZT and radiotherapy. Used the method of tonifying qi-blood to treat bone marrow depression caused by long-term use of AZT. Used the method of tranquilizing by nourishing the heart and promoting blood circulation to remove meridian obstruction to treat nervous system reaction caused by long-term use of AZT. So, we

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have a lot of successful experience about combine traditional Chinese medicine and western medicine to reduce the side effects of Western medicine.

According to traditional Chinese medicine, Qi is the commander of blood, blood is the mother of Qi. Qi is dynamic of supply and distribute, produce the composition of blood, nourish the body. If qi is insufficient, it may lead to bodily weakness, Digestion and absorption capacity of the spleen and stomach be decreased, there is no source can be transformed into blood. So, when the Chinese medicine clinical treatment of various types of bone marrow depression, anemia and other diseases often need to meet with tonifying Qi and lifting yang. Qi and blood are interdependent and mutually dependent. If disharmony between Qi and blood, all kinds of diseases will come. ZQFZ granules is composed of *Astragalus mongholicus* and *fructus ligustri lucidi*. It is the role of tonifying Qi and enrich the blood and used for a variety of asthenic disease. It can improve the immune function of the human body and protect the bone marrow and adrenal cortex. It is commonly used in clinical treatment of acute leukemia with chemotherapy, and the curative effect is remarkable (Zhu et al., 2014; Gao et al., 2017).

According to our previous research foundation, we used of bone marrow depression model induced by Zidorf (AZT) to study the effect of ZQFZ granules can ease bone marrow depression. And preliminary study on the effect and mechanism of Chinese patent drug on bone marrow depression induced by HIV. To provide experimental basis for the combination of Chinese and Western medicine for the treatment of AIDS.

2. Material and methods

2.1. Animals and drugs

C57BL/6 mice, SPF grade, female, 18–20 g. Provided by the experimental animal center of Henan Province, No.: 410213.

Zhen Qi Fu Zheng granules (Gansu pharmaceutical Polytron Technologies Inc., NO. 040803); Batilol (Jiangsu Pengyao Pharmaceutical Co., Ltd, NO. 0411161); Zidovudine Tablets AZT (Northeast General Pharmaceutical Factory, NO. 20041201); Erythropoietin (EPO) RIA Kit, Interleukin-2 (IL-2) RIA Kit (Science and technology development center of PLA General Hospital by RIA).

2.2. Apparatus

BI-2000 medical image analyzer, Chengdu Taimeng Electronics Co., Ltd.; Type MEK6318 blood cell analyzer, Japan photoelectric; SN-695B type intelligent release gamma measuring instrument, Shanghai Institute of nuclear research rihuan instrument plant.

2.3. Methods

Fifty-four females C57BL/6 mice, SPF grade, 18–20 g, randomly divided into 6 groups, blank group, model group, batyl alcohol group (positive control 10 mg·kg⁻¹), the high, medium and low

dose of ZQFZ granules group (15 mg·kg⁻¹, 10 mg·kg⁻¹, 5 mg·kg⁻¹). In addition to the blank group, Drench AZT to other group mice in the morning, and in the afternoon to give the corresponding drugs, blank group and model group was given the same volume of normal saline. 1 times every day, lasted 15 days. Whole blood was collected 24 h later after the last administration from the orbit. And then test hemogram (RBC-red blood cell, WBC-white blood cell, HB- hemoglobin) [6]**. The remaining blood serum separation, according to the kit method to detected interleukin -2 (IL-2), erythropoietin (EPO). The bone marrow cells were washed out of the right side of the femur by the leukocyte diluting fluid 1 ml. Statistics on the number of bone marrow mononuclear cells (BMC). The thymus and spleen of formalin fixed and prepared for pathology.

3. Results

3.1. Effects of ZQFZ granules on WBC, RBC and Hb in bone marrow depression mice induced by AZT

As can be seen from Table 1: Compared with the blank group, the number of WBC were decreased in the model group mice ($P < 0.01$), the result showed that the bone marrow depression model induced by AZT was successful. The RBC numbers and Hb levels in model group were slightly lower than those in the blank group. However, there was no significant difference between the two groups. It showed that AZT had little effect on the RBC number and Hb level in a short time. Compared with the model group, batyl alcohol and each dose of ZQFZ granules could increase the number of WBC in bone marrow depression mice induced by AZT ($P < 0.01$). See Table 1.

3.2. Effects of ZQFZ granules on BMC, EPO, IL-2 in bone marrow depression mice induced by AZT

As can be seen from Table 2, Compared with the blank group, the number of BMC were decreased in the model group mice ($P < 0.05$), which showed that the bone marrow cells were significantly inhibited, so the model was successful. Compared with the model group, the number of BMC were decreased in the model group and the medium dose of ZQFZ granules group mice ($P < 0.01$), as well as, the number of BMC were decreased in the low dose of ZQFZ granules group ($P < 0.05$). The results showed that the medium and low dose of ZQFZ granules was significantly effective in improving the number of BMC in bone marrow depression model.

Compared with the blank group, the content of IL-2 in serum of model group was decreased ($P < 0.05$), which indicated that AZT could lead to the decrease of immune level in model mice. Compared with the model group, the low dose of ZQFZ granules can improve the content of IL-2 in the serum of mice ($P < 0.01$). There was no significant effect of batyl alcohol and the high and medium dose of ZQFZ granules on IL-2 in serum of mice with bone marrow depression ($P > 0.05$). The results showed that the low dose of ZQFZ

Table 1
Hemogram of each group mice.

Group	Number (N)	Dose (mg·kg ⁻¹)	WBC ($\times 10^9 \cdot L^{-1}$)	RBC ($\times 10^{12} \cdot L^{-1}$)	Hb (g·L ⁻¹)
Blank group	9	–	6.77 ± 1.45	8.76 ± 0.96	150.22 ± 19.76
Model group	9	–	3.48 ± 0.54**	8.36 ± 0.58	143.78 ± 10.83
Batyl alcohol group	9	10	6.36 ± 1.06 $\Delta\Delta$	8.03 ± 1.53	139.11 ± 27.48
The high dose of ZQFZ granules group	9	15	6.56 ± 2.28 $\Delta\Delta$	8.71 ± 0.80	149.22 ± 13.56
The medium dose of ZQFZ granules group	9	10	8.03 ± 0.93 $\Delta\Delta$	8.07 ± 0.87	139.22 ± 14.67
The low dose of ZQFZ granules group	9	5	5.90 ± 1.84 $\Delta\Delta$	9.34 ± 0.99 Δ	158.44 ± 18.70

Note: compared with the control group: * $P < 0.05$, ** $P < 0.01$; compared with the model group, Delta $P < 0.05$, Delta $P < 0.01$.

Table 2

The number of BMC and the content of EPO, IL-2 in each group mice.

Group	Number (N)	Dose (mg.kg ⁻¹)	BMC ($\times 10^7$ /femur)	IL-2 (ng/ml)	EPO (ng/ml)
Blank group	9	–	1.64 \pm 0.14	4.39 \pm 1.56	0.23 \pm 0.22
Model group	9	–	1.31 \pm 0.19 [†]	3.20 \pm 1.73 [†]	0.19 \pm 0.15
Batyl alcohol group	9	10	1.73 \pm 0.20 ^{△△}	3.19 \pm 0.74	0.18 \pm 0.04
The high dose of ZQFZ granules group	9	15	1.45 \pm 0.33	3.84 \pm 0.58	0.18 \pm 0.05
The medium dose of ZQFZ granules group	9	10	1.73 \pm 0.36 ^{△△}	3.52 \pm 0.63	0.24 \pm 0.20
The low dose of ZQFZ granules group	9	5	1.58 \pm 0.40 [△]	4.82 \pm 1.25 ^{△△}	0.16 \pm 0.06

Note: compared with the control group: [†] $P < 0.05$, ^{**} $P < 0.01$; compared with the model group, [△] $P < 0.05$, ^{△△} $P < 0.01$.

granules was better in improving the IL-2 in the serum of model mice.

In addition, the content of EPO in the model group was slightly lower than that in the blank group, but there was no significant difference between the two groups ($P > 0.05$). It showed that AZT had little effect on the content of EPO in short term administration. See Table 2.

3.3. Effects of ZQFZ granules on pathological changes of spleen and thymus in bone marrow depression mice induced by AZT

Pathological changes of thymus in each group mice: In the blank group, the lobuli thymi of mice was sharply demarcated, the boundary of cortex of thymus and medullary substance was clear (Atta et al., 2017; Ishaq and Jafri, 2017). Cortex of thymus was thicker, lymphocyte was concentrated (Fig. 1). In the model group, the thymus gland volume was reduced, the lobuli thymi were obviously atrophic, the thymus cortex became thinner, the lymphocyte thinning (Fig. 2). In the alcohol group (Fig. 3) and dose of ZQFZ granules group (Fig. 4), the lobuli thymi of mice was sharply demarcated, the boundary of cortex of thymus and medullary substance was clear, cortex markedly became thicker, lymphocyte was concentrated (Peng et al., 2017; Shiri et al., 2016). In the middle dose group, In the middle dose group, the thymus volume was obviously reduced, the boundary of the leaflet was not clear, the cortex and medulla were not clear, the cortex became thinner,

and the lymphocytes were sparser (Fig. 5). In low dose group, the thymus gland volume was reduced, and the boundaries of the lower dose were clear. The boundary between cortex and medulla was clear (Fig. 6).

Pathological changes of spleen in each group mice: In the blank group, the red pulp and white pulp of the spleen were clear boundaries, splenic nodule were clearly visible, Spleen volume were larger, and have tightly packed lymphocytes (Fig. 7). In the model group, the red pulp and white pulp of spleen were clear boundaries although, but the splenic nodule became decreased obviously, lymphoid tissue cells around splenic nodule became sparser (Fig. 8).

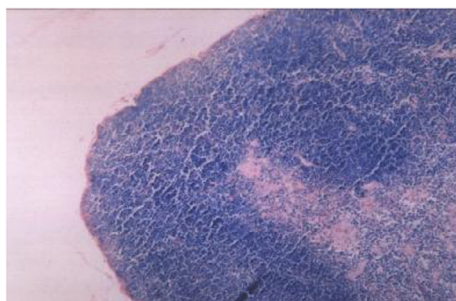


Fig. 1. Blank group.

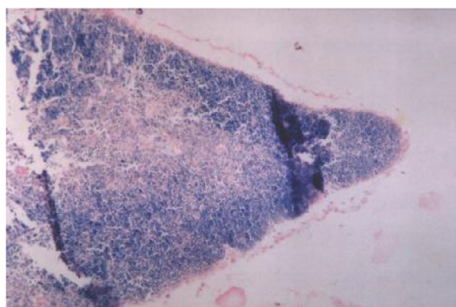


Fig. 2. Model group.

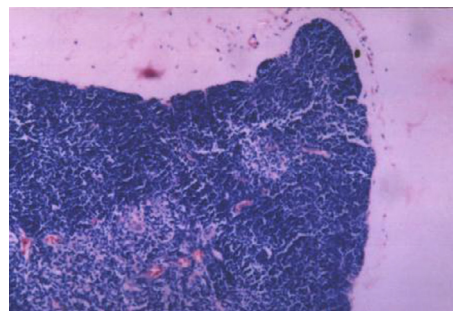


Fig. 3. Batyl alcohol group.

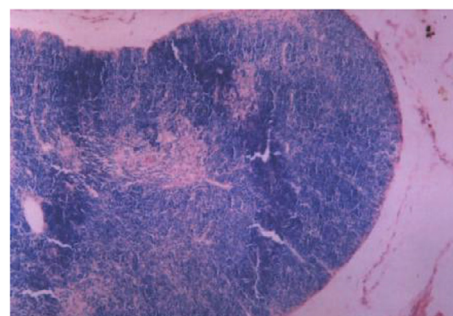


Fig. 4. The high dose of ZQFZ granules group.

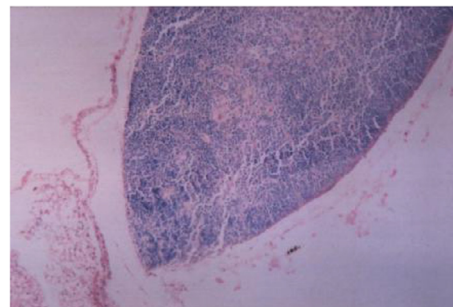


Fig. 5. The medium dose of ZQFZ granules group.

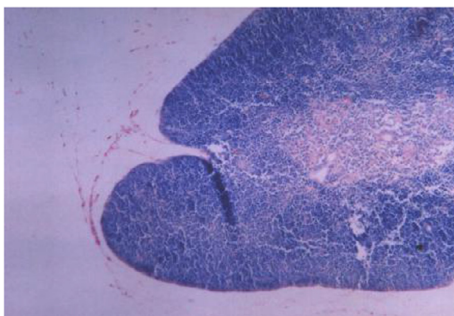


Fig. 6. The low dose of ZQFZ granules group.

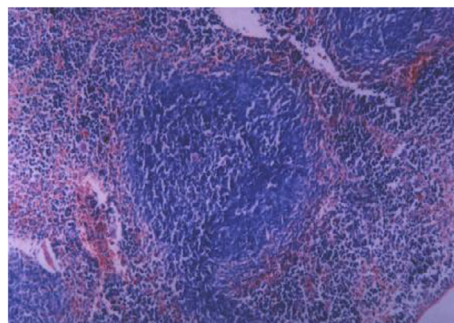


Fig. 9. Batyl alcohol group.

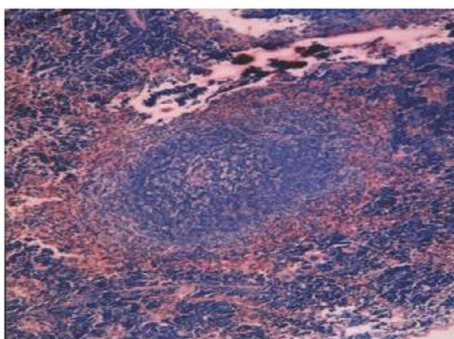


Fig. 7. Blank group.

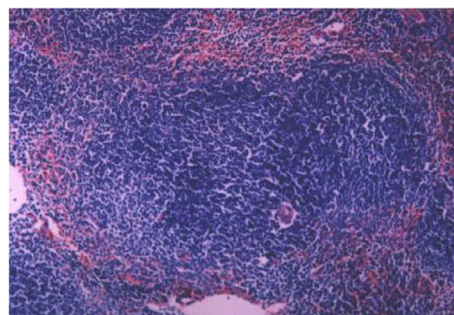


Fig. 10. The high dose of ZQFZ granules group.

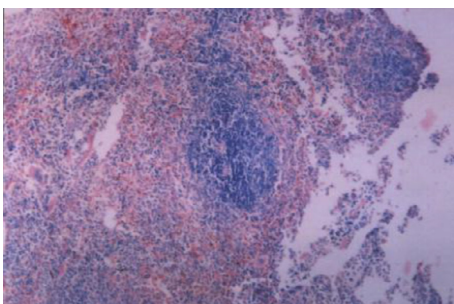


Fig. 8. Model group.

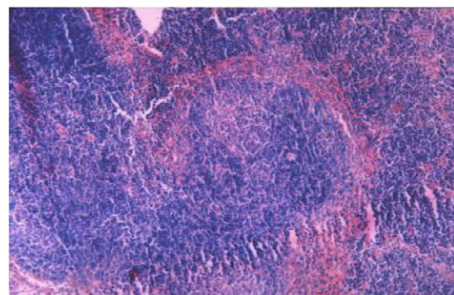


Fig. 11. The medium dose of ZQFZ granules group.

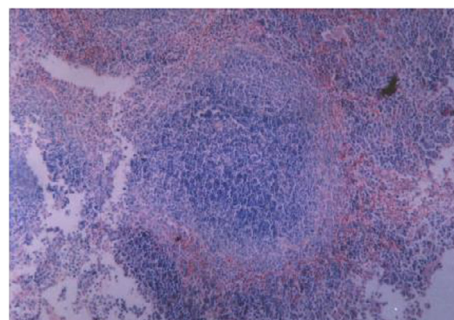


Fig. 12. The low dose of ZQFZ granules group.

Compared to model group, the alcohol group (Fig. 9) and dose of ZQFZ granules group (Fig. 10), the red pulp and white pulp of the spleen were clear boundaries, splenic nodule was significantly increased, Lymphocytes were becoming denser (Wu and Liu, 2016; Muhammad et al., 2017). In the medium dose of ZQFZ granules group, the red pulp and white pulp of the spleen were clear boundaries, splenic nodule was significantly increased although, but lymphoid tissue cells around splenic nodule became sparser (Fig. 11). In the low dose of ZQFZ granules group, the red pulp and white pulp of the spleen were not clear boundaries, splenic nodule was significantly increased although, but lymphoid tissue cells especially around splenic nodule became sparser (Fig. 12).

As can be seen from Table 3, compared with the blank group, the thymus cortical thickness, the number of thymic lymphocyte, the size of splenic corpuscle and the leukomonocyte number of spleen were decreased ($P < 0.01$). It showed that the immune level of the bone marrow depression model was decreased in the research. This model has the symptoms of deficiency of vital energy.

Compared with the model group, the thymus cortical thickness, the number of thymic lymphocyte, the size of splenic corpuscle and the leukomonocyte number of spleen in the batyl alcohol group and each dose of ZQFZ granules group mice were increased ($P < 0.01$). It showed that the immune level of the bone marrow depression model was improved and adjusted by ZQFZ granules.

Table 3
Effects of ZQFZ granules on Pathological changes of spleen and thymus in bone marrow depression mice induced by AZT.

Group	Thymus cortical thickness (μm)	Number of thymic lymphocyte	Size of splenic corpuscle (μm)	The leukomonocyte number of spleen
Blank group	28.39 \pm 7.43	37.42 \pm 5.27	19.68 \pm 4.26	23.78 \pm 5.21
Model group	11.27 \pm 3.65**	18.64 \pm 4.32**	6.24 \pm 2.37**	8.12 \pm 2.78**
Batyl alcohol group	30.45 \pm 4.28 $\Delta\Delta$	42.89 \pm 6.72 $\Delta\Delta$	21.36 \pm 5.47 $\Delta\Delta$	28.17 \pm 4.62 $\Delta\Delta$
The high dose of ZQFZ granules group	31.86 \pm 5.61 $\Delta\Delta$	48.22 \pm 5.78 $\Delta\Delta$	26.38 \pm 6.52 $\Delta\Delta$	34.62 \pm 6.23 $\Delta\Delta$
The medium dose of ZQFZ granules group	21.79 \pm 6.18 $\Delta\Delta$	26.17 \pm 4.23 $\Delta\Delta$	18.79 \pm 5.26 $\Delta\Delta$	20.38 \pm 4.72 $\Delta\Delta$
The low dose of ZQFZ granules group	26.54 \pm 4.78 $\Delta\Delta$	37.42 \pm 5.92 $\Delta\Delta$	25.32 \pm 5.74 $\Delta\Delta$	29.81 \pm 6.18 $\Delta\Delta$

Note: compared with the control group: * $P < 0.05$, ** $P < 0.01$; compared with the model group, Delta $P < 0.05$, Delta $P < 0.01$.

4. Discussion

AZT is a reverse transcriptase inhibitor that can block HIV replication in the cell. In the current clinical treatment of AIDS occupies a very important position, and its most significant adverse reactions are bone marrow depression and neutropenia.

The hemogram can indirectly reflect the bone marrow hematopoietic function. The drug can affect any one step and link of the bone marrow hematopoiesis and will be reflected in the blood eventually (Elizabeth et al., 2015; Gao et al., 2017; Lee et al., 2016), so to observe the effect of drugs on the hemogram can be used as an indicator to measure the inhibitory effect of drugs on bone marrow (Paul et al., 2014).

Bone marrow suppression is the drug directly or indirectly affect the hematopoietic function of bone marrow, so the detection of bone marrow can be directly to evaluate the role of drugs on bone marrow hematopoietic function. BMC can roughly represent the division and proliferation of bone marrow hematopoietic cells (Mustafa et al., 2017). If the number of BMC is more, the number of immature blood cells will be more. This reflects the hematopoietic function of bone marrow is better. Otherwise, it reflects the hematopoietic function of bone marrow is poor, and bone marrow hematopoietic function is suppressed.

Thymus, spleen is an important immune organ, while the spleen has a certain hematopoietic function, when the bone marrow hematopoietic function is impaired, the spleen can be compensated. The thymus cortex thickening, spleen nodule enlargement, thymus cortex lymphocyte and spleen lymphocyte increase, suggesting that the body immune function is enhancement.

In the human body, IL-2 is a broad-spectrum immunopotentiator, and it has function of anti-tumor, anti-microbial infection, immune regulation and so on. In this experiment, we use the above of indexes which can directly or indirectly reflect the bone marrow hematopoietic function as the basis (Nawaz et al., 2017). And from three aspects of the hemogram bone marrow, immune level to study the effect of ZQFZ granules on the bone marrow depression model induced by AZT.

The results showed that AZT could significantly reduce the number of WBC in mice, which indicates that AZT could inhibit bone marrow hematopoietic function in mice. ZQFZ granules can be reduced the bone marrow depression model induced by AZT. And to restore WBC to normal levels. AZT could induce the decrease of IL-2 content in the serum of model mice also. At the same time, the pathological morphology of thymus and spleen showed that the immune level of the model mice is decreased. ZQFZ granules can regulate the immune level of the model mice, so that it can be recovered.

The experimental results show that AZT can not only cause common myelosuppression and neutropenia, but also affect the patient's immune level. The AIDS patients who have decreased immune levels due to HIV were once again affected by antiviral drug AZT.

We treat AIDS by antiviral therapy, at same time to apply ZQFZ granules that can improve the symptoms of bone marrow depression and hypo immunity, which is conducive to the smooth progress of AIDS antiviral therapy.

The results of our study have important significance in theoretical and practical. So, we can use integrated traditional Chinese and western medicine therapy to reduce the toxicity and side effects of antiviral drugs, that can improve the clinical efficacy and patients' quality of life, prolong the life of AIDS patients and enrich the theory. And then experience of treating AIDS.

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