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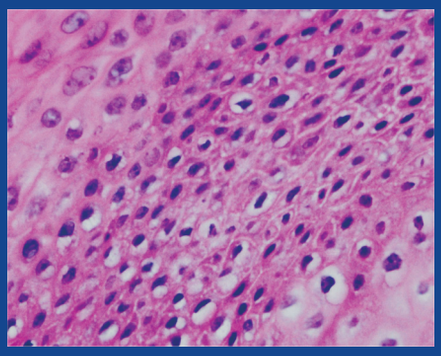

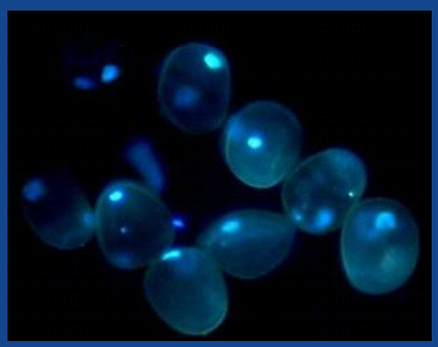

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Research Report

COLOSTRUM-COLLAGEN-HYDROXYAPATITE COMPOSITE, AN EXCELLENT CANDIDATE BIOMATERIAL FOR BONE REPAIR AND BONE INFECTION MANAGEMENT

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ABSTRACT

In the case of bone fracture or defect after surgery, which is common in patients with bone cancer (osteosarcoma), it takes a long time for closure and it may cause an infection problem. The use of collagen-hydroxyapatite composite with a blend of colostrum as a scaffold is aimed to accelerate the process of osteoblast growth, inhibite the emergence of infections, and act as bone tissue repair material. The method used was the hydrogel formation process and freeze dry process to remove the solvent and to form pores. The composition of scaffold composite manufactured was 15% collagen, 75% hydroxyapatite and 10% colostrum. Combination of scaffold collagen-hydroxyapatite-colostrum has quite reliable properties because SEM test showed that scaffold could bind to both and could bind to both and could form sufficient pores to provide enough place for bone cells (osteoblats) to grow. The results of MTT assay revealed percentage of above 60%, which indicates that the material is not toxic. In conclusion, collagen-hydroxyapatite-colostrum combination is an excellent biomaterial candidate for bone repair and bone infection management.

Key words: *collagen, hydroxyapatite, colostrums, osteoblasts, bone repair*

ABSTRAK

Pada kasus fraktur atau defek tulang setelah operasi yang biasa terjadi pada penderita osteosarkoma (kanker tulang), membutuhkan waktu yang lama dan bisa menimbulkan problem infeksi. Penggunaan komposit kolagen-hidroksiapatit dengan paduan colostrums sebagai scaffold diharapkan dapat mempercepat proses pertumbuhan sel osteoblast. Metode yang digunakan yaitu dengan proses freeze dry untuk menghilangkan pelarut dan membentuk pori. Perbandingan pembuatan komposit scaffold ini 15% kolagen, 75% hidroksiapatit, dan 10% colostrums. Paduan colostrums scaffold Kolagen-Hidroksiapatit memiliki sifat cukup baik karena pada hasil uji SEM scaffold dapat berikatan dengan baik dan dapat terbentuk pori yang cukup untuk tumbuhnya sel tulang (osteoblast). Hasil MTT Assay menunjukkan jumlah sel hidup diatas 60% yang berarti bahwa material tidak bersifat toksik.

Kata kunci: *kolagen, hidroksiapatit, kolostrum, osteoblas, perbaikan tulang*

INTRODUCTION

According to World Health Organization (WHO), traffic accidents cause about 1.2 million deaths each year. Losses due to traffic accidents, in addition to death, are physical damage as well. Physical damage most often occours in an accident is fracture (broken bone). High accident rate results in high fracture incidence. Fracture is a situation where bone disintegrating. The most common cause is accidents, but other factors, such as degenerative processes, can also affect the incidence of fracture.

Scaffold is one component of tissue engineering applications that can be used as application in bone tissue repair.[1] In producing scaffold, we require hydroxyapatite (HA). Hydroxyapatite it self has osteoconductive and biocompatibility properties.[2] However, HA also has characteristics of brittle and fatigue failure, so that in health applications HA is only used for unloading bearing repair and as a substitute.[3] In scaffold formation, we need mixed materials for quality enchancement, and the collagen. Approximately 25–35% of body proteins are composed by collagen.[3–6,]

In the case of fracture or bone defect after surgery, which is common in patients with bone cancer (osteosarcoma), it takes a long time for closure. To overcome this problem, additional material other than HA and collagen is required to accelerate the regeneration of bone cells. Regeneration of bone cells is also affected by immune quality of the human body. Self-immunity is provide by many living things, including mammals. There is a fact in the society that drinks containing colostrums can accelerate healing, especially in adult to elderly whose healing process requires longer time.

In this study, we added bovine colostrums to collagen-HA scaffold. Bovine colostrums has content which is almost similar to that of human colostrums. Colostrums itself has properties to stimulate body cells regeneration, peptide imunotheraphy, help fighting viruses, and so on.[7] We expect that a combination of blend collagen-HA scaffolds and colostrums may accelerate cell regeneration, so that it may implicate the acceleration of bone grafting.[2,4]

MATERIALS AND METHOD

Materials that used in this research were hydroxyapatite of bovine obtained from Tissue Bank and Biomaterial Center Dr. Soetomo General Hospital Surabaya, East Java, Indonesia. Collagen powder is derived from the skin of bovine, and colostrums powder is derived from dairy cattle.

Preparation of Collagen-Hidroxyapatite Addition Colostrums. 15% collagen dissolved in 0.5 mol/L cold acetic acid, then added with Na_2HPO_4 0.02 mol/L and controlling pH up to 7.2 with aqueous NaOH solution at temperature below 10°C. Then collagen solution was added 75% hydroxyapatite are stirred in NH_4OH for 2 hours, at pH 7. After dissolved, add 10% colostrums and they were stirred for 4 hours, and then incubated at a temperature of 35°C for 20 hours. The results scaffold obtained, then washed with aquadest, and then centrifuged, thus a mixture is obtained in the form of hydrogel and done printing. Solid phase separation technique and liquid is done with composite cooling up to –20°C for 24 hours, while the solvent removed by freeze-drying. Characterizations were carried out with Scanning Electron Microscope (SEM). Biocompatibility was tested by MTT Assay.

RESULTS AND DISCUSSION

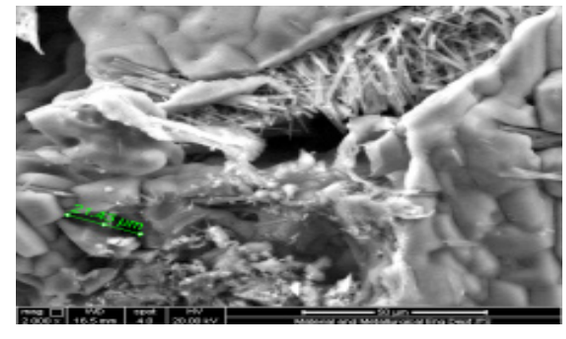
In collagen - HA - colostrums composite facilitate interaction between cells and implants material. It will cause the occurrence of osteogenic cells, adhesion, attachment and spreading phase which triggered the proliferation and differentiation of cells. Attachment phase and physicochemical linkage formed appear at the same time with biomaterial implantation to bone cells.[8] Adhesion and spreading phase will occur when focal contacts and adhesion plaque between the surface of the implant material and cell membrane is formed. Then actin filament reorganized cause adhesion process causes change cell and transmit signal transduction through proteins of the cytoskeleton to become nuclear matrix, changing the arrangement of the genes, and determine the number of cells for proliferation and differentiation.[9]

Composite of collagen-HA as bone tissue engineering should have physichocemical binding and crystal structure to be recognized as good material. These will affect the characteristic of the osteogenic cells, determine the quality of them and success to perform new bone tissue. Calcium phosphate powders is required on the average diameter 200–500 m, and if the size of particles less than 50 m then it will cause cytotoxicity.[10] The pore size which are ideal for calcium phosphate is around 200-400 m. It provide the space for blood vessels and trigger migration, adhesion, proliferation, and differentiation of osteoblast in pores.

The results of this research material products could be seen in Figure 1.

Figure 1. Scaffold Collagen – HA – colostrums

SEM profile with EDAX in Figure 2 below shows that the third main material in this research have been well-mixed.



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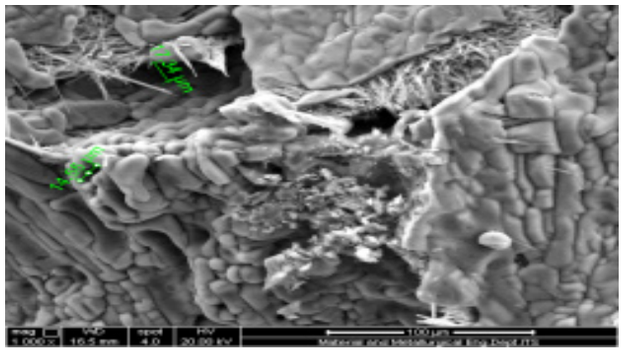

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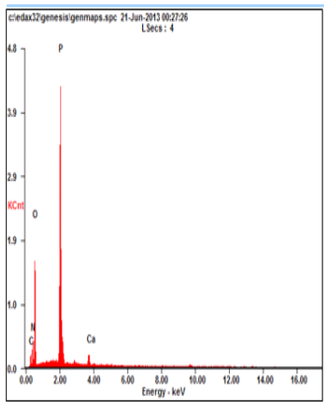

Element	Wt%	At%
CK	09.10	13.12
NK	17.08	21.13
OK	47.09	50.99
PK	25.32	14.16
CaK	01.40	00.61
Matrix	Correction	ZAF

(c)

Figure 2. Result (a) SEM with magnification 2000×, (b) SEM with magnification 1000×, (c) Energy X-Ray Dispersion.

SEM results are showed shape of HA grain and collagen fibers. While the fiber shape of colostrum is already bind to HA. MTT assay is showed that the material biocompatibility exceeds 50% by the procentage of living cell.[11,12]

Combination of colostrum on scaffold collagen - hydroxyapatite is showed good physical properties. this can be evidenced from the test results the main material of the SEM, result can bind to either and form a good pore as a condition the growth of osteoblast cells. Interpretation of MTT assay result which exceed 60% could be considered that the material is not toxic. Colostrum can actively support the body immunity, antibodies, and other protective proteins. Colostrum provides 'first immunity' and the mechanism is to protect the body against many infections. The main immunity substances are immunoglobulin that can prevent and fight bacteria, viruses, fungi and toxins. Immunoglobulin (IgA) was act as the protectors in the area susceptible to bacteria commonly in the membranes of lung, colon and throat. Colostrum contains white blood cells (leukocytes) which its function could fight microorganism. Colostrum contains growth factors which could accelerate wound healing. Colostrum which is rich in vitamins A and E will support to reduce infection. In addition, Colostrum also contains vitamin B6, B12, C, D, K and minerals, especially iron and calcium. Colostrum also contains several substances in such high quantities of sodium, potassium and cholesterol.[13] Based on the phenomena above, a blend of collagen-hydroxyapatite-colostrum is a candidate for an promising biomaterial for bone repair and bone infections treatment.

CONCLUSION

The composition of scaffold composite manufactured was 15% collagen, 75% hydroxyapatite and 10% colostrums has quite reliable properties because SEM test showed that scaffold could bind to both and could bind to both and could form sufficient pores to provide enough place for bone cells (osteoblats) to grow. The results of MTT assay revealed percentage of above 60%, which indicates that the material is not toxic. So that collagen-hydroxyapatite-colostrum combination is an excellent biomaterial candidate for bone repair and bone infection management.

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Research Report

HEART ABNORMALITY CLASSIFICATIONS USING FOURIER TRANSFORMS METHOD AND NEURAL NETWORKS

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ABSTRACT

Health problems with cardiovascular system disorder are still ranked high globally. One way to detect abnormalities in the cardiovascular system especially in the heart is through the electrocardiogram (ECG) reading. However, reading ECG recording needs experience and expertise, software-based neural networks has designed to help identify any abnormalities of the heart through electrocardiogram digital image. This image is processed using image processing methods to obtain ordinate chart which representing the heart's electrical potential. Feature extraction using Fourier transforms which are divided into several numbers of coefficients. As the software input, Fourier transforms coefficient have been normalized. Output of this software is divided into three classes, namely heart with atrial fibrillation, coronary heart disease and normal. Maximum accuracy rate of this software is 95.45%, with the distribution of the Fourier transform coefficients 1/8 and number of nodes 5, while minimum accuracy rate of this software at least 68.18% by distribution of the Fourier transform coefficients 1/32 and the number of nodes 32. Overall result accuracy rate of this software has an average of 86.05% and standard deviation of 7.82.

Key words: *Cardiac Abnormalities, Image Processing, Electrocardiogram, Fourier Transforms, Artificial Neural Networks*

ABSTRAK

Masalah kesehatan dengan gangguan sistem kardiovaskular masih menduduki peringkat tinggi secara global. Salah satu cara untuk mendeteksi kelainan pada sistem kardiovaskular terutama di hati adalah melalui membaca rekaman elektrokardiogram (EKG). Namun, membaca rekaman EKG membutuhkan pengalaman dan keahlian, jaringan saraf berbasis software telah dirancang untuk membantu mengidentifikasi kelainan jantung melalui gambar digital elektrokardiogram. Gambar ini diproses menggunakan metode pengolahan citra untuk mendapatkan grafik ordinat yang mewakili potensi listrik jantung. Ekstraksi fitur menggunakan transformasi Fourier yang terbagi menjadi beberapa jumlah koefisien. Sebagai input software, transformasi Fourier koefisien telah dinormalkan. Output dari program ini dibagi menjadi tiga kelas, yaitu jantung dengan fibrilasi atrium, penyakit jantung koroner dan normal. Tingkat akurasi maksimum dari software ini adalah 95,45%, dengan distribusi Fourier transform koefisien 1/8 dan jumlah node 5, sedangkan tingkat akurasi minimal software ini setidaknya 68,18% dengan distribusi Fourier transform koefisien 1/32 dan jumlah node 32. Secara keseluruhan hasil tingkat akurasi software ini memiliki rata-rata 86,05 % dan standar deviasi 7.82.

Kata kunci: *Abnormalitas jantung, pemrosesan citra, elektrokardiogram, fourier transform, Jaringan Saraf Tiruan*

INTRODUCTION

Health problems with cardiovascular system disorder is still ranked high, according to data from the World Health Organization (WHO) reported that approximately 31% of the cause of death globally was cardiovascular disease. Variety of prevention and detection of cardiac abnormalities such as by using the device as a diagnostic tool, where the most commonly used is the Electrocardiograph (ECG).

Electrocardiograph (ECG) used to capture and record the potential changes of heart using leads which are placed on the patient's body at a particular location. ECG results are in a form of image called the electrocardiogram.[13] Although knowing how the ECG works is relatively easy,

but determining the information on the ECG recording data requires experience and knowledge about heart disease and its symptoms. Manual extraction of the essential information on ECG signal is inefficient because of the amount of data that must be observed.[16]

On the other side, this recent year's studies using Artificial Neural Network (ANN) have been developed. ANN is a computational method of artificial intelligence based on human biological neural model of a computer or a machine that can duplicate human intelligence.[18] From this phenomenon, one solution to analyze the heart's electrical signals on the ECG is by using a software based on Artificial Neural Network (ANN) into a computational analysis to identify and classify abnormalities of the heart through the scanned ECG records. To reduce the computational load due to the amount of data that needs to be observed, feature extraction with image transformation is used.

Several studies about the use of scanned ECG records has done by Endarko[6] by image processing in order to obtain numerical data as an ANN input to detect coronary heart disease. At Karimah.[11] Bachrowi[2] and Asmaria[1] research, using a ECG graph ordinate retrieval feature extraction as input to ANN. The use of image transformation as feature extraction previously done by Kaur[10] and Sarkaleh[15] by using wavelet transform.

Some of these studies become the basis of this study as an attempt to help identify heart abnormalities. Feature extraction done with the Discrete Fourier Transform, and also because the Fourier transform can bring in the form of frequency characteristics of image that often appears in the image, which can't be seen with the eye.[5]

The study consists of pre-processing, segmentation and morphological operations, feature extraction, and classification of cardiac abnormalities. Transformations done at ECG graph to obtain Fourier coefficients as an input feature for ANN. Input patterns were divided into 3 groups, namely normal heart, atrial fibrillation, and coronary heart disease. The whole program is created using MATLAB.

METHODS

Data Collection

Research data collections include the acquisition of ECG image that has been diagnosed by a cardiologist manually. From the data collection obtained 87 data; 33 cardiac disorder atrial fibrillation, 13 coronary heart, and 41 normal heart.

Initial preparation which is cutting the image, with the intention of making the entire cycle on one ECG lead, where in one lead consisted of three ECG cycles. Lead which used in this study is data from the lead II, with the length of 530 pixels.

Software Design

Broadly the image will be processed by pre-processing, grayscaling, followed by image segmentation with thresholding to obtain binary image, which then continued by morphological image processing. From the resulting image, ordinate value of the image soughted to show the electrical potential value of cardiac which will form the graphic visualization of ECG image. The starting point was taken from the tip of electrocardiogram isoelectric line, with upward deflection is positive and downward deflection is negative. So that obtained pixel value equal to the height of the image pixels on the electrocardiogram. Feature extraction in image processing is done by Fourier transformation on the value.

Data were normalized before feature transformation results of are used as networks input data. Normalization aims to facilitate the Artificial Neural Networks in the training process, the process of finding the weight, and the testing process. Normalization performed on the input features and the target for the network whilst denormalization to the output value of the network to return to its original shape. Training process using Backpropagation network according to flowchart in Figure 1:

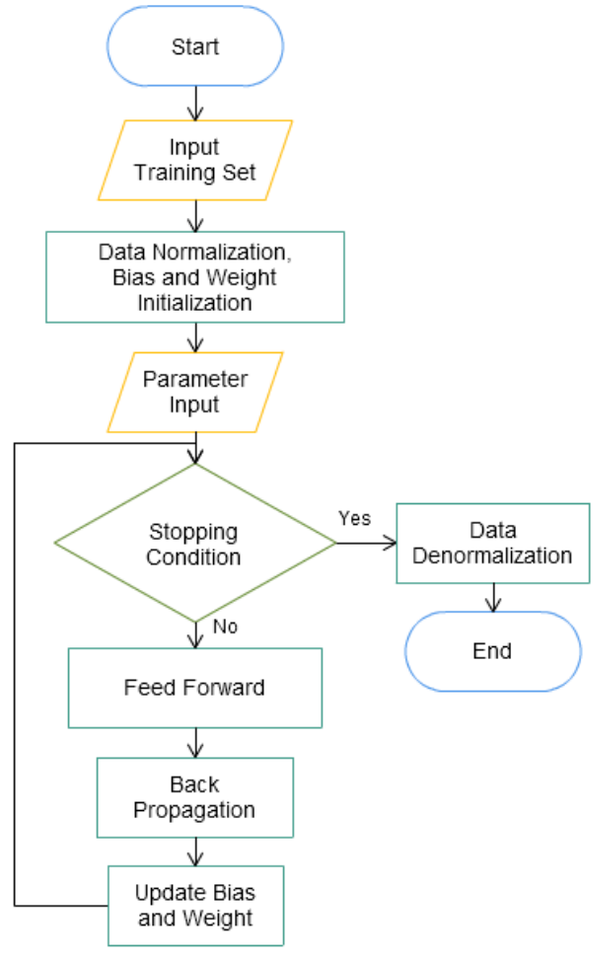


Figure 1. Training process flowchart.

RESULT AND DISCUSSION

Data Processing Result

A total of 87 data is passing through a series of image processing, include grayscale, segmentation, dilation and erosion morphological operations, and feature extraction. From this amount of data are divided into two, namely 65 training data and 22 testing data. Both groups include all of data categories, which are heart with atrial fibrillation disorder, coronary heart disease, and normal heart. Testing data used in Test Validation, this aims to determine the accuracy of the program that has been created.

Preprocessing

This preprocessing includes grayscale using MATLAB process that aims to transform the RGB image into 8 bit image that has a scale range of 0-255.

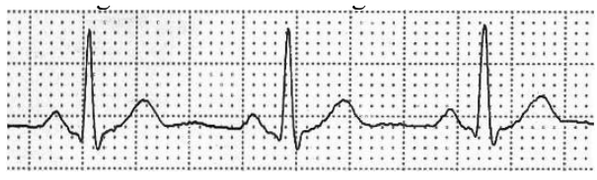


Figure 2. Normal heart image after grayscale process.

Segmentation

The image that has been through a preprocessing segmentation then has the background removed by segmentation. This process causing only the graph remains. Segmentation is done by delivering threshold value, so that the image obtained is a binary image which simply made up by black and white color.

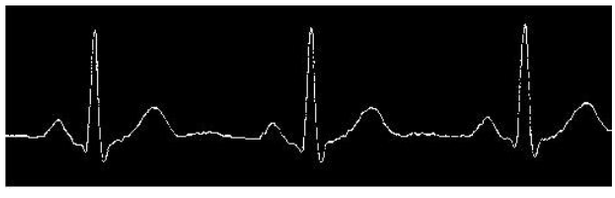
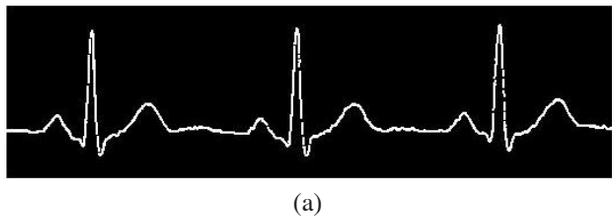


Figure 3. Segmentation process result.

Morphology Operations

Earlier segmentation process causes the binary image in Figure 7 produces intermittent graphs in some parts, that it is necessary to conduct morphology operations to rebuild disconnected parts of the graph. Operations performed include dilation and erosion.



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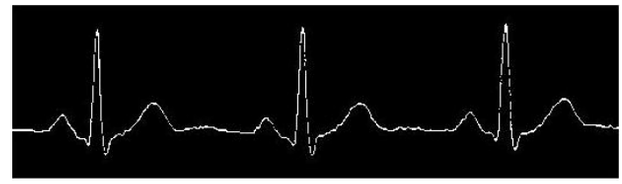

(b)

Figure 4. Morphological image improvement (a) Dilation (b) Erosion.

Feature Extraction

Feature extraction process aims to obtain the characteristic features of the image. Prepared image is a binary image that has been repaired through morphological operations. Initial stages feature extraction is to find the value of each pixel ordinate in the image which represents the potential value of EKG graph.

Ordinate value search includes the starting point of the graph, which is point 0 on the image Y axis. Point 0 on Y axis adjusted to the isoelectric line of the ECG graph, so its value will be in accordance with the high of pixel graphs. Graph visualization derived from the matrix which contains the values obtained from the Y axis.

Next, Fourier coefficients calculated from each value, in order to get 530 pieces of Fourier transform coefficients which in accordance to the number of pixels at the image length.

On this Fourier transform results, conducted coefficient part retrieval as an input for artificial neural networks training and testing. Coefficient part retrieval aims to reduce the high computational load because of the many data features were trained, and find the smallest number of

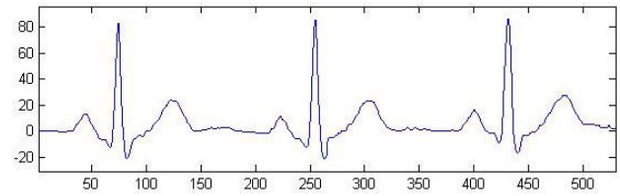

Figure 5. Graph visualization

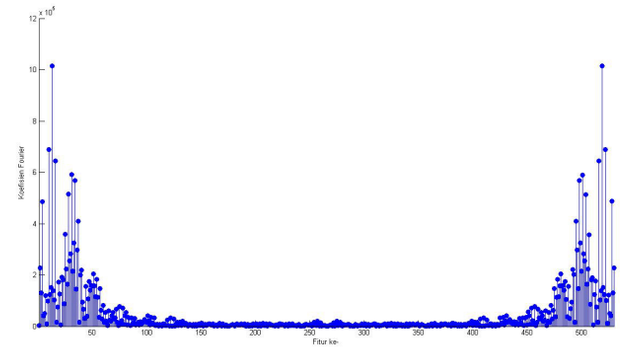

Figure 5. Fourier Transforms plotting

Table 1. Fourier coefficient parts and number of features for neural network input

Coefficient parts	Number of input features
Whole coeffients	530
1/2 coeffients	265
1/4 coeffients	133
1/8 coeffients	66
1/16 coeffients	33
1/32 coeffients	16

input features that can provide the best results. A complete Fourier coefficient parts and number of features for neural network input is presented in Table 1.

Backpropagation Network Formation

Backpropagation Network Training

The training process uses 65 data that divided into three classes. The data used for training consisted of 30 normal heart data, 9 coronary heart data and 25 atrial fibrillation data.

In this study, the manipulated variable is number of neurons in a hidden layer network. The weights used are the random weights to bias, input and hidden weight. Thus in this study weight training which has the best accuracy results for each neuron are used. Activation function used is bipolar sigmoid function which ranged (-1,1), because network output target is -1 for atrial fibrillation, 0 for coronary heart and 1 for normal heart. Searching the best weight without normalization tends to be more difficult and less efficient because there is a quite far numbers range differences in the Fourier coefficients.

Training accuracy results obtained from neural network training parameter changes can be found in Table 2.

Table 2 shows that the greater number of neurons, the smaller MSE generated where this result applies to any number of features. The smaller number of features also led to smaller MSE generated. Weight searching also tends to be faster on fewer input features. This can be seen in the table above, which generating smaller MSE. The use of coefficient parts peaked at 1/16 coefficient, where on the use of 1/32 coefficient, MSE results are no smaller from the use of 1/16 coefficient.

Backpropagation Network Testing

The network testing process uses 22 data which haven't been used for training. This testing data consists of 10 normal heart data, 4 coronary heart data and 8 atrial fibrillation data. The testing process is done with the same parameter variation as was done during the training process, yet only using the final weights of each variation, to obtain the best results without repeating the training process. Backpropagation network test results can be seen in Table 3.

From Table 3 can also be seen the influence of the parameter changes; number of neurons on the number of features. The greater the number of features, the greater the number of neurons needed to achieve the highest level of accuracy. Rate of accuracy will decrease after reaching the optimal number of neurons. Based on the results of accuracy rate in Table 3, the highest accuracy rate of this network is 95.45%. This rate is can be found on several variations of Fourier coefficient parts and number of neurons. However, if associated with the MSE of training results in Table 2, and considering the amount of computational load, the highest accuracy rate and optimal parameters found in the

Table 2. Training data results

Neuron	Coefficient Parts	MSE	Accuracy
3	1	0.0134	100%
	1/2	0.0134	100%
	1/4	0.0128	100%
	1/8	0.0122	100%
	1/16	0.0120	100%
	1/32	0.0324	98.46%
5	1	0.0121	100%
	1/2	0.0121	100%
	1/4	0.0120	100%
	1/8	0.0118	100%
	1/16	0.0117	100%
	1/32	0.0306	98.46%
10	1	0.0119	100%
	1/2	0.0118	100%
	1/4	0.0118	100%
	1/8	0.0118	100%
	1/16	0.0117	100%
	1/32	0.0119	100%
20	1	0.0118	100%
	1/2	0.0118	100%
	1/4	0.0118	100%
	1/8	0.0117	100%
	1/16	0.0117	100%
	1/32	0.0119	100%
30	1	0.0118	100%
	1/2	0.0118	100%
	1/4	0.0117	100%
	1/8	0.0117	100%
	1/16	0.0117	100%
	1/32	0.0118	100%

Tabel 3. Testing data accuracy

		Fourier Coefficient Parts					
		1	**1/2**	**1/4**	**1/8**	**1/16**	**1/32**
Neuron	3	81.81%	95.45%	81.81%	86.36%	86.36%	72.72%
	5	86.36%	90.90%	95.45%	95.45%	81.81%	72.72%
	10	90.90%	86.36%	90.90%	90.90%	81.81%	72.72%
	20	90.90%	95.45%	86.36%	90.90%	90.90%	77.27%
	30	95.45%	90.90%	90.90%	86.36%	81.81%	68.18%

coefficient parts of 1/8 with number of neurons 5, and the final MSE 0.0118. Lowest accuracy rate obtained on the use of coefficient parts of 1/32 and the number of neurons 30, which is 68.18%. From the overall results in Table 3, overall accuracy rate of this software has an average of 86.05% and a standard deviation of 7.82.

CONCLUSION

Image features for neural network software in this study was obtained through image processing, which begins from grayscaling, segmentation, dilation, erosion and followed by ECG signal graphs feature extraction with Fourier transforms.

This software using artificial neural networks Backpropagation, with processed scanned ECG records image as an input. This image converted to a one-dimensional time series signal to obtain the value that is equivalent to voltage value on the ECG image which is then transformed with Discrete Fourier Transform. Output of this software is a numerical value cardiac abnormalities classification. Maximum accuracy rate of this software is 95.45%, with the distribution of the Fourier transform coefficients 1/8 and number of nodes 5, while minimum accuracy rate of this software at least 68.18% by distribution of the Fourier transform coefficients 1/32 and the number of nodes 32. Overall result accuracy rate of this software has an average of 86.05% and standard deviation of 7.82.

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Case Report

ROLE OF BREAK CLUSTER REGION (BCR) - ABELSON MURINE LEUKIMIA (ABL) EXAMINATION IN CHRONIC MYELOGENOUS LEUKEMIA (CML)

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ABSTRACT

Chronic myelogenous leukemia (CML) is a clonal bone marrow stem cell disorder associated with a characteristic chromosomal translocation called the Philadelphia chromosome which caused a proliferation of mature granulocytes (neutrophils, eosinophils and basophils) and their precursors, increasing unregulated growth of predominantly myeloid cells in the bone marrow and its accumulation in the blood. As myeloproliferative disease, Chronic Myelogenous Leukemia or CML is a malignancy of the sixth-highest, reaching 15% of all blood malignancies in adults with an incidence of 1.1 per 100,000 population (Ugroseno, 2012). The CML diagnosis is made based on a presence of Philadelphia chromosome due to the existence of a reciprocal translocation of chromosomes 9 and chromosome 22 t (9.22), and raises the fusion of Break Cluster Region (BCR) gene of chromosome 22 on band q11 by Abelson Murine Leukemia (ABL). The fused BCR-ABL gene has BCR sequences of different length, so it produces a protein that has a different molecular weight. Despite having different length of BCR sequences, however, the length of fuses ABL gene sequence is constant. Associated with this different BCR sequence length are the three variations of the BCR-ABL gene fusion. The first variation is a Major Break Cluster (M-BCR), the BCR gene break is found in exon 2 in e13-E14 region. This type of CML is the fusion of BCR exon b2 or b3 to ABL exon a2, forming two major transcripts of the b2a2 or b3a2, which has a protein product with 210 kD weight or referred to as p210. The second variation is Minor BCR (m-BCR), which has e1a2 fusion. CML with BCR-ABL gene fusion of this type has a protein product with a molecular weight of 190 kDa or called p190. The third variation is micro-BCR (m-BCR), with BCR gene break between exons E19 and e20b that form mRNA transcripts e19a2, with BCR-ABL protein P230. This fused gene can be detected with qualitative multiplex PCR.

Key words: *CML, Philadelphia Chromosome, translocation t(9,22), fuse gene BCR ABL, Qualitative Multiplex PCR*

ABSTRAK

Chronic myelogenous leukemia (CML) adalah kelainan klonal dari stemsel sumsum tulang belakang terkait dengan adanya translokasi kromosom t (9,22) atau yang lebih dikenal dengan kromosom philadelphia. Translokasi kromosom t (9,22) menyebabkan terjadinya proliferasi dari granulosit dewasa (neutrofils, eosinofils dan basofil). Proliferasi sel granulosit ini menyebabkan terjadinya peningkatan dari pertumbuhan yang tidak terkendali pada sel mieloid di bone marrow dan terakumulasi dalam darah. Sebagai suatu kelainan myeloproliferatif, Chronic Myelogenous Leukemia atau CML merupakan malignansi urutan ke enam terbesar, di mana kelainan ini mencapai angka 15% dari seluruh malignansi darah pada orang dewasa dengan insidensi 1.1 per 100,000 populasi penduduk (Ugroseno, 2012). Diagnosis CML dibuat berdasarkan pada adanya kromosom Philadelphia, yang terjadi sebagai akibat adanya translokasi resiprokal antara kromosom 9 dan kromosom 22 atau t (9.22). Translokasi ini menyebabkan munculnya fusi gen BCR(Break Cluster Region) pada chromosome 22 lengan q11 dengan gen Abl atau Abelson Murine Leukemia. Fusi gen BCR-ABL memiliki sekuen gen BCR dengan panjang sekuen yang berbeda, sehingga menghasilkan produk protein dengan berat molekul yang berbeda. Terkait dengan perbedaan panjang sekuen gen BCR, menimbulkan adanya variasi fusi gen BCR-ABL, yakni pertama Major Break Cluster (M-BCR), fusi gen BCR ditemukan pada exon 2 di daerah e13-E14. Tipe ini merupakan fusi gen BCR exon b2 atau b3 dengan gen ABL exon a2, membentuk 2 jenis transkrip utama, yakni b2a2 atau b3a2, di mana produk proteinnya memiliki berat 210 kD atau biasa ditulis dengan p210. Variaso kedua adalah Minor BCR (m-BCR), yang memiliki fusi pada titik e1a2. CML dengan fusi

gen BCR-ABL type ini memiliki produk protein dengan berat molekul 190 kDa atau disebut p190. Variasi ketiga adalah micro-BCR (m-BCR), di mana gene BCR terletak pada exons E19 dan e20b membentuk transkrip mRNA e19a2, dengan produk protein p230. Keseluruhan variasi tersebut dapat dideteksi dengan qualitative multiplex PCR.

Kata kunci: *CML, Kromosom Philadelphia, translokasi t(9,22), fuse gen BCR ABL, PCR Multipleks kualitatif*

INTRODUCTION

Chronic Myelogenous Leukemia or CML is a malignancy of the sixth-highest, reaching 15% of all blood malignancies in adults with an incidence of 1.1 per 100,000 population[1]. Specific characteristics of CML is the presence of Philadelphia chromosome due to the existence of a reciprocal translocation of chromosomes 9 and chromosome 22 t (9.22). The presence of the translocation t (9; 22) raises the fusion of Break Cluster Region (BCR) gene of chromosome 22 on band q11 by Abelson Murine Leukemia (ABL), which causes adult granulocytes proliferation grown without being interrupted by differentiation[1]. Chromosomal translocation, the gene ABL from chromosomes 9, which is replaced by the BCR gene on chromosome 22, is translated as Bcr-Abl fusion protein that has the ability to transform.

The fused BCR-ABL gene has BCR sequences of different length, so it produces a protein that has a different molecular weight. Despite having different length of BCR sequences, however, the length of fuses ABL gene sequence is constant. Associated with this different BCR sequence length are the three variations of the BCR-ABL gene fusion. The first variation is a Major Break Cluster (M-BCR), the BCR gene break is found in exon 2 in e13-E14 region. This type of CML is the fusion of BCR exon b2 or b3 to ABL exon a2, forming two major transcripts of the b2a2 or b3a2, which has a protein product with 210 kD weight or referred to as p210. The second variation is Minor BCR (m-BCR), which has e1a2 fusion. CML with BCR-ABL gene fusion of this type has a protein product with a molecular weight of 190 kDa or called p190. The third variation is micro-BCR (m-BCR), with BCR gene break between exons E19 and e20b that form mRNA transcripts e19a2, with BCR-ABL protein P230. The transcript is even rarer, ie, with a clinical picture of netrophilia and or thrombocytosis.[2]

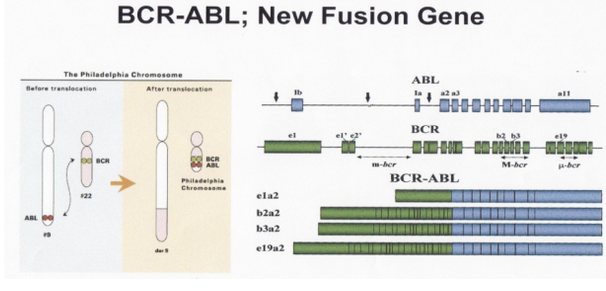

Figure 1. BCR-ABL gene fusion as a result of chromosomal translocation t (9,22) (Goh *et al.*, 2006)

In CML, the form of the BCR-ABL gene fusion will then be transcribed into Bcr-Abl fusion protein that has the ability to phosphorylate a substrate which further activates transduction cascade Ras-signaling pathways[2]. A tyrosine kinase is an enzyme that can transfer a phosphate group from ATP to a protein in a cell. The Ras pathway is a signaling center that forwards signals both upstream and downstream, with 3 signaling pathway downstream of Ras, namely Ras-Raf-MAP-kinase pathway, Akt/PKB pathway and RAL pathway. The substrate phosphorylation may activate Ras/Raf/MAPK/ERK JUN kinase, Myc, and JAK-STAT, and form PI3K (phosphatidylinositol-3 kinase)-AKT protein, which plays a role in the inhibition of apoptosis, cell cycle progression, and DNA repair, thus resulted in the deregulation of cell proliferation, through increased leukocytes proliferation.[3]

CML Diagnosis

CML diagnosis is made based on history, physical and laboratory examination, which includes a complete blood count, peripheral blood smear, cytogenetic examination to identify the presence of the Philadelphia chromosome or the inspection of Bcr-Abl gene fusion.[4] Most of these are found adults. CML is rare in children.

Complete blood examination is intended to determine the amount of various kinds of cells in blood. In complete blood count examination, white blood cells often increase, typically > 25 109/L and could even above 100 109/L. Differential cell shows granulocytes in all stages of maturation, ranging from the blast to the mature form. Basophils also increases, but only at 10–15% of the patients who have basophils ? 7% in peripheral blood. Eosinophils also increases lightly. Platelets increases in 30–50% of the patients and only a few per cent were in excess of 1,000 109/L.[1,4]

Cytogenetic examination of philadelphia chromosome or molecular examination of BCR-ABL gene fusion are performed to confirm the diagnosis. In some cases, about 5% of Philadelphia chromosome cannot be detected, so that it requires other methods, such as fluorescent in situ hybridization (FISH) and molecular detection of BCR-ABL gene fusion by examination of Polymerase Chain Reaction (PCR) for establishing CML diagnosis.[5]

CML examination with Polymerase Chain Reaction (PCR)

PCR is an in vitro DNA amplification technique in specific regions bounded by two oligonucleotide primer. Primer is used as a barrier region is propagated single-stranded DNA sequence with its complementary DNA template. The process is similar to the process of DNA replication in vivo, which is semi-conservative. PCR works

to help speed up the diagnosis of malignant diseases such as chronic leukemia with BCR-ABL gene fusion.[1]

Stages of BCR-ABL examination include RNA isolation of peripheral blood samples of CML patients using the High Pure RNA Isolation Kit, cDNA synthesis, using RNA that had been isolated, converted into cDNA using Transcriptor First Strand cDNA Synthesis Kit, and examination of the BCR-ABL gene fusion using multiplex PCR technique.

Multiplex PCR assay for the detection of BCR-ABL gene fusion

Multiplex-PCR is a modification of PCR reaction in order to be faster in detecting gene deletions or duplications. This process amplifies genomic DNA samples using multiple primers and a temperature-mediated DNA polymerase in a thermal cycler. Multiplex-PCR was first described in 1988 as a method to detect deletions in the dystrophin gene.[5] It has also been used with the steroid sulfatase gene.[6] In 2008, the multiplex-PCR was used for analysis of microsatellites and SNPs.[7] Multiplex-PCR consists of multiple primer sets within a single PCR mixture to produce amplicons of varying sizes that are specific to different DNA sequences. By targeting multiple genes at once, additional information may be gained from a single test run that otherwise would require several times the reagents and more time to perform. Cross *et al*, (1994) have used a multiplex-PCR for the identification of BCR-ABL transcripts simultaneously from two or more genes in the same reaction. The goal is to qualitatively detect the BCR-ABL gene fusion. One example of the use of Multiplex PCR Examination is to identify for the presence of BCR-ABL gene fusion by using the following primers:

Sense primers A1: caacagtccttcgacagcag (5'–3') on bcr exon 1
B1: gctacggagaggctgaagaa (5'–3') on bcr exon 11
Anti-sense primer C1: cgtgatgtagttgcttggga (5'–3') on abl exon 3
Primer sequences in nested RT-PCR
Sense primers A2: caacagtccttcgacagcag (5'–3') on bcr exon 1
B2: gtgcagagtggagggagaac (5'–3') on bcr exon 12
Anti-sense primer C2: acaccattccccattgtgat (5'–3') on abl exon 3

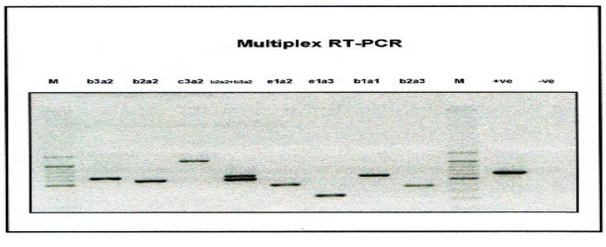

Figure 2. Example of electrophoresis results of BCR-ABL qualitative examination.[8].

The next phase is gel electrophoresis using 2% agarose. Results of electrophoresis was stained with ethidium bromide (by soaking for 15–20 minutes). PCR results is positive when 627 bands are obtained for b3a2 transcript (e13a2), 552 for the b2a2 (e14a2), 378 for b2a3, and 580 for b1a1.[8]

Examination of response to therapy using RQ-PCR

Examination of response to therapy aims to quantitatively detect BCR-ABL fusion gene transcript derived from mRNA isolation of the patients' blood samples, using Real Time PCR or better known as Quantitative-PCR atau Real Time Quantitative–PCR atau RQ PCR. Using RQ-PCR the quantity of PCR products generated from each amplification cycle is done by measuring the strength/increase in fluorescence generated by the fluorescent molecules used in the reaction.

RQ PCR products can be quantified relative to control genes or house keeping gene. In particular, quantification process relies on a standard curve obtained from known concentration of plasmid DNA. RQ-PCR has many advantages over conventional PCR. RQ-PCR allows amplification and detection process carried out simultaneously in one tube so that the process takes place more quickly and efficiently.

In CML treatment management, Real Time Quantitative PCR is used to evaluate molecular response of BCR-ABL therapy, namely by calculating residual BCR-ABL transcripts within 2 weeks after reaching CcyR (Complete Cytogenetic Response) and then performed every 3 months. Molecular response can be divided into complete molecular response (CMR), in which BCR-ABL transcript concentrations cannot be detected by RQ-PCR, and MMR or Major Molecular Response, in which BCR-ABL decreases? 3-log or the ratio of BCR-ABL/ABL is < 0.1.

Resistance and examination of mutation detection with ASO PCR

According to National Comprehensive Cancer Network (NCCN) and LeukemiaNet Guidelines, resistance to tyrosine kinase inhibitors is defined as failure to achieve complete hematologic response (CHR) in 3 months, cytogenetic response (CR) in 6 months, or major cytogenetic response (MCR) in 12 months. Resistance to tyrosine kinase inhibitor of a drug can be divided into three, namely hematologic, cytogenetic and molecular resistance.

Failed therapy is defined as not achieving hematologic response after 3 months of therapy, or loss of complete hematological response at any time, or after 6 months not achieving cytogenetic response, or after 12 months not achieving major cytogenetic response, and or BCR-ABL > 10%, or after 18 months not achieving complete cytogenetic response and or BCR-ABL of > 10%.[1]

According to Branford et al[6] (2003), patients who fail to achieve a 1-log reduction in BCR-ABL transcripts in 3 months or a decrease of > 2-log within 6 months, tend

not to give a significant response and at high risk for progressiveness. Molecular resistance is defined as the lack or loss of complete molecular response (BCR-ABL transcripts cannot be detected) using PCR RQ- or as a lack of major molecular remission (ie, a decrease of BCR-ABL transcripts > 3-log or the ratio of BCR-ABL/ABL < 0.1%, respectively).[9]

According to Corbin *et al*[11] (2003), certain mutations, such as M244V, M351T, and Phe311L also causes resistance to Tyrosine Kinase Inhibitors (imatinib), which, using biochemical and cellular tests, the mutation will show decreased sensitivity to imatinib respectively of 1, 8 and 2.8-fold. Slight shifts in terms of sensitivity causes kinase activity becomes sufficient to cause disease progression. However, in theory, the resistance caused by these mechanisms can be overcome with increased doses of imatinib.

Mutation found in T315I frequently causes of resistance to inhibitors of first-generation (imatinib) or second generation. This mutation is also associated with secondary imatinib resistance that usually occurs in the later stages of the disease and is associated with advanced age, receiving interferon previously, a high Sokal score, and failure to reach the CCR in 12 months.[10]

Detection of ABL kinase domain mutations is performed when in chronic phase the CML patients, after treatment with TKI drugs, provide inadequate therapeutic response (failure to achieve hematologic complete response in the first 3 months, minimal cytogenetic response within 6 months, or a major cytogenetic response within 12 months) or loss of therapeutic response (defined as hematologic relapse, cytogenetic relapse, 1-log increase of BCR-ABL transcripts ratio, and the loss of major molecular response), or the disease becomes progressive (the occurrence of accelerated phase or blastic crisis).[1]

Mutation analysis can be done in various ways. One is by using Allele-Specific Olygonucleotide (ASO)-PCR. This method is a technique that is highly sensitive and specific for the detection of known mutations[1]. This method is even more sensitive than mutation detection with sequencing method because DNA sequencing method can only be useful for point mutation if the proportion of mutated cells is more than 30%. In cases where the number of mutated cells is less than 30% of total cells in the sample of the patients, at least 10 independent clones from patients should be analyzed for mutations detection, a quite expensive and time consuming procedure. In contrast, the ASO-PCR is comparatively more sensitive, specific and "economical", so it is a rapid method for mutation detection.[12]

CONCLUSION

The use of qualitative multiplex PCR to detect BCR-ABL fused gene becomes one of the methods to detect the Chronic Myelogenous Leukemia (CML). It is easier to be performed while the use of karryotyping was complicated to detect this fused genes that called philladelphia chromosome

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Research Report

PREDICTION OF DENGUE FEVER EPIDEMIC SPREADING USING DYNAMICS TRANSMISSION VECTOR MODEL

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ABSTRACT

Increasing number of dengue cases in Surabaya shows that its city has high potential of dengue fever epidemic. Although some policies were designed by Surabaya Health Department, such as fogging and mosquito's nest eradication, but these efforts still out of target because of inaccurate predictions. Ineffectiveness eradication of dengue fever epidemic is caused by lack of information and knowledge on environmental conditions in Surabaya. Developing spread and prediction system to minimize dengue fever epidemic is necessary to be conducted immediately. Spread and prediction system can improve eradication and prevention accuracy. The transmission dynamics vector simulation will be used as an approach to draw a complex system of mosquito life cycle in which involve a lot of factors. Dynamics transmission model used to build model in mosquito model (oviposition rate and pre adult mosquito), infected and death cases in dengue fever. The model of mosquito and infected population can represent system. The output of this research is website of spread and prediction system of dengue fever epidemics to predict growth rate of Aedes Aegypti mosquito, infected, and death population because of dengue fever epidemics. The deviation of infected population is 0,519. The model of death cases in dengue fever is less precision with the deviation 1,229. Death cases model need improvement by adding some variables that influence to dengue fever death cases. Spread of dengue fever prediction will help the government, health department to decide the best policies in minimizing the spread of dengue fever epidemics.

Key words: *Dengue Fever Epidemic, Knowledge Sharing, Transmission Dynamics Vector*

ABSTRAK

Peningkatan jumlah kasus DBD di Surabaya menunjukkan bahwa kota ini memiliki potensi tinggi epidemi demam berdarah. Meskipun beberapa kebijakan yang dirancang oleh Departemen Kesehatan Surabaya, seperti fogging dan pemberantasan sarang nyamuk, namun upaya ini masih tidak tepat sasaran karena prediksi yang tidak akurat. Ketidakefektifan pemberantasan wabah demam berdarah disebabkan oleh kurangnya informasi dan pengetahuan tentang kondisi lingkungan di Surabaya. Mengembangkan penyebaran dan sistem prediksi untuk meminimalkan wabah demam berdarah perlu segera dilakukan. Penyebaran dan sistem prediksi dapat meningkatkan akurasi pemberantasan dan pencegahan. Simulasi dinamika penularan vektor akan digunakan sebagai pendekatan untuk menarik suatu sistem yang kompleks dari siklus hidup nyamuk yang melibatkan banyak faktor. Dinamika model transmisi yang digunakan untuk membangun model Model nyamuk (tingkat oviposisi dan pra nyamuk dewasa), kasus yang terinfeksi dan kematian pada demam berdarah. Model nyamuk dan populasi yang terinfeksi dapat mewakili sistem. Output dari penelitian ini adalah situs penyebaran dan prediksi sistem epidemi demam berdarah untuk memprediksi tingkat pertumbuhan Aedes Aegypti, terinfeksi, dan populasi kematian karena demam berdarah epidemi demam. Penyimpangan populasi yang terinfeksi adalah 0519. Model kasus kematian demam berdarah kurang presisi dengan deviasi 1,229. Kematian kasus Model perlu perbaikan dengan menambahkan beberapa variabel yang berpengaruh terhadap kasus kematian demam berdarah. Penyebaran prediksi demam berdarah akan membantu, departemen kesehatan pemerintah untuk menentukan kebijakan terbaik dalam meminimalkan penyebaran epidemi demam berdarah.

Kata kunci: *Epidemik Demam Berdarah, Knowledge Sharing, Transmission Dynamics Vector*

INTRODUCTION

Dengue fever is the most frequent arthropod-borne viral disease in humans.[1] Over 50 million people living in tropical and subtropical urban and semi-urban areas are infected with dengue annually, and up to 500,000 people develop potentially lethal complications called dengue hemorrhagic fever/dengue shock syndrome. Dengue fever was founded in tropical and subtropical regions. The data from the Directorate of Animal Disease Control Source, Ministry of Health Department Republic of Indonesia, in 2010 Indonesia was the highest dengue cases in ASEAN with 150,000 cases and 1,317 deaths from the disease and in 2011 dengue cases were 126,908 cases with 1,125 deaths. Based on those data, the cases of dengue fever in Indonesia is first rank in the world.

Regarding to figure 1 about world spread of dengue fever shows that dengue activity in Indonesia is very high compared to other countries in the world. This condition becomes concentration for the government to decrease the number of dengue fever epidemics in Indonesia. A research was conducted by Fitriyani[3] to determine dengue critical epidemic areas in Indonesia. The research output is severity rate mapping of dengue fever in East Java and its classification in very critical, critical, and medium critical condition in East Java. Dengue fever cases classified into very critical when the cases in a city is more than 1,000 cases. Critical condition is happen when dengue fever cases reach 999–500 cases and dengue fever cases are less than 500 for medium critical category. Surabaya has high potential in spreading of dengue fever epidemics based on temperature and meteorology factors. (Figure 1)

The very critical level of dengue fever was 24% and Surabaya was included in this level with Blitar, Bondowoso, Gresik, Magetan, Mojokerto, Situbondo, Sumenep, and Tuban (fig. 2). Based on data, Surabaya was the city had the largest number of dengue cases in East Java with the amount up to 4,187 cases in 2006.[4] Figure 3 gives an overview of the high number of patients with dengue cases in Surabaya.

Surabaya Health Department has done some efforts in order to minimize the spread of dengue fever such as fogging (fumigation to kill dengue mosquitoes), "*abateseae*" (larvicides that aims to kill mosquito larvae), and mosquito's nest eradication (In Indonesian term called as Pemberantasan Sarang Nyamuk – PSN). Some efforts and policies that created by the government are still not working effectively. The current policies are less accordance in the real situation. If these problems happen every year then the spread of the Aedes Aegypti mosquito cannot be controlled optimally. Consequently in dengue fever cases, the health experts and government are required to decide the right policy to decrease the spread of dengue fever determine precisely, effectively, and efficiently in a short time, because dengue spread is relatively fast.[7]

Our previous research has been conducted in 2010[6] and 2011[7], it was integrated with knowledge sharing in

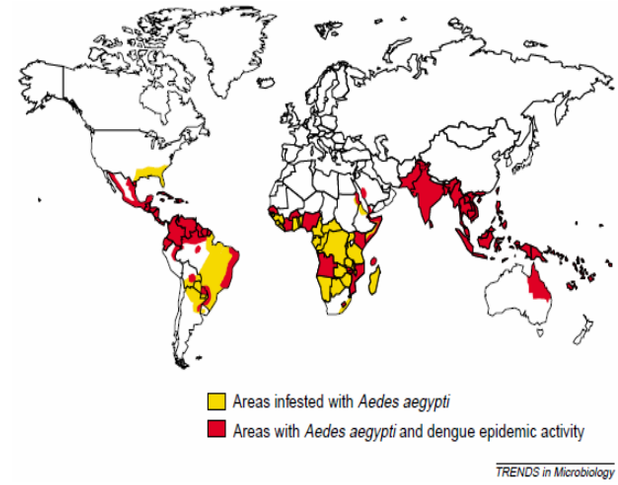

Figure 1. World Spread of Dengue Fever[2]

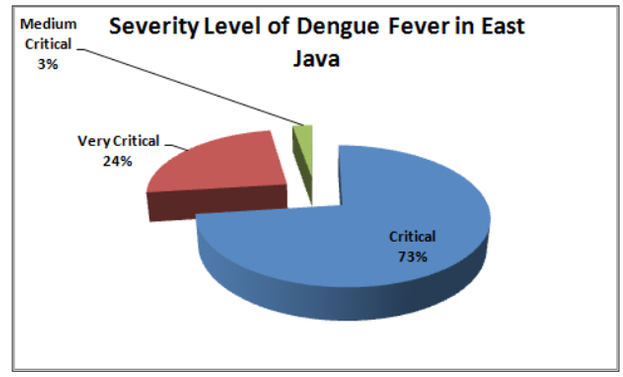

Figure 2. Dengue Fever Cases in East Java[4]

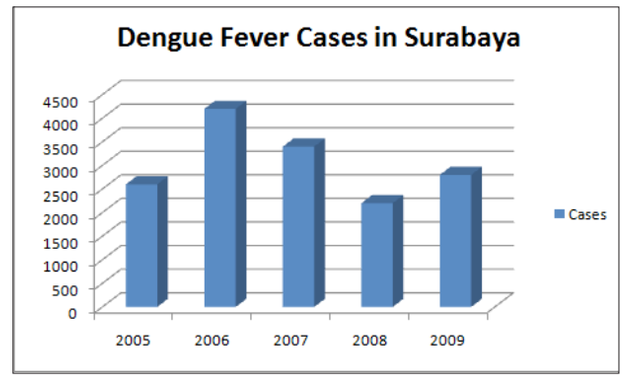

Figure 3. Dengue Fever Cases in Surabaya[5]

preventing epidemic. It has developed a communication media (website) that aims to control the spread of tropical diseases. The website only displays information without give prediction of epidemics distribution in future time. When the prediction of disease distribution can be seen in future time or next period, the government or health department can easily make policies to minimize the

spread of the epidemic. In 2011, previous research showed the pattern of spread of dengue fever by using a dynamic system. In the dynamic system control method used the time factor; observe behavioral changes that occur in the system due to the change of time. Based on these aspects, it was tried to build models to predict the spread of dengue fever by using a dynamic system.

The results of dengue fever prediction using dynamics system were validated, but there was still inefficiency so this research still needs to be developed. Some lacks of condition in dynamics system are the modeling of dynamic system using Stella software integrated with the website. It was still unable to predict in the following years because of the different software logic in the computer. It caused the predictions only calculate in a next month, and for the next few months the programmer should be calculating again in Stella software to get the prediction of dengue fever spread. It is not efficiency when every month the programmer must run software to predict the spread of dengue fever. The lack of dynamics system model that conducted in previous research are there was no loop in model to balance steady state condition in system, the sub-models in continuous variable did not have a balance loop, so the model can be invalid and there are many variables used to build system dynamics model and some variables that used have less precise functions such as random function.

Based on some lacks of our previous research, it can become an opportunity for the development in spread and prediction system in dengue fever virus. It is necessary to do a research that able to predict the spread of dengue fever by using a method which is able to model the interaction between mosquito larvae, female mosquitoes, and people in complex system.[9]

In 2012, Chen, Szu Chieh and Hsieh, Meng Huan[8] showed the transmission dynamic modeling of dengue fever in subtropical Taiwan by the contributing temperature-dependent entomological parameters of Aedes Aegypti. This study adopted vector-host transmission model[9] and implemented for modeling transmission dynamics of dengue fever in Southern Taiwan. The study was conducted by Chen, Szu Chieh and Hsieh, Meng Huan[8] aims to incorporate temperature factor as entomological parameter and investigate the transmission potential using vector host dynamics model. It was focused on Aedes Aegypti mosquito parameters of pre-adult, mosquito maturation, oviposition rate, adult mosquito death rate, and virus incubation rate in the mosquito.

In this research tried to apply the dynamics transmission vector model to predict the spread of dengue fever cases in Surabaya. Dynamics transmission vector model is a mathematical model used to describe the development of an epidemic disease in detail by observing the life cycle of Aedes Aegypti mosquito and the transmission of dengue fever in human as host.[9]

The objectives of this study are determining variable in transmission dynamics vector in spreading of dengue fever epidemics and developing and simulating variable in models with transmission dynamics vector in spreading of dengue fever epidemics.

MATERIAL AND METHOD

Study Data

This study was conducted using some data, namely infected and death cases of dengue fever from Surabaya Health Department and Dr. Soetomo Hospital, population data from Bureau of Central Statistics in Surabaya and temperature data from Bureau of Meteorology and Geophysic Surabaya. Data collection is taken from 2011 until March 2013. Surabaya is second big city in Indonesia with high severity level of dengue fever cases in East Java. According data from Surabaya Health Department, Surabaya is largest dengue fever cases in 2006 up to 4,187 cases.

Vector Host Dynamics Models

Dynamic transmission model use some mathematical model implemented to predict Aedes Aegypti mosquito growth from oviposition rate, virus incubation rate, pre adult mosquito maturation rate, and adult mosquito maturation rate and human infected in dengue fever virus. Figure 6 about diagram in vector host transmission describe the interaction between vector (pre adult) mosquito, vector (adult), and host (human).

The interaction of vector in pre adult mosquito has two parts that is oviposition and oviposition vertical infection. Oviposition vector will continue in mature phase, if the condition or environment is good, so the Aedes Aegypti will continue in oral infection phase then become infection mosquito with Aedes Aegypti mosquito that can spread dengue fever virus to human. When the environment and weather is not good its growth then it will be death in every phase.[2,7,18,19]

The interaction between Aedes Aegypti and host vector (human) was described in host vector, figure 6. Host vector begin with birth then infection phase with Aedes Aegypti mosquito. When the immune system of human was good, then infected people will recover from dengue fever. When the human immune system was bad, it can cause death to infected people with dengue fever virus. Based on diagram vector host transmission model, there are two simulations, mosquito simulation and human simulation.

The mosquito simulation used to predict the oviposition rate, pre adult mosquito maturation rate, adult mosquito death rate, and virus incubation rate in mosquito. The models that used in mosquito simulation are:

a. **Ovipositon Rate**

$$y = -0.0163x2 + 1.897x - 15.837 \quad (1)$$

b. **Pre Adult Mosquito Maturation Rate**

$$y = -0.0000002x^5 + 0.00003x^4 - 0.0012x^3 + 0.0248x^2 - 0.2464x + 0.9089 \quad (2)$$

c. **Adult Mosquito Death Rate**

$$y = 205.03 - 1.91x + 0.15x1.5 - (725.9 / \ln x) + (1247.68 / x) \quad (3)$$

d. **Virus Incubation Rate in Mosquito**

$$y = 0.008x - 0.1393 \quad (4)$$

where:

x = temperature dependent in observation area.

Temperature in observation area is variable that include in mosquito model, because temperature was importance things that affect in mosquito growth rate and virus incubation in mosquito. Mosquito eggs can hatch due to the temperature reaches above 28°C in the area, so that the temperature becomes a significant thing in mosquito growth.

Human infected of dengue fever (host) model used to simulate and predict the infected population because of dengue fever. This model combined with mosquito model because infected and death population depends on mosquito growth and virus incubation in mosquito. This is the model of human infected of dengue fever:

a. Susceptible Population (Se)

$$\frac{dSe}{dt} = bv\left(1 - v\left(\frac{Iv}{Sv + Ev + Iv}\right)\right) \quad (5)$$

b. Infected Population (Ie)

$$\frac{dIe}{dt} = bv * v\left(\frac{Iv}{Sv + Ev + Iv}\right) - \omega * Ie \quad (6)$$

c. Number at Time t Susceptible

$$\frac{dSv}{dt} = \omega * Se - \beta\frac{Ih}{Nh}Sv - \mu v * S \quad (7)$$

d. Infected but not Infectious

$$\frac{dSv}{dt} = \beta\frac{Ih}{Nh}Sv - \varepsilon Ev - \mu vEv \quad (8)$$

e. Infected Female Mosquito

$$\frac{dIv}{dt} = \varepsilon Ev + \omega Ie - \mu vIv \quad (9)$$

f. Sizes at Time t of Susceptible

$$\frac{dSh}{dt} = \mu hbNh - \beta\frac{Sh}{Nh}Iv - \mu hdSh \quad (10)$$

g. Recovered / Immune Human Population

$$\frac{dIh}{dt} = \beta\frac{Sh}{Nh}Iv - {}^{\gamma}Ih - \mu hdIh \quad (11)$$

h. Infected / Infectious

$$\frac{dRh}{dt} = {}^{\gamma}Ih - \mu hdRh \quad (12)$$

Table 1. Variable of Vector Host Dynamics Models

Variable	Meaning (Units)
Se	Susceptible population
Ie	Infected population
Sv	The number at time t of susceptible
Ev	Infected but not infectious
Iv	Infectious female mosquito
Ih	Infected/infectious
Rh = γ Ih/μhdRh	Recovered/immune human population
bv	Oviposition rate of the egg (per days)
v	Proportion vertical infection rate
ω	Pre adult mosquito maturation rate (per days)
Sv+Ev+Iv	Total size of vector population
Iv/Sv+Ev+Iv	Infected Probability
Nv	Total number of mosquitoes
Nh	Total size of human population
1/bv	Average oviposition periods
1/ω	Pre-adult mosquito average transition time hatched eggs into adults form
β	Transmission biting rate (per day) if β = 1 and 1.5 imply that 1–1.5 bites per day for one women mosquito
β(Ih/Nh)Sv	Infected by the dengue virus during a blood meal
β(Sh/Nh)Iv	Infected mosquitoes transmit the virus to susceptible people
γ	Human recovery rate (per day)
μhbNh	Human birth number
γ Ih	Human recovery number
MhdRh	Human death number
μv	Mosquito death rate
ε	Virus incubation in mosquito
μhd	Human death rate (per day)
μhb	Human birth rate (per day)

Source: [9]

Based on mathematical model in vector host dynamics models, the variable that used is:

Implementation Dynamics Transmission Vector Model

Dynamics transmission vector model was implemented in mosquito simulation, infected and death population of dengue fever for every sub district in Surabaya. Infected and death population in dengue fever simulate based on the model formulation with the input from mosquito formulation. In this model considered some factors such as environmental factors: temperature [8], social factors:

Table 2. Input parameter value in Dynamics Transmission Vector

Variable	Meaning	Value	Reference
v	Proportion vertical infection rate	0.028	[8]
ω	Pre adult mosquito maturation rate (per days)	0.099	[8]
β	Transmission bitting rate (per days) if β =1 and 1.5 imply that 1-1.5 bites per days for one women mosquito	0.33	[9]
bv	Oviposition rate of the egg (per days)	6.218	[8]
ε	Virus incubation in mosquito	0.0607	
μv	Mosquito death rate	0.0331	
γ	Human recovery rate (per days)	0.143	[9]

amount of population growth mortality rate [9] and [8], and medical factors: recovery factor of infected person with dengue fever and the immune system in their body [9] and [8].

RESULT AND DISCUSSION

Dynamics transmission model integrated with temperature data in Surabaya, number of population in Surabaya, number of infected and death population that is caused by dengue fever cases. Some parameters are used for applying this model to predict dengue fever cases in Surabaya. This is the input table of parameter in Dynamics Transmission Vector Model.

Based on the input parameter above, the quantitative calculation is used to know the oviposition mosquito rate,

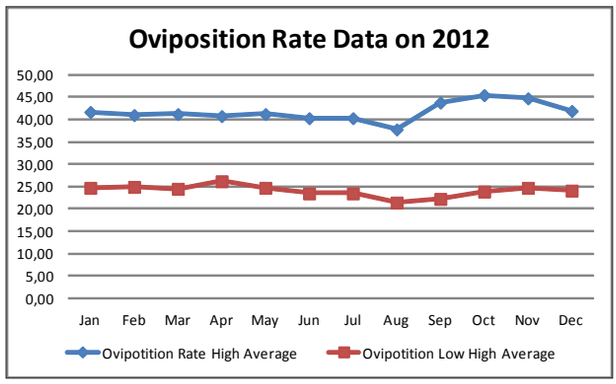

Figure 4. Oviposition Rate Data on 2012

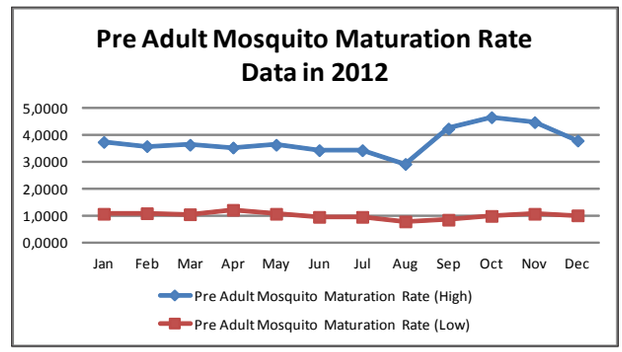

Figure 5. Maturation Rate of Pre Adult Mosquito Data on 2012

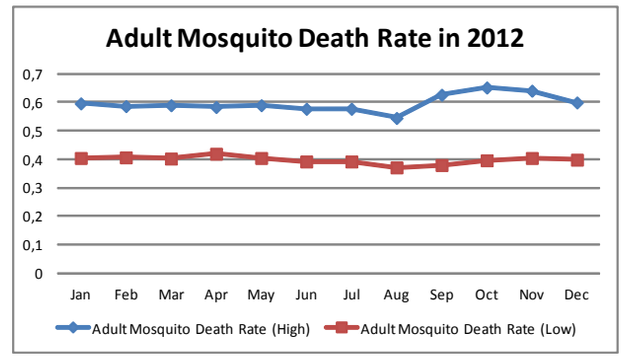

Figure 6. Adult Mosquito Death Rate Data on 2012

pre adult mosquito maturation rate, and virus incubation rate in mosquito.

Oviposition is the way ovipositor (Aedes Aegypti mosquito) to deposit or lay egg in the medium where it can mature likes in water and container. Based on that formulation, the simulation of mosquito vector was simulated in 2012 shown below:

Maturation rate is condition that mosquito in pre adult stage. This stage, mosquito's wings are fully expanded and hardened. So they can fly around and require blood meal to visit. This stage is dangerous for human because they bring dengue fever virus.

Adult mosquito death rate is depended on condition of the temperature, environment condition, and fogging policy. This is the graphic of adult mosquito death rate.

Virus incubation rate in mosquito is very important aspect because it will affect spreading virus dengue fever. The rate in every month is changing based on temperature in region. This is the rate of virus incubation in Aedes Aegypti mosquito.

Data for the oviposition rate of the mosquito egg, infected probability, proportion vertical infected rate, pre adult mosquito maturation rate, and infected population calculate with the formulation above. This is the data that used to calculate infected population in January 2012 in Tandes.

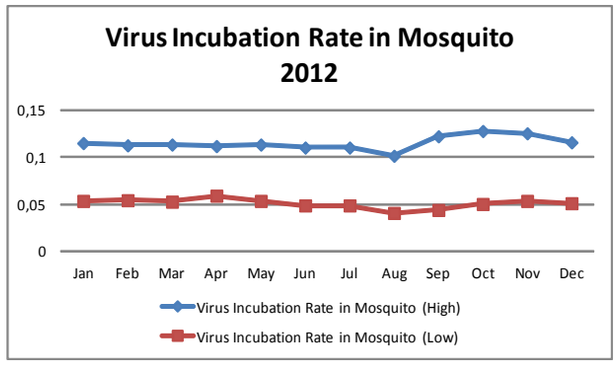

Figure 7. Virus Incubation Rate Data on 2012

= (bv * v * Iv / Sv + Ev + Iv) – (ω * Ie)
= (33.1853225 * 0.028 * 4.15776E- 05) – (2.404788935 * 2)
= 4.809536

Based on the calculation above, infected population in Tandes January 2012 is 4 people. The value of oviposition rate and pre adult mosquito maturation rate was based on mosquito simulation. Proportion vertical infected rate is constanta from mosquito bite human and infected human body by dengue fever virus and the value is 0.028. Infected probability value come from infected probability in December 2011 divided by population amount in Tandes in January 2012. Infected population data based on infected population in Tandes about dengue fever in December 2011.

The calculation of Death Population Tandes in January 2012 =

= ((bv * v * Iv / Sv + Ev + Iv) – (ω * Ie)) * Ie
= (33.1853225 * 0.028 * 4.15776E-05) – (2.404788935 * 2)) * 2
= 0.687077 – 0 person

Based on the calculation above, death population in Tandes January 2012 is 0 people. The value of oviposition rate and pre adult mosquito maturation rate is based on mosquito simulation. Proportion vertical infected rate is constanta from mosquito bite human and infected human body by dengue fever virus and the value is 0.028. Infected probability value come from infected probability in December 2011 divided by population amount in Tandes in January 2012. Infected population data based on infected population in Tandes about dengue fever in December 2011. Human recovery rate is constanta from the process of human immune system for human to survive from dengue fever virus. The result of simulation was round down to get the exactly numbers of death population.

Validation

The graphics bellow is shown the comparation result from real and simulation of infected and death population in Tandes.

Validation model of transmission dynamics vector is using mean average deviation. Mean average deviation used to measure the error in simulation of infected population and death population in every sub districts that caused by dengue fever virus.

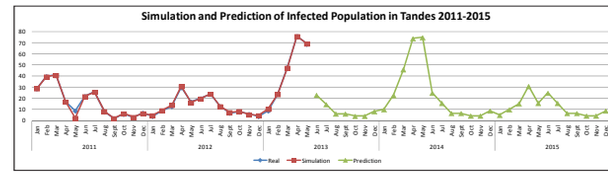

Figure 8. Simulation and Prediction of Infected Population in Tandes 2011–2015

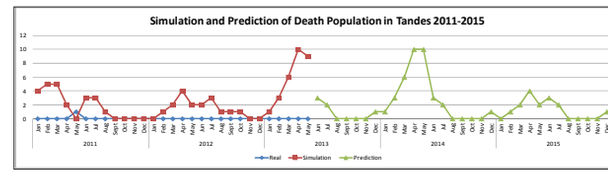

Figure 9. Simulation and Prediction of Death Population in Tandes 2011–2015

Table 3. Total and Average of MAD for Infected and Death Cases of Dengue Fever

MAD	Infected	Death
MAD 2011	0.209001	0.637097
MAD 2012	0.270383	0.610215
MAD 2013	1.076757	2.43871
TOTAL	1.556141	3.686022
AVERAGE	0.518714	1.228674

The average of MAD is 0.5187 that quite a bit for the error in forecasting and predicting infected population and with that result the model can represent the prediction of dengue fever infected people quite precision. The average of MAD is 1.228674 that quite big error in forecasting and predicting death cases and with that result the model cannot represent the prediction of dengue fever death cases because the validation result is less precision.

Severity Level Classification

Severity level classification is method that used to classify the condition of sub district in dengue fever epidemics. Severity level classification is divided into three condition by color red, yellow, and green.

Table 4. Color Classification on Severity Level

Colour	Mean
	Dangerous
	Warning
	Safe

Table 5. Severity Level Classification of Dengue Fever Epidemic

VARIABLE	RED	YELLOW	GREEN
Death Population	≥ 1	< 0	< 0
Infected Population	≥ 7	6–3	2–0

Variable that consider in it is death population and infected population. The table bellow will show the category and value on severity level classification.

In the table above, death population is one factor which is used to determine the severity level of sub district from dengue fever virus. Quantitative calculation using normal distribution from total data of dengue fever in every districts calcululate using ± 3σ. When there is a death cases a minimum 7 person infected by dengue fever then the sub district declared as dangerous category. In warning category, there is 6-3 infected population in dengue fever. The last is safe category there are 2-0 infected population in dengue fever. Severity level classification as a reference to decided the best policy to minimize spread of dengue fever virus and apply it effectively and efficiently.

The model is applied to predict the growth of mosquito, dengue fever cases by Dynamics Transmission Vector approach using mathematical model approach using differential. The models use to simulate three aspects include oviposition rate and pre adult mosquito maturation rate, infected population, and death cases caused by dengue fever.

Oviposition and pre-adult mosquito maturation rate simulation shows that the highest number of oviposition rate and pre adult mosquito maturation rate is in October. It is because the temperature in October very high temperature with average of temperature is 28.55°C. Mosquitoes can incubate the eggs when temperatures are high. Mosquito growth rate is higher than the other months. In the other hand, the oviposition and pre adult mosquito maturation rate is very low in August. It is due to the temperature in August is quite low at 26.3°C and in August has entered the rainy season. The lower temperature can cause the growth rate of mosquitoes was low too. Then, simulation results on oviposition rate and pre adult mosquito maturation rate is used as an input in simulation of infected population and death cases caused by dengue fever.

Human simulation in this model is infected population and death population caused by dengue fever. The input variables in this model are population number in every sub district, infected population in previous month, vertical infected rate, oviposition rate and pre adult maturation rate in mosquito. Based on these inputs, it is used to simulate each sub-district every month to provide prediction in infected population and population death. Simulation and prediction of infected population models show that the results did not have many different or variance between the simulation and the real number of dengue fever infected population, an example in Tandes sub district on

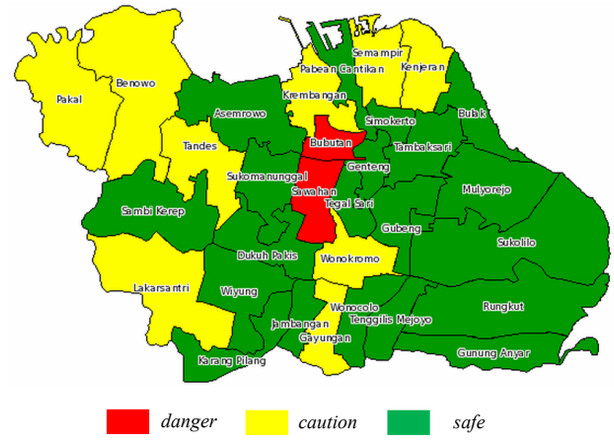

Figure 10. Spread and prediction System Dengue Fever (follow this link to view in detail : http://www.sebarandbd.ie.its.ac.id/)

January 2012 the results of the simulation was 4.8 while the real cases are 4 people. The deviation between actual and simulation are small. Sometimes, there are conditions when the simulation result is smaller or higher than the real infected number in sub district which is affected by several factors that are not considered in the model such as environmental factors and social factors. Both aspects are not included in the model and the simulation because the input of model is just temperature. If the simulation result is lower than the real infected population, then it can be influenced by poor of environmental condition and social factors likes lack of public knowledge in anticipation and treatment of dengue fever cases. The implementation of dynamics transmission model for infected population prediction is using MAD (Mean Average Deviation) to validate the models. The result of MAD is small enough, 0.5187. So the model appropriate in predicting the number of dengue cases. The low levels of accuracy between simulation and real outcomes in deaths cases caused this model needs modification with add some variables that can represent between the simulation results with the real value of the death cases in dengue fever.

As the continuity and maximise the benefit of this calculation to improve human health quality of life, it is necessary to develop the communication media by adding the map of spread dengue fever as predictions for the next period. The research also provided additional information to users about the condition of the region in Surabaya about the critical level of dengue fever epidemics based on historical data of dengue fever. The development can integrate health expert, health department, and people in spread and prediction system to minimize the number of dengue cases. This system also can help the health department in making policy about prevent dengue fever epidemics. This research will design and build an effective spread and prediction system to determine the spread, prevention, and treatment efforts of dengue fever epidemic. It will develop spread and prediction system, deployment patterns, and

designing spread and prediction systems spread of dengue fever by using Dynamic Transmission Vector approach based on sharing knowledge using website. The benefit of developing early warning system in dengue fever are to increase public knowledge about the development of the spread of dengue in the region, increase public knowledge about the prevention and control of dengue fever epidemics, and improving the health quality of life in Surabaya. Another advantage in government sides are for assisting the government, health Department in Surabaya, to predict the spread of dengue fever based of development function time to increase response level in preventing dengue fever epidemics and to make policies and control the spread of dengue fever epidemics effectively and efficiently.

In dengue fever spread and prediction system allow users to identify the location that is needed to predict using Surabaya maps with 31 sub districts. The knowledge sharing for spread and prediction system that needed as anticipation in preventing dengue fever. The figure bellow will show the design of dengue fever spread and prediction system.

CONCLUSION

There are some lacks of variable in this study needed to be considered for future research. The model in this study is limited in temperature as input variable in spread of dengue fever. It is important to consider social factor, environmental factor, and people's behavior in model in order to capture the real condition of dengue fever epidemics. Requires advanced studies related to the effective website design and website content to appropriate it with cognitive principles. The difficulty of collecting data and information about dengue fever cases in Surabaya, therefore it is needed more accurate and integrated data in order to achive accurate calculation.

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Literature Review

MANAGEMENT OF HIV/AIDS INFECTION IN PREGNANCY

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ABSTRACT

Twenty years since identified for the first time, the disease of HIV/AIDS spread and cause greater damage than the previous prediction. According to the Director General of P2M and Environmental Sanitation Department of Health by the end of 1999, there were 1066 people in Indonesia who are infected with HIV even though this must be realized that the rate is still far lower than the actual numbers, because there are many cases of HIV infection reported in addition to energy awareness health of the possibility of HIV infection has not been evenly distributed. Management of HIV infection/AIDS in pregnancy is done in time of antepartum, intrapartum and post partum, for mother and the baby, in general and specific. The important matters include the use of ART, nutrition and psychological support. Prevention and management of opportunistic infections to PWHA are not different with that of non pregnant woman. However, it is not routinely advised because of drug toxicity.

Key words: *HIV, AIDS, pregnancy, anti retroviral, PLWHAt*

ABSTRAK

Dua puluh tahun sejak pertama kali diidentifikasi, penyakit HIV dan AIDS menyebar dan menyebabkan kerusakan yang lebih besar dari prediksi sebelumnya. Menurut Direktur Jenderal Pemberantasan Penyakit Menular (P2M) dan Sanitasi Lingkungan Departemen Kesehatan pada akhir tahun 1999, terdapat 1066 orang di seluruh Indonesia yang terinfeksi HIV meski harus disaadari bahwa angka ini masih jauh lebih rendah daripada jumlah sesungguhnya, karena ada banyak kasus infeksi HIV yang dilaporkan disamping kesadaran tenaga kesehatan dari kemungkinan infeksi HIV yang belum merata. Manajemen infeksi HIV dan AIDS pada kehamilan dilakukan pada saat antepartum, intrapartum dan post partum, untuk ibu dan bayi, secara umum dan khusus. Hal yang penting adalah penggunaan terapi anti retroviral, dukungan gizi dan psikologi. Pencegahan dan pengendalian infeksi oportunistik dari ODHA untuk tidak berbeda dengan yang non wanita hamil. Akan tetapi, hal ini tidak dianjurkan secara rutin karena narkoba.

Kata kunci: *HIV, AIDS, kehamilan, anti retroviral, OHDHA*

INTRODUCTION

Twenty years since identified for the first time, the disease of HIV/AIDS spread and cause greater damage than the previous prediction. This disease can affect men, women and children around the world. In 1999 it was noted that HIV/AIDS is the fourth leading cause of death in the world, while in Africa is a cause of death terbanyak. Dalam 2000, about 3 million people, including 500,000 children died of AIDS, and 5.3 million people, including 600,000 children received new HIV infections, most due to mother-to- child transmission.[1]

The disease caused a crisis on various sectors including health. The majority of patients, ie 95 % are in developing countries, so far-reaching impact in the increase and population growth is even said to the population of a Contracting State may decline not because of the family planning program but rather due to AIDS deaths[1]

According to the Director General of Infectious Disease Eradication and Environmental Sanitation Department of Health by the end of 1999, there were 1066 people in Indonesia who are infected with HIV even though this must be realized that the rate is still far lower than the actual numbers, because there are many cases of HIV

infection reported in addition to energy awareness health of the possibility of HIV infection has not been evenly distributed.[2]

Although various attempts have been made to control the increasing number of incidence and mortality due to HIV/AIDS but the transmission still continues until now. HIV transmission occurs through three main lines, namely: horizontal transmission is contact with blood (transfusions contaminated, use needles interchangeably in drug addicts, injury, etc.), vertical transmission (from mother to fetus during pregnancy, childbirth and breastfeeding), sexual transmission (homosexual or heterosexual) [3]

Management of infectious diseases of HIV/AIDS in pregnancy need to consider two important things, namely the impact of HIV/AIDS infection in pregnancy and the impact of pregnancy on the progression of infection than HIV/AIDS. Various important things that need to be considered in the management of HIV/AIDS infection in pregnancy, namely the provision of anti- retroviral therapy, nutrition, psychological support.

Here are discussed the management of HIV/AIDS infection in pregnancy with the hope to increase knowledge of the health workers, reducing the incidence of HIV infection, reduced mortality due to AIDS, and reduces transmission of HIV infection.

PREGNANCY AND HIV INFECTION

Effect of pregnancy on HIV Disease Journey

In normal pregnancy there is a decrease in the number of CD4 + fetus early in pregnancy to maintain. In women who do not have HIV +, CD4 + percentage will rise again started the third trimester to 12 months after birth; whereas in HIV decline persist during pregnancy and after childbirth.[4]

Pregnancy is only slightly increase levels of virus (viral load) HIV. Kehamilan also does not accelerate disease progression to AIDS. (DN Burns, 1998; Crombleholme WR MD, 2002).[4,5]

Effect of HIV Infection in Pregnancy

Research in developed countries before the era of antiretroviral showed that HIV does not cause an increase in prematurity, low birth weight, or intrauterine growth retardation. While in developing countries, HIV infection increases the incidence of abortion, prematurity, intrauterine growth retardation, especially at an advanced stage. This is because the mother ‘s physical condition is worse and the possibility of a higher perinatal transmission.[1]

Vertical Transmission of HIV

Without intervention, the risk of HIV transmission from mother to fetus are reported to range between 15–40%. [6,7] The risk of vertical transmission varies in different countries, depending on anti- retrovirals that can be given. The risk of transmission is higher in developing countries than in developed countries. Transmission can occur during pregnancy, intrapartum and post partum. Most of the intrapartum transmission occurs.[8]

Transmission mechanism in pregnancy is unclear, presumably through the placenta. Pathological examination finding in the placenta in HIV-infected women HIV. Sel lymphocytes or monocytes infected mother or HIV virus itself can be reached directly through the fetal syncytiotrophoblast layer, or indirectly through the trophoblast cells and infect placental macrophages (Hofbauer cells) that have CD4 + receptor. According to the Pediatric Virology Committee of the AIDS Clinical Trials Gruoup (PACTG), said in utero transmission/infection if the initial positive virological test within 48 hours after birth and the next test is also positive.[9]

In the intrapartum transmission, infection was diagnosed if a negative virological examination in the first 48 hours after birth, and the first test next week to be positive and the baby is not breastfeeding.[9] As long delivery, the baby may be infected blood or servikovaginal fluid containing HIV through exposure to tracheobronchial or ingested in the birth canal.[9]

Infections associated with post partum lactation. Virus particles can be found in the cell components and nonmilk cells ibu.Konsentrasi highest virus in colustrum. Kadar highest HIV in breast milk occurred from the first week to three months after delivery. HIV in low concentrations can still be detected in breast milk to 9 months after delivery.[6,9]

MANAGEMENT OF HIV/AIDS INFECTION IN PREGNANCY

Management of HIV/AIDS infection in pregnancy during antepartum, intra -partum and post partum for mother and baby, both generally and specifically.[10]

A. General Treatment:
   - Take a rest
   - Adequate Nutrition Support
   - Psychosocial Therapy

B. Special Treatment
   - Provision of antiretroviral therapy (ART) combination, by Highly Anti Retroviral Therapy (HAART)
   - Management of obstetric
   - Treatment of Opportunistic Infections
   - Treatment of malignant

Provision of Antiretrovirus (ART)

ART is recommended for all people with HIV who are pregnant to reduce the risk of perinatal transmission. The purpose of the provision of antiretroviral therapy in pregnancy is to maximize maternal health and reduce the risk of HIV transmission as low as possible. The advantage must be weighed against the potential toxicity, teratogenesis, and long -term side effects. Side effects are expected to increase in the provision of a combination ART.

Namun, recent research by Toumala, et al showed that, compared with monotherapy, combination antiretroviral therapy does not increase the risk of prematurity, low birth weight, or intrauterine fetal death.[11]

Currently in Indonesia, some of HAART has been available in generic form at a lower price, such as zidovudine, lamivudine, nevirapine and stavudin. Antiretroviral drugs are first examined to reduce perinatal transmission is zidovudine (ZDV). In PACTG protocol 076, ZDV given orally start week 14 of pregnancy, followed by the time iv ZDV intrapartum to the mother, followed by ZDV syrup given to infants from the age of 6-12 hours to 6 weeks. In this study, infants are not breastfed. This method was effective at lowering the perinatal transmission of 25.5 % in the control group to 8.3 %.[12]

The longer the use of antiretroviral therapy, the more likely a reduced risk of transmission HIV. Joao, et al revealed in infants who are not infected with HIV, the average duration of use of ART in mothers compared with 16.63 weeks old maternal ART use 6.28 weeks in the group of infants infected with HIV.[13]

Explanation

Category B: There is no risk to the fetus in animal studies, but there has been no studies in pregnant women; or animal studies showed side effects according to controlled studies in pregnant women first trimester (and no proven risk in subsequent trimesters).

Category C: In animal studies found adverse effects on the fetus (teratogenic or embriosidal, or other), and there has been no controlled studies in pregnant women, there has been no research or drug side effects in animals or pregnant women. Drugs in this category is given only if the benefits exceed the potential risk to the fetus.

Category D: There is positive evidence of fetal risk of side effects in humans, but the gain in pregnant women may be acceptable than the risks, especially for life-saving.

Perinatal HIV Guidelines Working Group in the United States put forward the recommendations of antiretroviral with some scenarios.[14] (Table 2)

Tabel 1. Categories Food and Drug Administration (FDA) antiretroviral for use in pregnancy (Watts DH, 2002)[10]

Division	Drug	Categories FDA
Nucleoside Reverse Transcritase Inhibitor (NRTI)	Zidovudin/ZDV/ AZT	C
	Zalsitabin/ddC	C
	Didanosin/ddI	B
	Stavudin/d4T	C
	Lamivudin/3TC	C
	Abacavir/ABC	C
	Tenofovir DF	B
Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI)	Nevirapin	C
	Delavirdin	C
	Efavirenz	C
Protease Inhibitor (PI)	Indinavir	C
	Ritonavir	B
	Saquinavir	B
	Nelvinavir	B
	Amprenavir	C
	Lopinavir	C
Others	Hidroksiurea	D

Nutritional Support in HIV/AIDS

Nutritional management is important to prevent and cope with HIV infection. Provision of antiretroviral therapy is still needed, but without adequate nutrition therapy intervention difficult to stem the negative effects of reactive oxygen species (ROS), which induces cell death as well as disease progression. Management of nutrition in pregnant women with HIV/AIDS, people live with HIV/ AIDS (PLWHA) can increase resistance to opportunistic infections and to improve the tolerance to the side effects of drugs, protection of cell viability, ensure continuity of organ function, improve the function of the immune system to prevent other microorganisms including viruses, bacteria, tumor cells and fungi.

In pregnancies with HIV/AIDS infection is often accompanied by a deficiency of antioxidant vitamins and minerals, increased levels of ROS which promotes apoptosis in immune cells and increased morbidity. ROS can trigger the onset of the crisis scavenger enzyme-deficit micronutrient components such as Fe, Zn, selenium, vitamin C, vitamin B6, vitamin E, or an imbalance of some nutrients, such as essential amino acids can cause damage to components of the immune system. Decreased antioxidant PLWHA very dangerous, because the more encouraging apoptosis in various cells and promotes the progression of HIV infection to AIDS.[15,16]

One complication that almost always accompanies HIV/AIDS patients is weight loss. When weight loss exceeds 10 % with chronic diarrhea over 1 month, and general weakness with fever or prolonged over 1 month called HIV/AIDS wasting syndrome.[16] The cause of wasting in PLWHA is a decrease in the intake, malabsorption and increased metabolism. Potential for more severe wasting in PLWHA. This is due to the higher nutritional needs with respect to pregnancy and emerging opportunistic infections, nutritional intake while on the other hand decreases with time and complexity of infections.

Immunocompromised immune system which can be inhibited by preventing through medical nutrition therapy (MNT).With MNT expected to reduce morbidity, improve quality of life, lower costs, shorten the hospital stay,

Tabel 2. Recomendation of antriretroviral (ART) to reduce perinatal transmission (Perinatal HIV Guidelines Working Group, 2002)[13]

Pregnancy Condition	Recomendation
HIV-positive pregnancy who had never used antiretroviral earlier	Pregnant HIV-positive who undergoing clinical examination, standard immunological and virology. Consideration of ART initiation and selection are the same as non-pregnant HIV-positive people with consideration of the effect of the three-part ZDV pregnancy. Regimen recommended after the first trimester regardless of the levels of HIV of mother. Regimen combination is recommended in HIV clinical status, immunological and its virology heavy or HIV levels > 1000 copies /mL. If people with HIV come in the first trimester of pregnancy, provision of ART can be delayed until 10-12 weeks gestation.
HIV-positive pregnancy who are getting pregnant and pregnant ART	If the pregnancy is known after the first trimester, prior antiretroviral therapy forwarded, preferably by including ZDV. If in the first trimester of pregnancy is known, people with HIV are given counseling about the benefits and risks of antiretroviral therapy in first HIV-positive. If trimester pick off treatment during the first trimester, all drugs should be stopped and then given simultaneously after the first trimester to prevent drug resistance. Without considering the previous regimen, ZDV is recommended to be administered during the intrapartum and infants.
HIV-positive pregnancy in childbirth and had never get ART before	There are several regimens are recommended : • single dose nevirapine during labor and a single dose to the infant at age 48 hours • oral ZDV and 3TC during labor, followed by ZDV / 3TC in infants during the week • intrapartum ZDV, ZDV in infants followed for 6 weeks • two-dose of nevirapine combined with ZDV during labor followed iv ZDV in infants for 6 weeks Immediately after delivery, such as people with HIV undergoing CD4 + and HIV levels to determine whether the treatment will be continued.
If infants of HIV-positive mothers came after childbirth, while the mother has not received antiretroviral therapy during pregnancy or intrapartum	ZDV syrup is given to infants for 6 weeks, starting as soon as possible within 6-12 hours after birth. Some doctors may choose a combination of ZDV with other antiretroviral drugs, especially if the mother is known to be resistant to ZDV. However, the efficacy of this regimen is not yet known and the dose for children not yet fully known. Immediately after delivery, HIV-positive undergo examination such as CD4 + and HIV levels to determine whether the treatment will continue. Infant undergo early diagnostic tests that antiretroviral therapy can be given as soon as possible if it were HIV positive.

improve the quality of life of patients with HIV/AIDS. Ideal in the handling of involving doctors and nutritionists. MNT can increase the intake of energy, protein and micronutrient that can improve nutritional parameters. To obtain optimal effect of MNT, the nutritional therapy should be programmed so the diagnosis of HIV infection is established.[17] According to The Canadian Dietetic Association and the ADA developed an HIV/AIDS Medical Nutrition Therapy protocol on medical therapy interventions are promptly determine satus PLWHA nutrition, maintain and prevent the loss of body mass and nutritional deficiencies, support and improve the quality of life PLWHA. The protocol was evaluated two times a year in people living with HIV asymptomatic, and six times a year in patients who are symptomatic or AIDS.

Macronutrients

1. Total calories, 35–40 kcal/kg weight/hr enough to fulfill the needs if patients in general
2. Glucose, 30–70% of the total heat supplied in the form of glucose.
3. Fat, 20–30% of the total calories. Omega-6 polyunsaturated fatty acid (PUFA) triglycerides should be given in doses sufficient to prevent fatty acid deficiency.
4. Protein, 15–20% of total calories given as a protein or amino acids.

Micronutrients

Purposes of vitamins, minerals and trace elements need to be taken into account in the preparation of nutrient PLWHA every day. Potassium, magnesium, Fe, Zn, phosphate is maintained in order to stay within normal levels in the blood.

Nutritional status assessment done based on anthropometric, clinical performance, and BMI laboratory parameters should be monitored every week. Every PLWHA need to be briefed about the weakness of the

immune system that allows the transmission of disease through food. Knowledge of the type, form, delivery and quality procedures is important to address these risks.

Counseling in People with Pregnancy

Implemented since antepartum care. HIV-positive people are given information about the effects of pregnancy on HIV infection, the effect of HIV on pregnancy including perinatal transmission, the role of viral load monitoring, the use of drugs in pregnancy, use of zidovudine benefit in pregnancy and possible protection to Sectio Caesaria intrapartum.[10,19]

Factors affecting HIV-positive woman's decision to continue or terminate a pregnancy, including stage of HIV infection, the use of antiretroviral and other drugs, pregnancy planning, the desire to have children, religion and belief, economic status, social support for children.[18]

Obstetric Management

Perinatal HIV Guidelines Working Group in the United States submit obstetric management recommendations to reduce vertical HIV transmission in some conditions.

Prevention and Management of Opportunistic Infections during Pregnancy

Prophylaxis therapy and therapy against infection with Mycobacterium tuberculosis, Pneumocystis carinii, M avium complex, Toxoplasma gondii, and herpes simplex virus in pregnant HIV-positive people are no different from non-pregnant. However, primary prophylaxis against cytomegalovirus, candida and invasive fungal infections is not recommended routinely given drug toxicity. Fluconazole for example, is known to cause skeletal and craniofacial deformities in long -term use during pregnancy.[10]

Tabel 3. Recomendation of childbirth method to reduce HIV transmission from mother to child[14]

Childbirth Method	Recomendation
HIV-positive pregnancy who come in pregnancies over 36 weeks, has not received antiretroviral therapy, and awaiting the results of the HIV and CD4 + levels are thought to exist before childbirth	HIV-positive people should receive antiretroviral therapy regimens PATCG (pediatric AIDS clinical trials group) 076. Performed as like counseling about caesarean section for reducing the risk of transmis and the risk of post operative complications, the risk of anesthesia and surgery was decided others. If SC, SC planned at week 38 pregnancy. Over SC, people living with HIV received ZDV intravenous who started three hours earlier, and infants received ZDV syrup for 6 weeks. Decission will continue therapy after delivery or not depends on the results of virus levels and CD4 +
HIV-positive pregnancy who came in early pregnancy, is being awarded a combination antiretroviral therapy, and HIV levels remained above 1000 copies/ml at week 36 of pregnancy	Anti retroviral therapy (ART) regimens used are continued. People living with HIV should be counseled that HIV levels may not go down to less than 1000 copies/mL before delivery, so it is recommended to the SC. Likewise, the increased risk of complications such as infection SC, anesthesia operation if disconnected SC, SC planned in the 38th week of pregnancy. During the SC, people living with HIV receive intravenous ZDV initiated at least 3 hours in advance. Another therapy be continued before and after childbirth. Infants received ZDV syrup for 6 weeks
HIV-positive pregnancy who are on combination antiretroviral therapy, and HIV RNA levels at week 36 of pregnancy	People living with HIV were counseled that the likelihood of transmission if HIV RNA levels may be less than 2% even in labor pervagina. Selection of mode of delivery should weigh the benefits and risks of complications SC
HIV-positive pregnancy who had planned elective SC, However came at the onset of labor or after rupture of membranes.	Intravenous zidovudine (ZDV) given immediately. If the rapid progress of labor, people with HIV are offered to undergo a vaginal delivery. If cervical dilatation is minimal and supposedly will last long labor, can be chosen between intravenous ZDV and do SC or provide pitosin to speed up delivery. If people with HIV decided to undergo a vaginal delivery, avoid the head electrode, invasive monitors and other tools. Infants should receive ZDV syrup for 6 weeks

Tabel 4. Management of Opportumistic Inffections in Pregnancy in Women with HIV Infection[10]

Causing	Explanation
Mycobacterium avium complex	Azithromycin is the first choice for primary prophylaxis during pregnancy; clarithromycin teratgenik in animals; for maintenance therapy of azithromycin plus ethambutol
Mycobacterium tuberculosis	Isoniazid is preferred for prophylaxis during pregnancy; for TB that are resistant to combination therapy, consult to the experts
Herpes simplex virus	Prophylaxis and therapy as in non- pregnant
Pneumocystis carinii	Prophylaxis and therapy as in non- pregnancy; attention to neonate in women who received therapy Sulfa
Cryptococcus neoformans	Primary prophylaxis is not recommended; abnormalities after long -term exposure; consider switching to amphotericin B in the first trimester for long-term suppression
Coccidioides immitis	Primary prophylaxis is not recommended; anomalies as mentioned above after long-term exposure to fluconazole; consider switching to Amphotericin B in the first trimester when the long-term suppression continues
Histoplasma capsulatum	Primary prophylaxis is not recommended, for causing anomalies due to exposure to Fluconazole and security is not yet clear from chronic Itraconazole during pregnancy, consider switching to Amphotericin B in the first trimester when the long -term suppression continues
Cytomegalovirus	Primary prophylaxis is not recommended; the management of long-term suppression should be consulted with the experts
Candida species	Prophylaxis is not indicated during pregnancy; craniofacial and skeletal abnormalities were reported in four infants after long-term exposure to fluconazole in utero
Toxoplasma gondii	Treatment and secondary prophylaxis (maintenance therapy) as in patients who are not pregnant; only primary prophylaxis with trimethoprim-sulfamethoxazole.

Vaccination against hepatitis B, influenza and pneumococcal remains can be given during pregnancy. The vaccination should be given after the levels dropped to undetectable HIV to prevent HIV-RNA levels after vaccination.[10]

SUMMARY

Management of HIV infection/AIDS in pregnancy is was performed in time of antepartum, intrapartum and post partum, for mother and the baby, in general and specific. The important matters including the use of ART, nutrition and psychological support. Prevention and management of opportunistic infections to people live with HIV/AIDS (PLWHA) are not different with that of non pregnant woman. However, the administration of ART is not routinely advised because of drug toxicity.

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Notes to authors

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- **Perspectives**. Articles should be under 3,500 words and should include references, not to exceed 40. Use of subheadings in the main body of the text is recommended. Photographs and illustrations are encouraged. Provide a short abstract (150 words), a one-sentence summary of the conclusions, and a brief biographical sketch**.** Articles in this section should provide insightful analysis and commentary about new and reemerging infectious diseases and related issues. Perspectives may also address factors know to influence the emergence of diseases, including microbal adaptation and change, human demographics and behavior, technology and industry, economic development and land use, international travel and commerce, and the breakdown of public health measures. If detailed methods are included, a separate section on experimental procedures should immediatelly follow the body of the text.
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one-sentence summary of the conclusions. This section comprises concise reviews of infectious diseases or closely related topics. Preference is given to reviews of emerging and reemerging diseases; however, timely updates of other diseases or topics are also welcome. If detailed methods are included, a separate section on experimental procedures should immediately follow the body of the text.

- **Research Studies and Scientific Review**. Articles should be under 3,500 words and should include references, not to exceed 40. Use of subheadings in the main body of the text in recommended. Photographs and ilustrations are encouraged. Provide a short abstract (150 words) a one-sentence summary of the conclusions. Report laboratory and epidemiologic results within a public health perspective. Explain the value of the research in public health terms and place the findings in a larger perspective.
- **Dispatches**. Articles should no more than 1,200 words and need not be devided into sections. If subheadings are used, they should be general, e, g., "The study" and "Conclusions." Provide a brief abstract (50 words); references (not to exceed 15); figures or illustrations (not to exceed 2). Dispatches are updates on infectious disease trends and research. The articles inlude descriptions of new methods for detecting, characterizing, or subtyping emerging or reemerging pathogens. Developments in antimicrobial drugs, vaccines, or infectious disease prevention or elimination program are appropriate. Case reports are also welcome.
- **Commentaries**. Thoughtful discussions (500–1,000 words) of current topics. Commentaries may contain references but not figures or tables.
- **Another Dimension**. Thoughtful essays, short stories, or poems on philosophical issues related to science, medical practice, and human health. Topics may include science and the human condition, the unanticipated side of epidemic investigations, or how people perceive and cope with infection and illness. This section is intended to evoke compassion for human suffering and to expand the science reader's literary scope. Manuscripts are selected for publication as much for their content (the experiences they describe) as for their literary merit.
- **Letters**. Letters commenting on recent articles as well as latters reporting cases, outbreaks, or original research are welcome. Letters commenting on articles should contain no more than 300 words and 5 references; they are more likely to be published if submitted within 4 weeks of the original article's publication. Letters reporting cases, outbreaks, or original research should contain no more than 800 words and 10 references. They may have 1 figure or table and should not be devided into sections. All latters should contain material not previously published and include a word count.
- **Books, Other Media**. Reviews (250–500 words) of new books or other media on emerging and reemerging disease issues are welcome. Name, publisher, number of pages, other pertinent details should be included.
- **Announcements**. We welcome brief announcements (50–150 words) of timely events of interest to our readers. (Announcements may be posted online only, depending on the event date).
- **Conference Summaries**. Summaries of emerging and reemerging infectious disease conference activities are published online only. Summaries, which should contain 500–1,000 words, should focus on content rather than process and may provide illustrations, references, and links to full reports of conference activities.